FUTURO
INIBITORE
IMMUNOTOLLERANZA
CURA
PERSONALIZZAZIONE
SISTEMA SANITARIO NAZIONALE
ACCESSO
ENGAGEMENT
EMOFILIA
PLASMA
EMOSTASI
DONATORI
OMEOSTASI
ERADICARE
FISIOTERAPIA
TERAPIA SOSTITUTIVA
PROFILASSI
PAZIENTE
SALUTE
FARMACOCINETICA
FATTORE VIII

27/28 GIUGNO 2019
TRIESTE
SAVOIA EXCELSIOR PALACE

EMOFILIA

LA CERTEZZA DELLA CURA

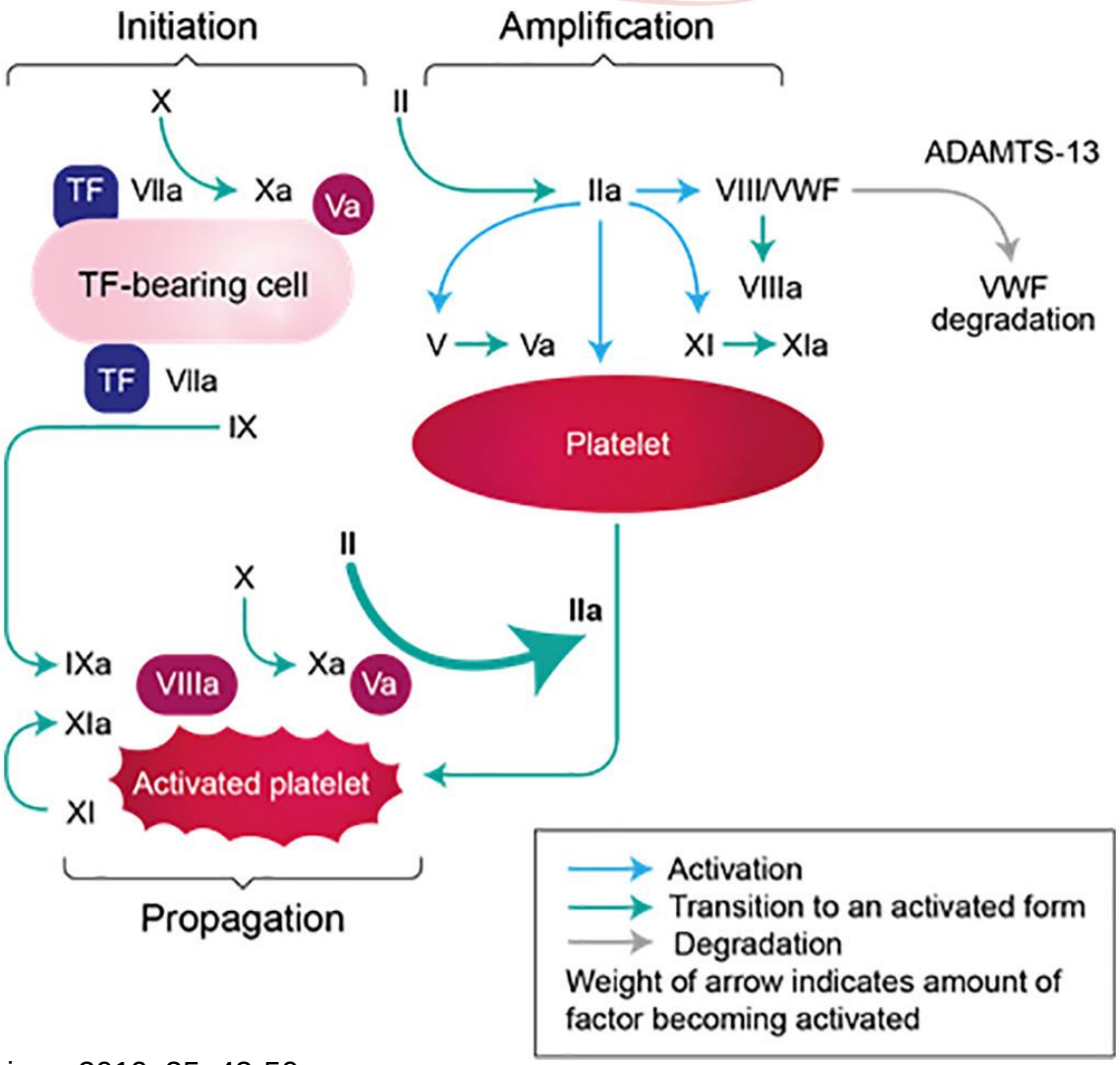
TERAPIA SOSTITUTIVA, PERSONALIZZAZIONE, ACCESSO

