Le indicazioni cliniche per l'utilizzo dei fattori della coagulazione

Elena Santagostino

Centro Emofilia e Trombosi A. Bianchi Bonomi
Fondazione Ca' Granda, Ospedale Maggiore di Milano

Current FVIII products for hemophilia A

FVIII plasmaderivato

Codice AIC	Denominazione farmaco	UI
Fattore VIII di coagulazione del sangue umano da frazionamento		
038541013	HAEMOCTIN*FL 250UI+FL 5ML+SIR	250
038541025	HAEMOCTIN*FL 500UI+FL 10ML+SIR	500
038541037	HAEMOCTIN*FL 1000UI+FL 10ML+SI	1000
Fattore VIII di coagulazione del sangue umano liofilizzato		
023564166	EMOCLOT D.I.*FL 500UI+FL 10ML	500
023564216	EMOCLOT*FL 500UI+FL 10ML+SET	500
041649017	KLOTT*FL 500UI+FL 10ML+SET	500
033866056	FANHDI*INF FL 500UI+SIR SOLV+S	500
023564178	EMOCLOT D.I.*FL 1000UI+FL 10ML	1000
023564228	EMOCLOT*FL 1000UI+FL 10ML+SET	1000
041649029	KLOTT*FL 1000UI+FL 10ML+SET	1000
026600041	HAEMATE P*FL 1000UI+FL30ML+SET	1000
027128014	HEMOFIL M*IV 1F 1000UI+F 10ML	1000
029225036	IMMUNATE STIM PLUS*1FL 1000UI+	1000
033657038	BERIATE P 1000*F 1000UI+SOLV+S	1000
033866031	FANHDI 1000UI*1F 1000UI+F 10ML	1000
033866068	FANHDI*INF FL1000UI+SIR SOLV+S	1000

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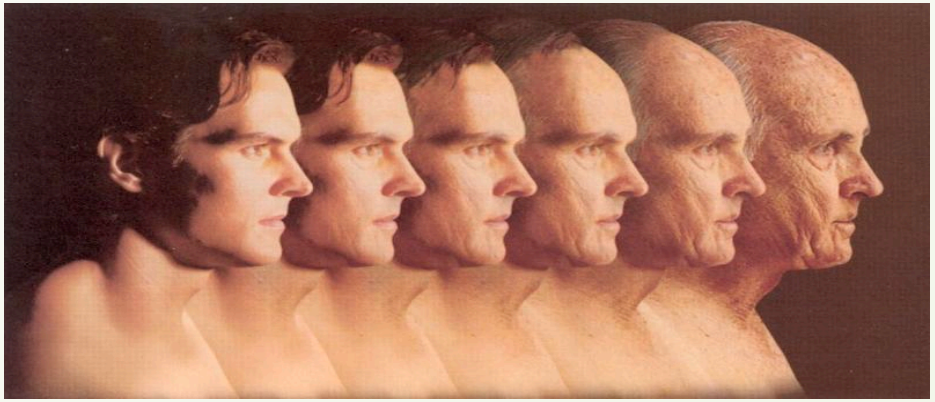
Rapporti ISTISAN 16/7

FVIII ricombinante

Codice AIC	Denominazione farmaco	UI
034421014	REFACTO AF*IV 1FL 250UI+FL 4ML	250
034421091	REFACTO AF*IV 1SIR 250UI+DISP	250
034955043	KOGENATE BAYER*FL250UI+SIR	250
034956019	HELIXATE NEXGEN*250UI+1FL+1KIT	250
036160012	ADVATE*FL 250UI+FL SOLV 5ML	250
028687022	RECOMBINATE*FL 500UI+FL SOLV	500
034421026	REFACTO AF*IV 1FL 500UI+FL 4ML	500
034421065	REFACTO AF*IV 1SIR 500UI+DISP	500
034955029	KOGENATE BAYER*500UI+1FL+1KIT	500
034955056	KOGENATE BAYER*FL500UI+SIR	500
034956021	HELIXATE NEXGEN*500UI+1FL+1KIT	500
036160024	ADVATE*FL 500UI+FL SOLV 5ML	500
028687034	RECOMBINATE*FL 1000UI+FL SOLV	1000
034421038	REFACTO AF*IV 1FL 1000UI+FL4ML	1000
034421077	REFACTO AF*IV 1SIR1000UI+DISP	1000
034955031	KOGENATE BAYER*1000UI+1FL	1000
034955068	KOGENATE BAYER*FL1000UI+SIR	1000
034956033	HELIXATE NEXGEN*1000UI+1FL	1000
036160036	ADVATE*FL 1000UI+FL SOLV 5ML	1000
036160048	ADVATE*FL 1500UI+FL SOLV 5ML	1500
034421040	REFACTO AF*IV 1FL 2000UI+SIR4M	2000
034421089	REFACTO AF*IV 1SIR2000UI+DISP	2000
034955106	KOGENATE BAYER*EV2000UI+SIR	2000
034956045	HELIXATE NEXGEN*2000UI+1FL+KIT	2000
036160051	ADVATE*FL 2000UI+FL SOLV 5ML	2000
034421053	REFACTO AF*IV 1SIR3000UI+DISP	3000
034955120	KOGENATE BAYER "3000UI	3000
034956058	HELIXATE NEXGEN 3000UI	3000
036160063	ADVATE*FL 3000UI+FL SOLV 5ML	3000