Cosa sappiamo davvero sul Fattore VIII

Elena SANTAGOSTINO

RESPONSABILE UOS EMOFILIA
CENTRO EMOFILIA E TROMBOSI A. BIANCHI BONOMI
IRCCS FONDAZIONE CA' GRANDA, OSPEDALE MAGGIORE POLICLINICO – MILANO

The role of FVIII is well known



Bannow et al. Blood Reviews 2019; 35; 43-50

How does emicizumab compare to FVIII?

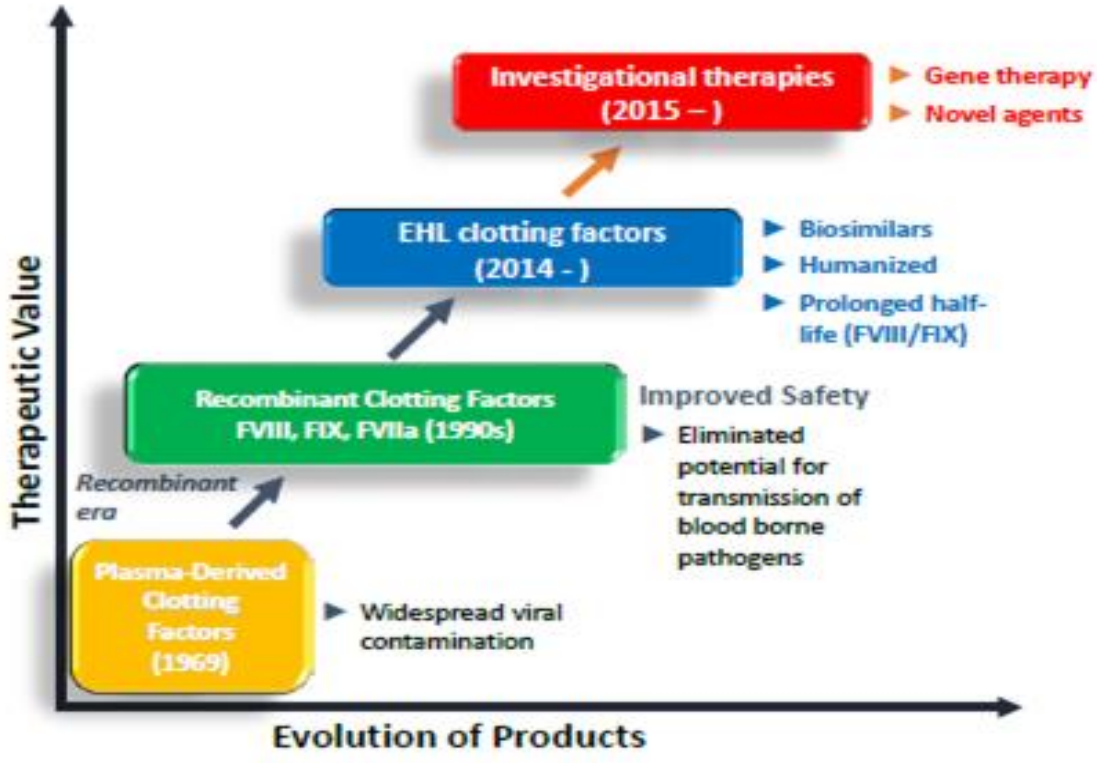
FVIII	Emicizumab
Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

Lenting et al. Blood 2017;130:2463-2468

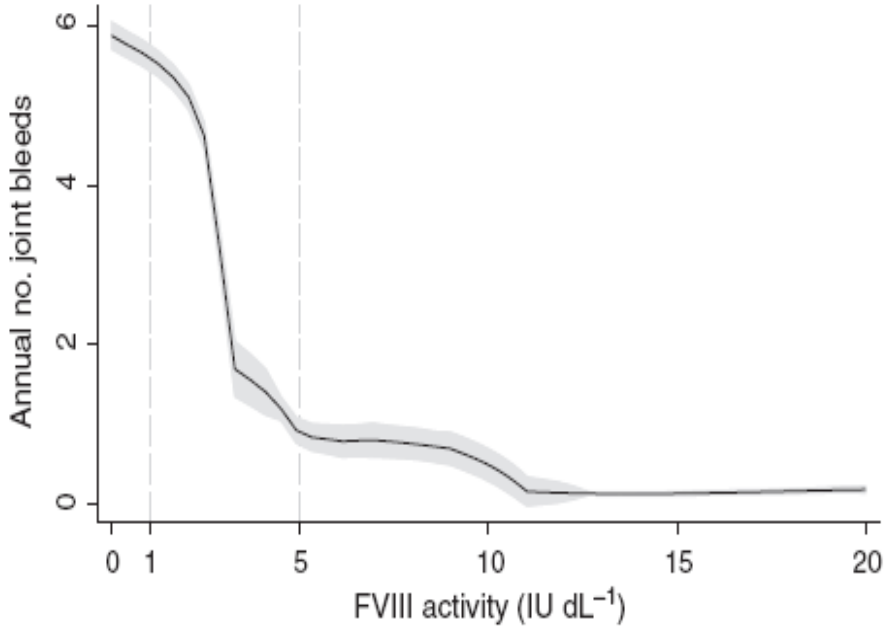
FVIII replacement in hemophilia

- FVIII therapy is the **only** strategy that restores what is missing
- Addressing the root cause of hemophilia, since ever it has been the gold standard