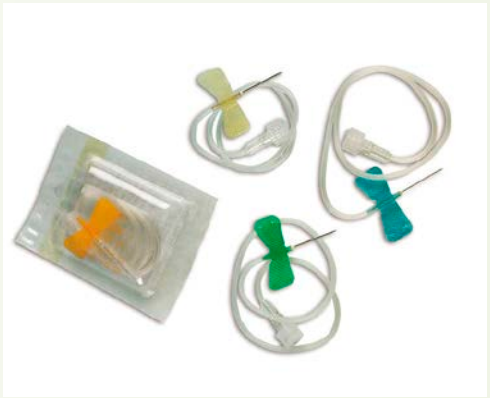
Current treatment for hemophilia

- Recombinant and plasma-derived FVIII/FIX products are highly effective in bleeding control and prevention
- Recombinant and plasma-derived FVIII/FIX products have a high degree of safety from pathogen risk



Challenges with current treatment

- Bleeding prevention needs optimization through individualization
- Inhibitor development is the main complication
- Repeated intravenous injections limit compliance and adherence
- High cost of products limits the implementation of best standards of care



Changes in haemophilia population: emerging needs in ageing individuals

- **Hemophilia-related:**

  - disabling arthropathy
  - chronic pain
  - long-lasting HIV infection
  - cirrhosis and HCC
  - inhibitors in PTPs and mild hemophiliacs

- **Age-related:**

  - cardiovascular disease
  - cancer
  - prostatic hypertrophy
  - osteoporosis
  - falls
  - obesity
  - hypertension
  - renal disease
  - diabetes
  - depression
  - erectile dysfunction
  - cataract
  - macular degeneration

Indication of prophylaxis

- **"Since the main goal is to prevent joint bleeding and its sequelae, prophylaxis should be considered as optimal management for persons with severe haemophilia A and B (baseline level < 1% FVIII or FIX).**

Bulletin of the World Health Organization, 1995, 73 (5) 691–701

… across different ages

Table 2. Types of prophylaxis and goals.

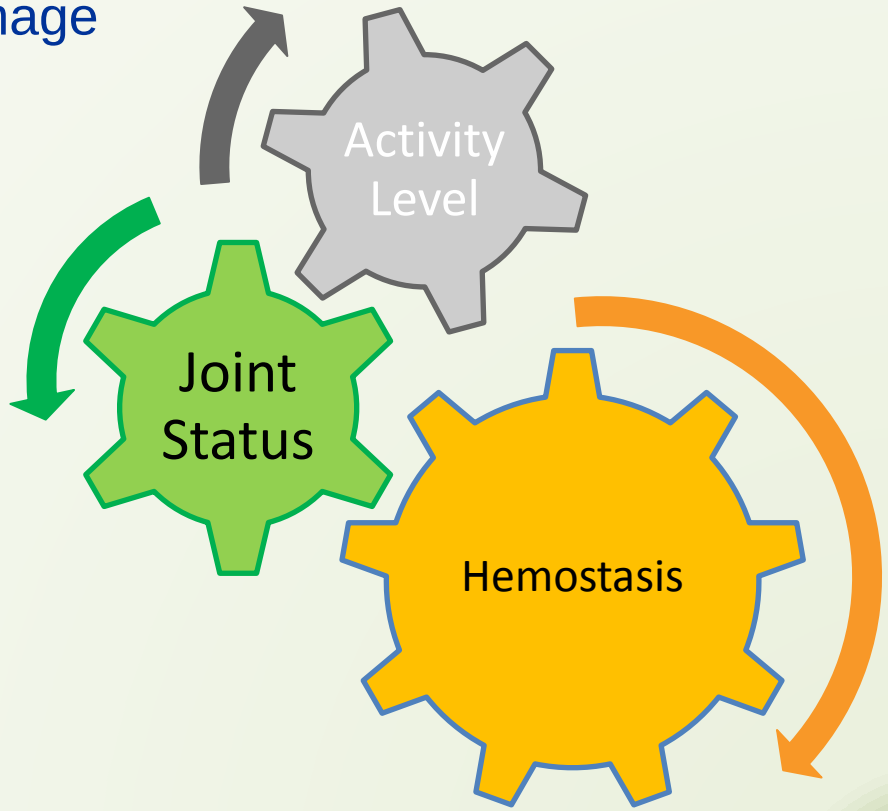
Primary prophylaxis	Secondary prophylaxis	Tertiary prophylaxis
Prevent life-threatening bleeds	Prevent life-threatening bleeds	Prevent life-threatening bleeds
Preserve pristine joints	Reduce the risk of arthropathy	Reduce the worsening of arthropathy
Minimize bleeding occurrence	Reduce bleeding frequency	Reduce bleeding frequency
Maintain high levels of QoL	Maintain high levels of QoL	Improve QoL
Support normal social participation and studying/working life	Support normal social participation and studying/working life	Improve social participation and maintain working activity and independence
Allow physical activities	Allow physical activities	Improve activity/autonomy levels
–	Prevent target joints	Reduce bleeding in target joints
–	–	Control pain
–	–	Permit physiotherapy
–	–	Reduce bleeding risk due to comorbidities