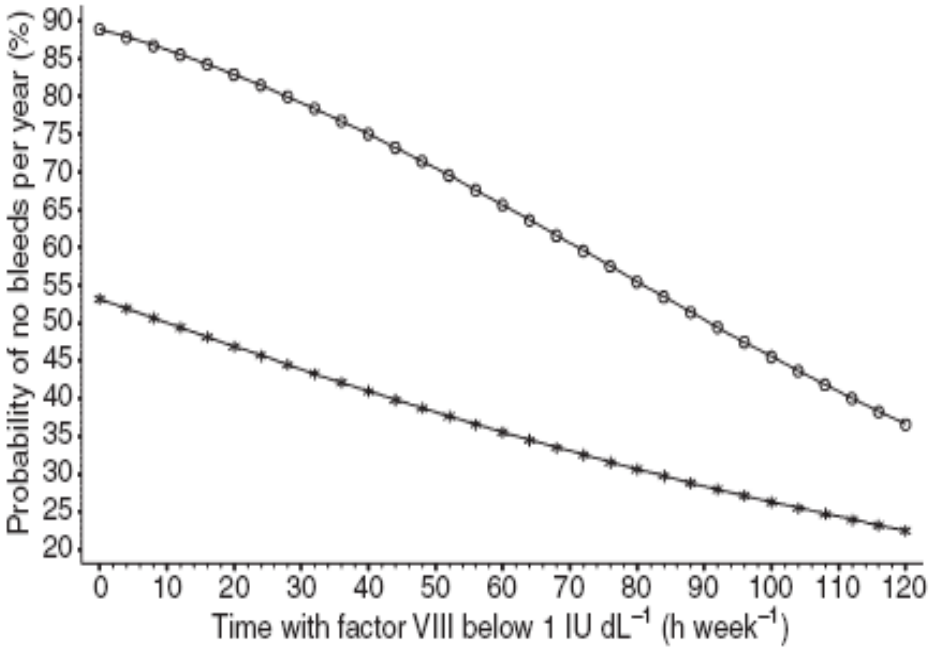
Evolution of hemophilia treatment



The importance of FVIII levels

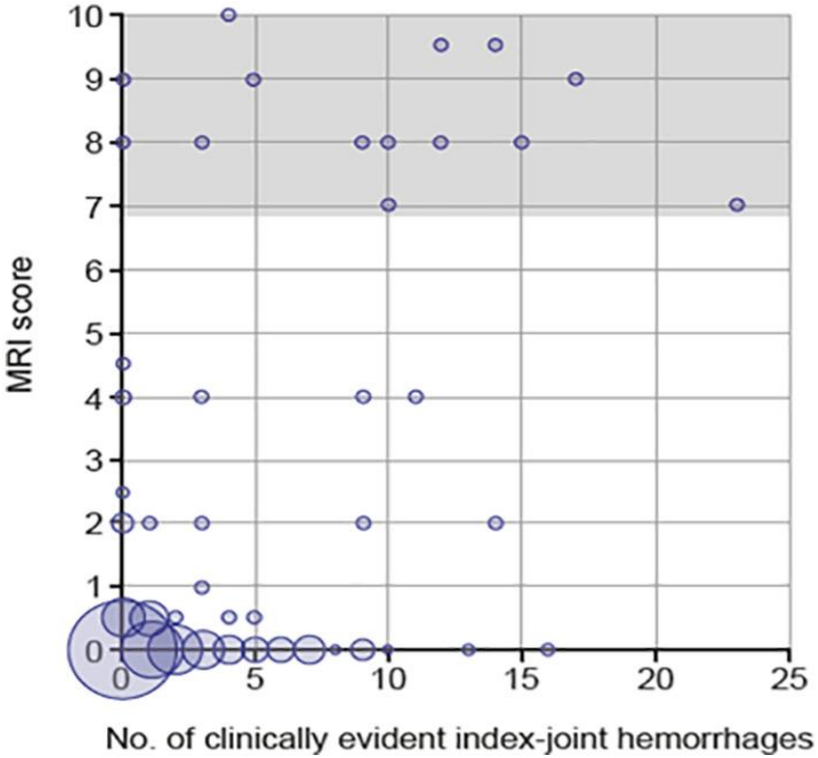


Den Uijl et al. Haemophilia 2011;17:849-53



Collins et al. JTH 2009;7:413-20

The outcome of maintaining FVIII levels



Manco-Johnson et al. NEJM 2007;357:535-44

Factor VIII: Long-established role in haemophilia A and emerging evidence beyond haemostasis

Bethany Samuelson Bannow[a,*], Michael Recht[a], Claude Négrier[b], Cédric Hermans[c], Erik Berntorp[d], Hermann Eichler[e], Maria Elisa Mancuso[f], Robert Klamroth[g], Jamie O'Hara[h], Elena Santagostino[i], Tadashi Matsushita[i], Craig Kessler[j]

Blood Reviews 35 (2019) 43–50

System/process	Influence of haemophilia	Specific role of FVIII
Coagulation	Impaired clotting: bleeding and joint damage	Forms the Xase complex with FIXa on the surface of platelets to potentiate FXa generation Treatment and prophylaxis of bleeding events
Bones	Increased fracture risk Decreased bone mineral density	RANKL (which increases bone breakdown) expression is decreased by FVIII treatment

Bone mineral density in haemophilia

- Patients with hemophilia have a significant reduction in lumbar spine mineral density compared with healthy controls
- This reduction is apparent even in childhood

Population	Number of studies	Standard mean difference in bone mineral density	95% CI
Adult	6	-0.56	-0.84, -0.28
Paediatric	4	-0.92	-1.77, -0.07
Total	10	-0.72	-1.08, -0.36

Paschou et al. Osteoporos Int 2014;25:2399–407

FVIII and bone remodelling

- Bone formation may be indirectly enhanced by FVIII via thrombin generation which has been associated with the activation of osteoblasts (rabbit model)[1]
- Direct role for FVIII-vWF complex: binding to OPG and RANKL[2]
- Direct role of FVIII: increased osteoblast formation after FVIII therapy in FVIII-deficient mice[3]