Gringeri et al, Haemophilia 2012

Prophylaxis strategy today

Individualized prophylaxis should be

- Based on bleed pattern
- Presence of target joints/joint damage
- Tailored to activity level
- Based on FVIII PK parameters
- Based on compliance
- Based on resources

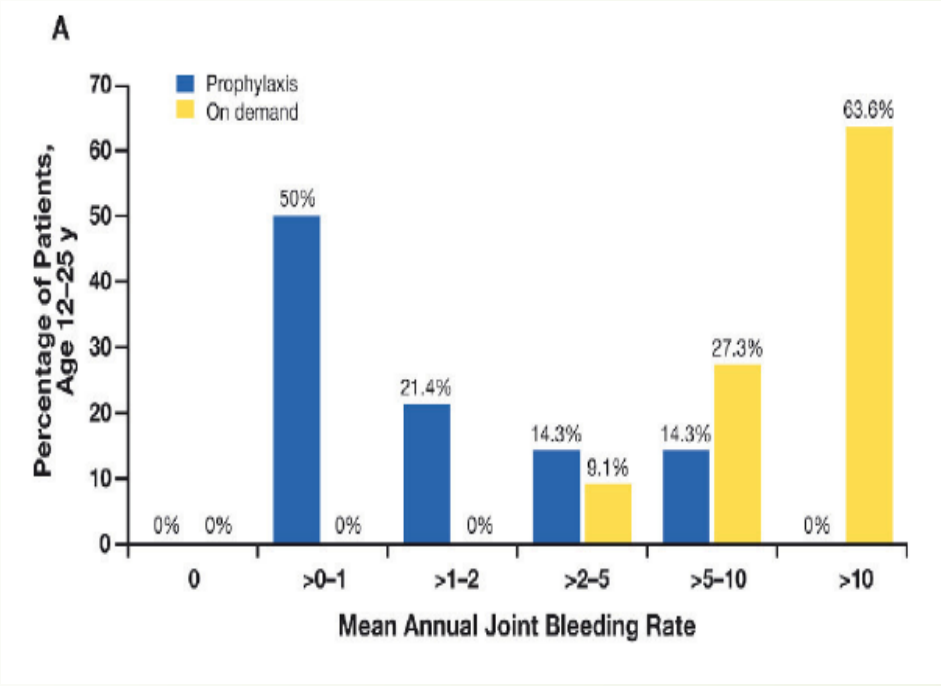


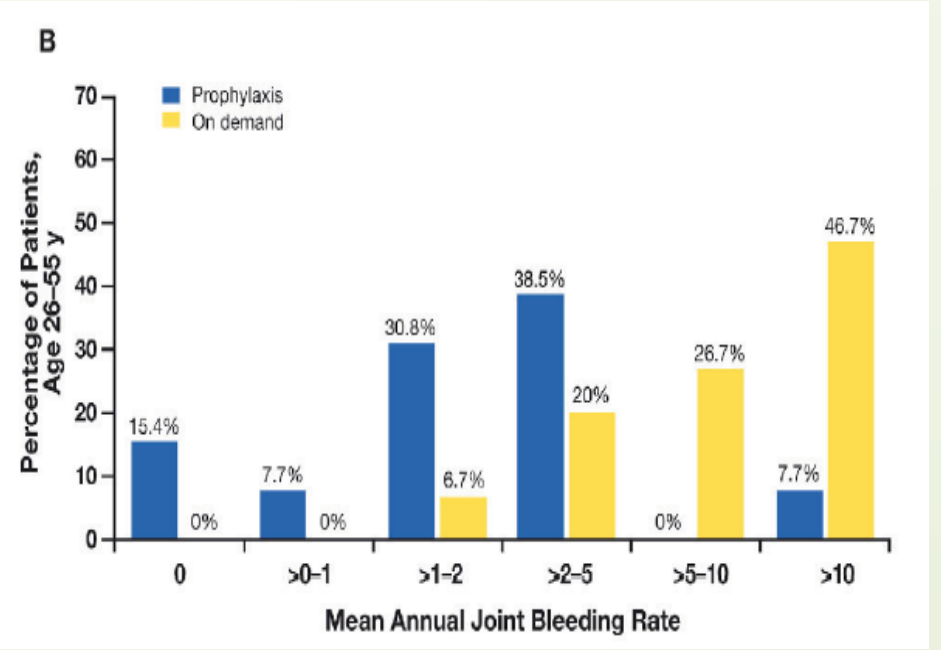
Valentino LA Haemophilia 2014; 1-9

Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study

Annarita Tagliaferri[1]; Giulio Feola[2]; Angelo Claudio Molinari[3]; Cristina Santoro[4]; Gianna Franca Rivolta[1]; Dorina Bianca Cultrera[5]; Fabio Gagliano[6]; Ezio Zanon[7]; Maria Elisa Mancuso[8]; Lelia Valdrè[9]; Luciana Mameli[10]; Susanna Amoresano[11]; Prasad Mathew[12]; Antonio Coppola[13]; for the POTTER Study Group*

- **53 pazienti valutabili: 27 profilassi, 26 on demand**





Thromb Haemost 2015; 114:35-45

Risk factors for inhibitor development in PUPs

Patient-related factors

Genetic factors

- *F8* gene mutation
- Family history of inhibitor formation
- Ethnicity
- Polymorphisms
  - Immune-regulating genes
  - MHC class II molecules

Non-genetic factors

- Age
- Infections
- Vaccinations
- Trauma/surgery

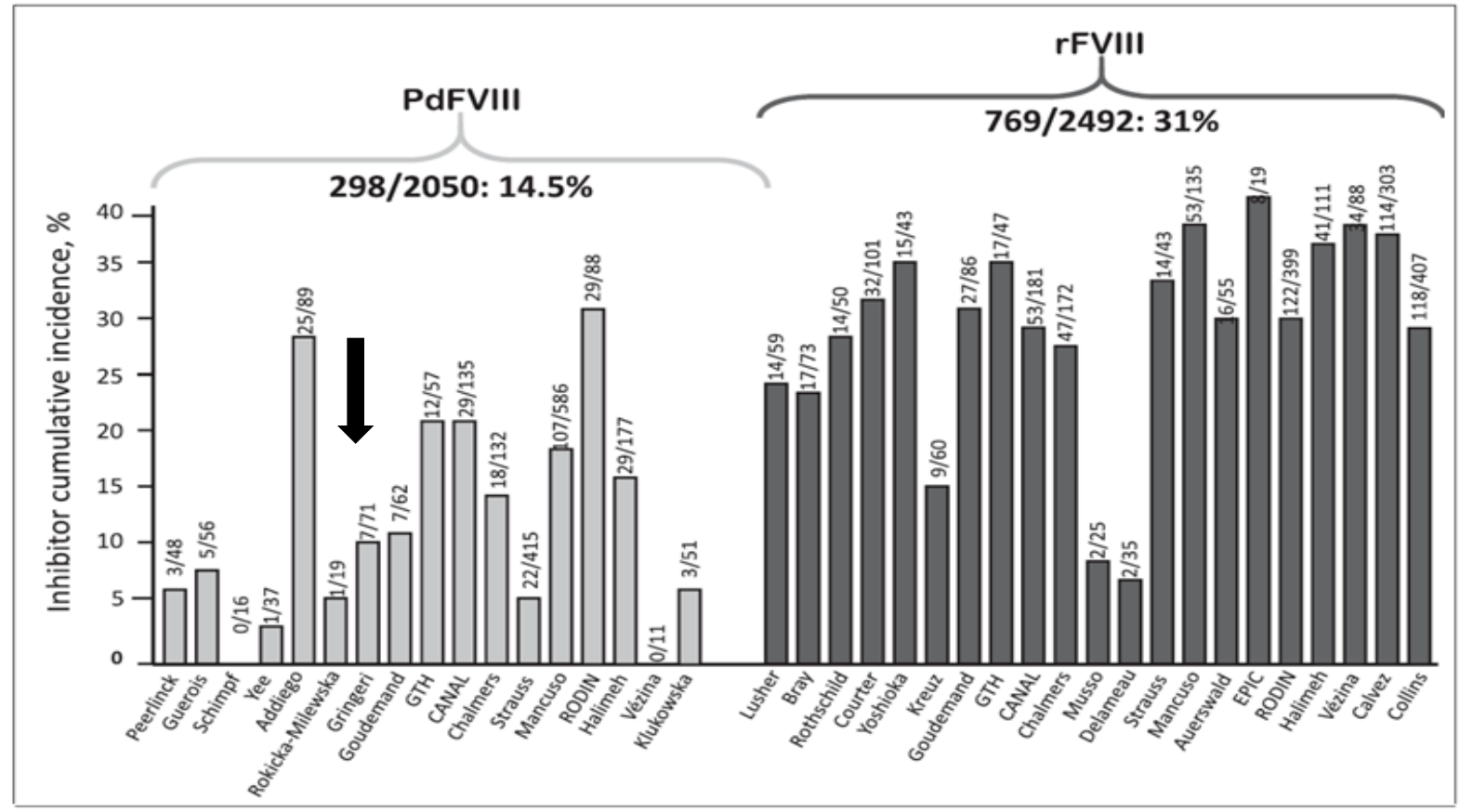
Treatment-related factors

- Intensity and mode of FVIII treatment
- Prophylaxis
- Source of FVIII product (plasma-derived *vs* recombinant)
- Switching between products
- Extravasation of FVIII and continuous infusion

Tunstall O & Astermark J. Eur J Haematol 2015;94(Suppl 77):45–50;
Álvarez T et al. Eur J Haematol 2015;94(Suppl 77):2–6;
Carcao M et al. Haemophilia 2016;22:22–31.

Multiple observational studies