OPG: osteoprotegerin

RANKL: RANK Ligand

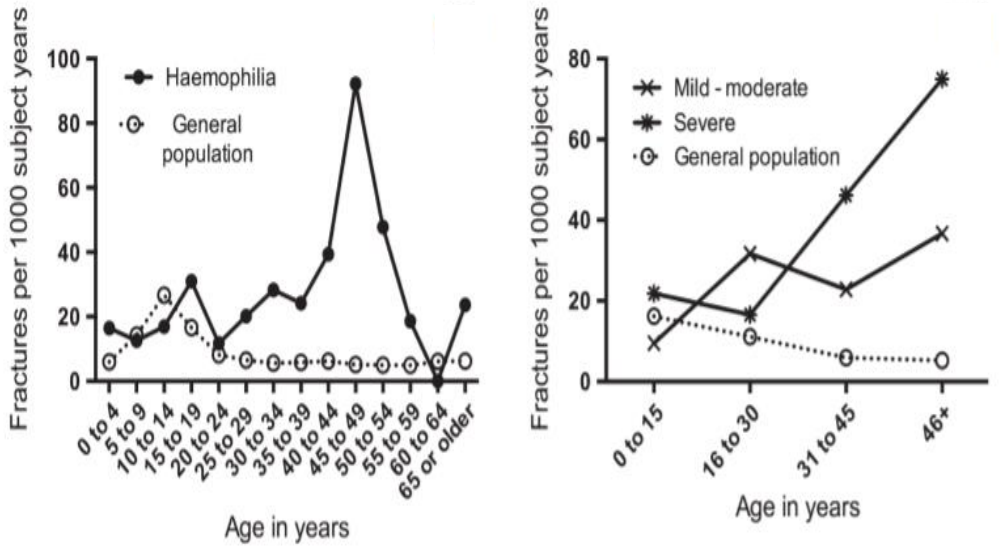
[1] Li G et al. J Orthop Res 2005; 23: 196-202

[2] Baud'huin et al. J Biol Chem 2009; 284: 31704-13

[3] Larson EA, Taylor JA. Blood 2017; 130: 3661

Fracture rates in haemophilia

- A 10-year retrospective analysis showed that fracture rates are significantly elevated in patients with haemophilia A (n=316) and B (n=66)
- The fracture rate is significantly higher in people with severe disease compared with mild-moderate disease
- This implies that the risk of fracture increases with decreasing factor levels



Gay et al. Br J Haematol 2015;170:584–6

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Blood Reviews 35 (2019) 43–50

System/process	Influence of haemophilia	Specific role of FVIII
Bones	Increased fracture risk Decreased bone mineral density	RANKL (which increases bone breakdown) expression is decreased by FVIII treatment
Cardiovascular system	Lower incidence of arterial disease in some studies	Supraphysiological FVIII levels are a risk factor for venous thromboembolism
Hypertension	Higher incidence of hypertension	Not established (see angiogenesis)
Kidney	Haematuria and increased risk of kidney disease	Not established
Cancer incidence and spread	Increased incidence of haematological malignancies and urinary organ cancers Decreased metastasis in a mouse model	Not established
Angiogenesis	Neoangiogenesis and abnormal vascular architecture	FVIII binding partner VWF is a regulator of angiogenesis

FVIII and brain function

- Reduced academic achievement, inattention, hyperactivity in boys with hemophilia[1]
- Lower intellectual functioning, visual-spatial and motor skills in patients with hemophilia and ICH[2]
- Cognitive dysfunctions and cerebral microbleeds (MRI) in adults with hemophilia A[3]

[1] Spencer et al. Haemophilia 2009; 15: 701-6

[2] Miles et al. Haemophilia 2012; 18: 229-34

[3] Zanon et al. Thromb Res 2014; 134: 851-5

A novel role for factor VIII and thrombin/PAR1 in regulating hematopoiesis and its interplay with the bone structure