- Several observational studies on 4542 PUPs showed that the risk of inhibitor development is at least **doubled in patients treated with rFVIII**



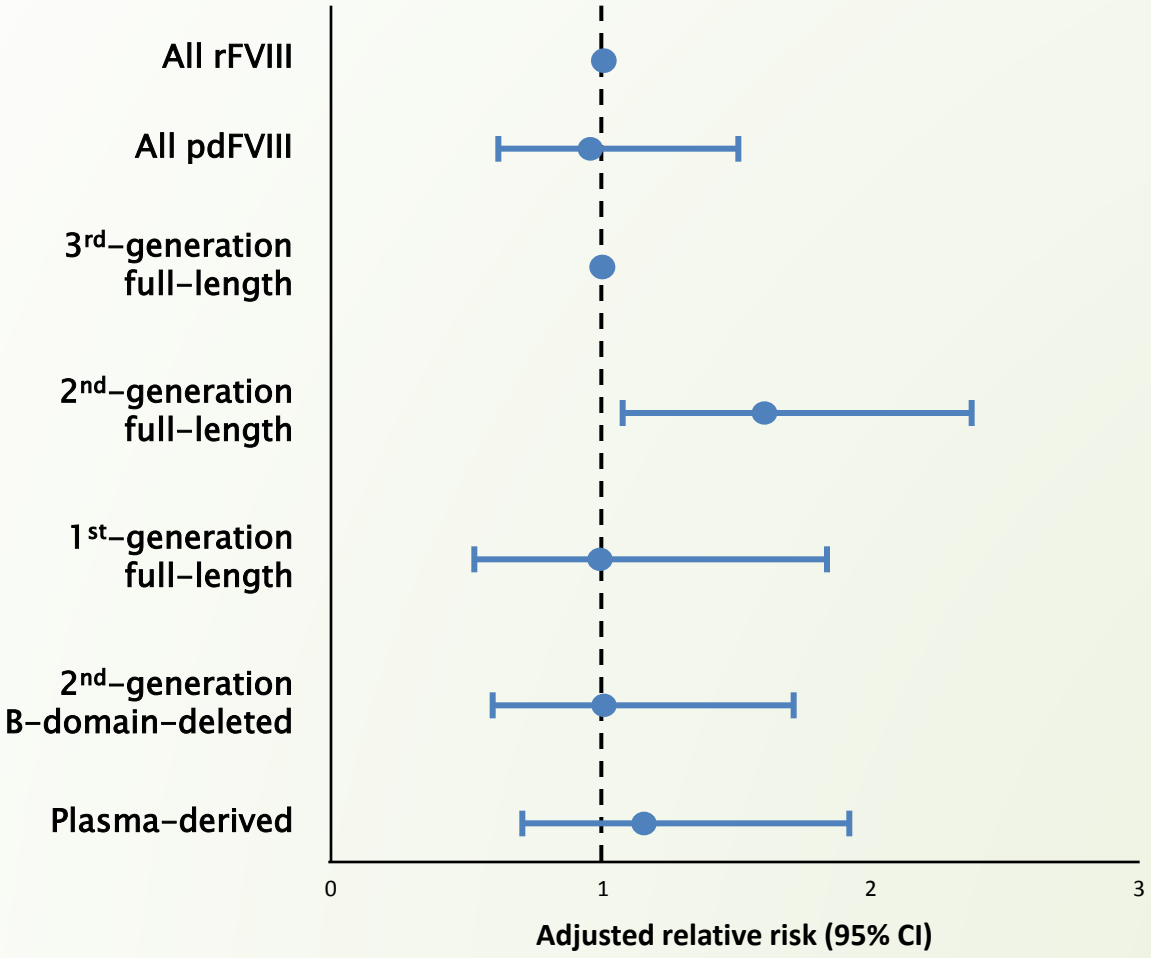
Wight J, Paisley S. Haemophilia 2003; Goudemand J, et al. Blood 2006; Chalmers EA, et al. Haemophilia 2007; Gouw SC, et al. Blood 2007; Iorio A, et al. J Thromb Haemost 2010; Gouw SC, et al. Blood 2013; Franchini M, et al. Semin Thromb Hemost 2013; Marcucci M, et al. Thromb Haemost 2015; Mannucci et al. Thromb Haemost. 2015

Large observational studies

	rFVIII (No. of patients)	pdFVIII (No. of patients)
CANAL	181	135
Inhibitor development (%)	53 (29%)	29 (21%)
RODIN	486	88
Inhibitor development (%)	145 (30%)	29 (33%)
EUHASS	366	51
Inhibitor development (%)	97 (26,5%)	11 (21,6%)

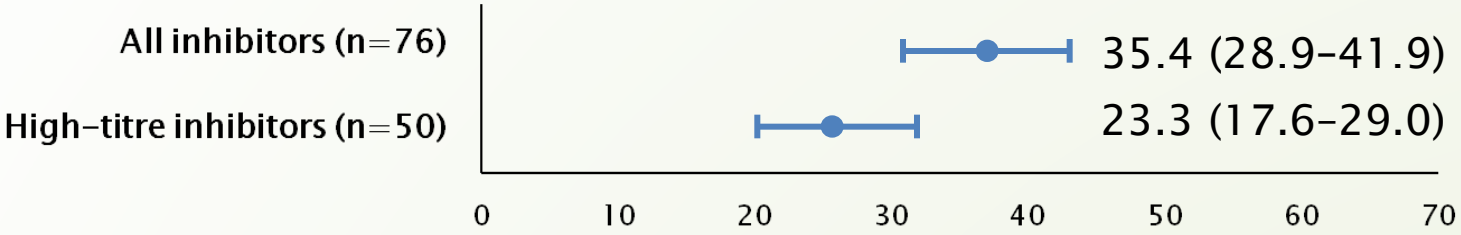
No difference in inhibitor rates between plasma-derived and recombinant FVIII product

RODIN: higher risk of inhibitors with 2° gen. full-length rFVIII



Gouw SC et al. N Engl J Med 2013;368:231–9.

SIPPET: RCT in PUPs



Cumulative incidence

Risk per treatment arm	rFVIII (n=126)		pdFVIII (n=125)	
	n	% (95% CI)	n	% (95% CI)
All inhibitors	47	44.5 (34.7-54.3)	29	26.8 (18.4-35.2)
High titre	30	28.4 (19.6-37.2)	20	18.6 (11.2-26.0)
HR - all inhibitors, % (95% CI)	1.87 (1.17-2.96)		1.0	
HR - high titre, % (95% CI)	1.69 (0.96-2.98)		1.0	

- Over 73% of all inhibitors were non-transient in both arms

Peyvandi F. Abstract, 57th American Society of Hematology Annual Meeting, Orlando, USA.

Inhibitor incidence in PTPs per 1000 patient/years

Authors	EDs	Rate
McMillan 1988	>150	2.6
Kempton 2006	>50	2.14
Darby 2004	age >15 years	3.8

McMillan et al. Blood 1988;71:344-48.
Kempton et al. J Thromb Haemost 2006;4:2476-81.
Darby et al. J Thromb Haemost 2004;2:1047-54

Reasons for switching clotting factor concentrates

- Improved safety (real or perceived)
  - Less risk of infection
  - Less inhibitor risk
- Fewer side-effects (e.g. allergic reactions)
- Newer generation of product
- Price
- National contracting
- Volume of final product
- Mixing and administration device
- Storage advantage
- Patient/family preference
- Longer half-life
- Participation in a clinical trial/research study