Anna Aronovich,[1] Yaniv Nur,[1] Elias Shezen,[1] Chava Rosen,[1] Yael Zlotnikov Klionsky,[1] Irit Milman,[1] Liran Yarimi,[1] David Hagin,[1] Gidi Rechavi,[2] Uriel Martinowitz,[3] Takashi Nagasawa,[4,5] Paul S. Frenette,[6] Dalit Tchorsh-Yutsis,[1] and Yair Reisner[1]

Key Points

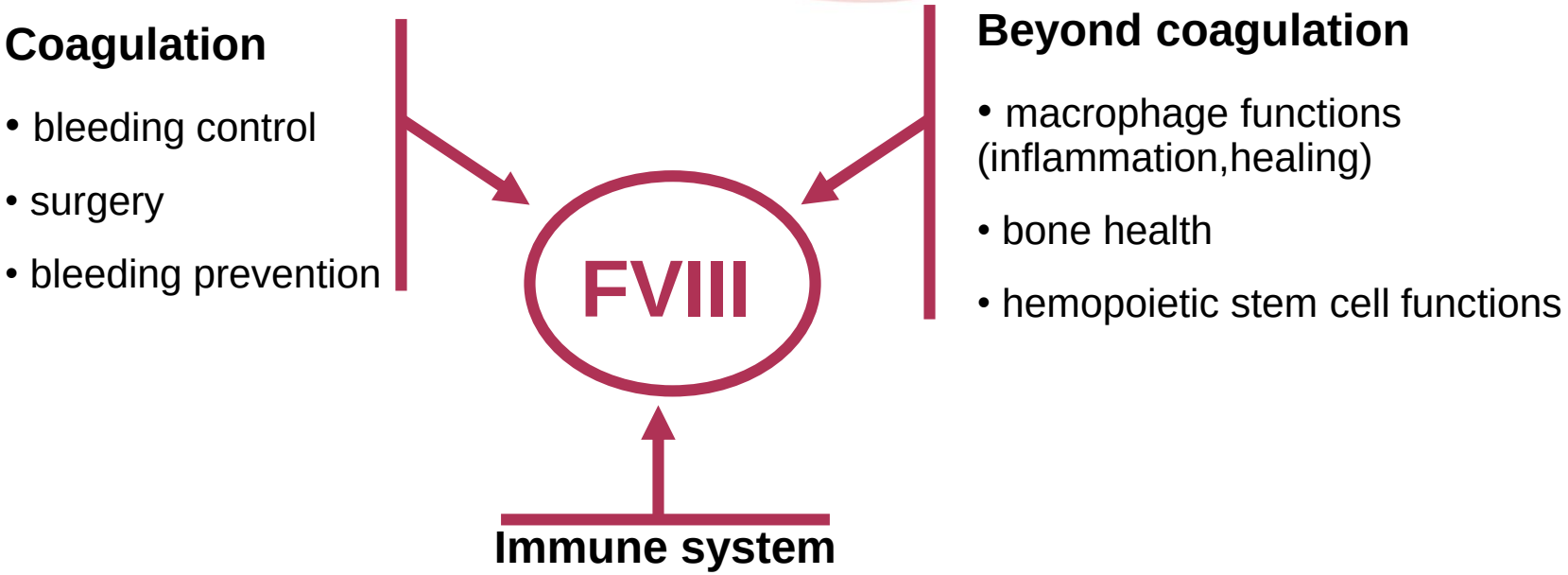
- The coagulation cascade via the factor VIII/thrombin/PAR1 axis regulates HSC maintenance.
- The coagulation cascade via factor VIII/thrombin/PAR1 axis regulates a reciprocal interplay between HSCs and the dynamic bone structure.

BLOOD, 10 OCTOBER 2013 • VOLUME 122, NUMBER 15

Macrophage Polarization is Deregulated in Haemophilia

Lynn M. Knowles[1] Daniela Kagiri[1] Martin Bernard[1] Eva C. Schwarz[2] Hermann Eichler[1] Jan Pilch[1]

Thrombosis and Haemostasis Vol. 119 No. 2/2019



Implications for non-FVIII replacement therapies:

- Need for long-term studies on efficacy (joint outcomes), safety and QoL
- Need for survellance on age-related illnesses and comorbidites in hemophilia