Iorio et al. Blood 2012; 120: 720-727

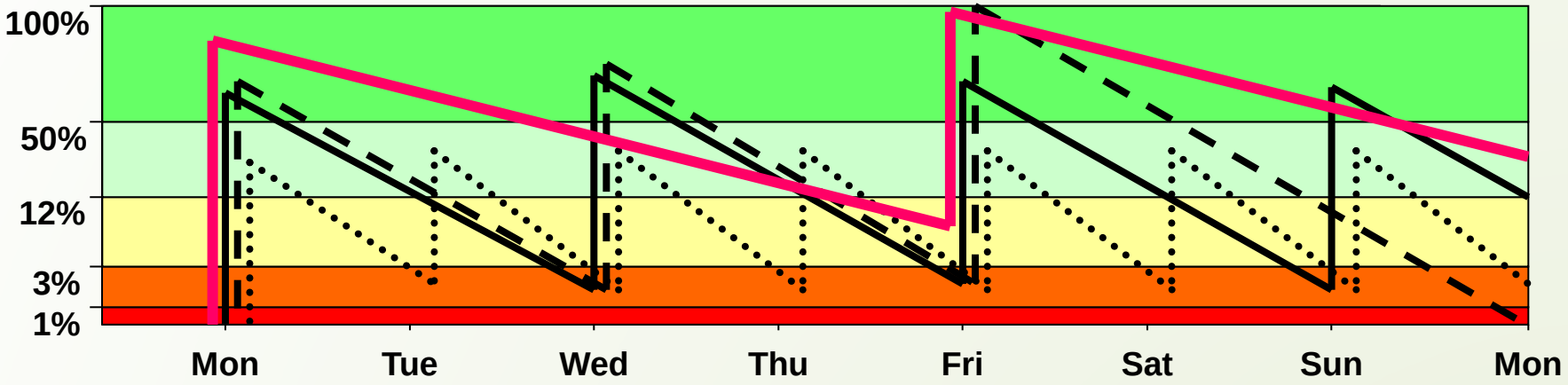
SPECIAL CONDITIONS FOR SWITCHING

- patients < 50 EDs.
- patients with family history of inhibitors or severe *F8* gene defect.
- patients with a previous history of inhibitors (including after ITI)
- during the peri-operative period or other periods of intensive treatment.

Long-acting products

Fewer infusions

Higher troughs



	Current products (# yearly i.v. injections)	Long-acting products (# yearly i.v. injections)
Hemophilia A	150-180	80-100
Hemophilia B	**100-120**	**30-40**

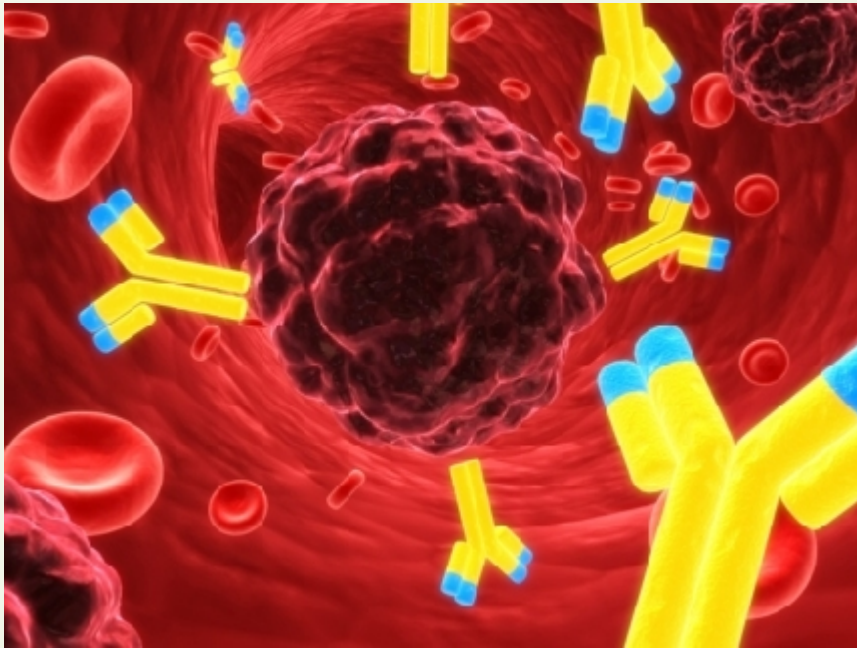
Immunogenicity

Will they result in:

- ✓ ***More (>25-30%) – won't be accepted***
- ✓ ***SAME – will be tolerated***
- ✓ ***Less (<25%) - hopefully***

So far so good in PTPs

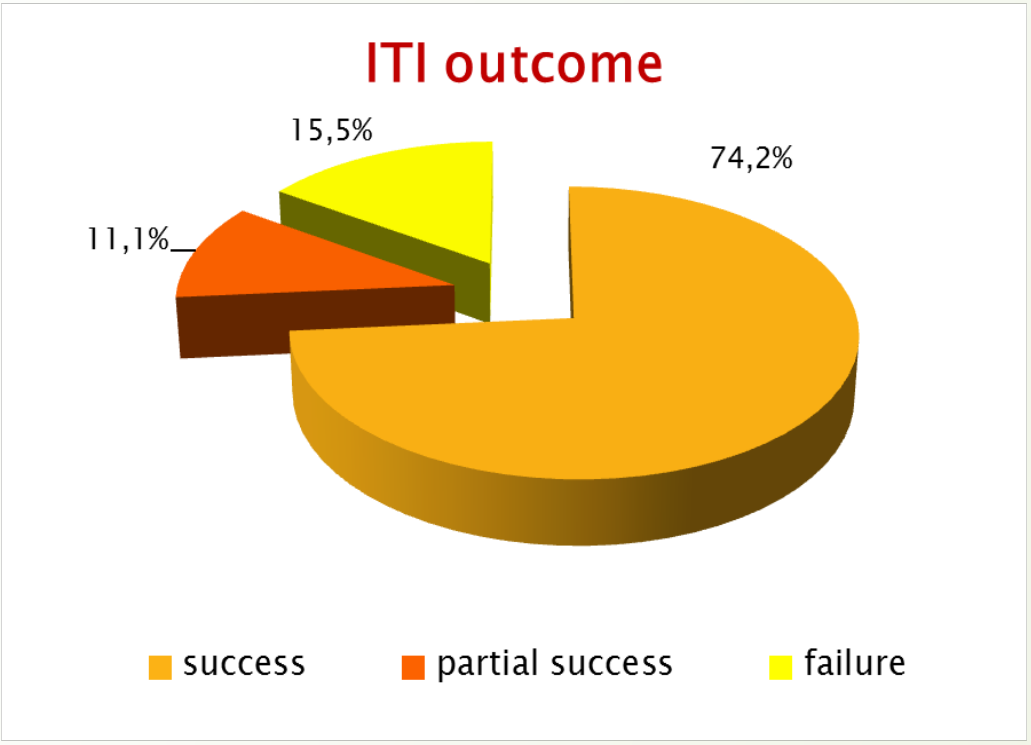
Awaiting for PUPs studies



Immune tolerance induction in patients with haemophilia a and inhibitors: effectiveness and cost analysis in an European Cohort (The ITER Study)

A. ROCINO,* P. A. CORTESI,†‡ L. SCALONE,†‡ L. G. MANTOVANI,†‡ R. CREA§ and A. GRINGERI,¶ ON BEHALF OF THE EUROPEAN HAEMOPHILIA THERAPY STRATEGY BOARD (EHTSB)[1]

*Hemophilia & Thrombosis Centre, San Giovanni Bosco Hospital, Naples; †CESP – Research Centre on Public Health, University of Milan-Bicocca, Monza; ‡CHARTA Foundation, Milan; §Baxalta Italia Srl, Rome, Italy; and ¶Baxalta Innovations GmbH, Vienna, Austria



71 patients (age: 0.4-41 years)
11 European Centers

Inhibitor relapse after 1 year: 8.3%.
Median ITI duration: 14.6 months (1.2-168.0 months).

Mean ITI cost: €60 000 per patient-month

International workshop on immune tolerance induction: consensus recommendations[1]

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

Incomplete / No response to first-line ITI

- Continue initial ITI regimen
- Maximize dose
- Switch to VWF-cointaining FVIII product if ITI was initiated with a monoclonal or recombinant product
- Consider adding rituximab or another immune-modulating drug to the current regimen

Haemophilia (2007), 13 (Suppl. 1), 1–22

Von Willebrand Disease Prophylaxis network survey

(Berntorp, 2013)

6208 “clinically severe” patients

(74 countries, from 2008 to 2011)

→ 1085 treated with plasmaderived concentrate in the previous 12 months

↓

102 patients on prophylaxis

indication: 40% joint bleeds, 23% epistaxis/oral bleeds, 14% GI bleeds

How to improve treatment?

Challenges and Perspectives

- Treatment individualization is the best strategy
- Product choice should be aimed at improving clinical outcomes, adherence and cost-effectiveness
- All novel investigative therapies are promising, but still associated with potential risks and real benefits are to be proven
- Continuous issues:
  - long-term safety
  - long-term outcomes
  - implemetation of best standard of care