Corso Malattie Emorragiche
SISET Training Center - Roma 07.06.2018

Gestione del paziente con Inibitore

Antonio Coppola

Centro Hub Emofilia e Malattie Emorragiche Congenite
AOU Parma

Achievements of haemophilia treatment

in the III millennium

Safe plasma-derived and recombinant concentrates largely available (in high-income countries)

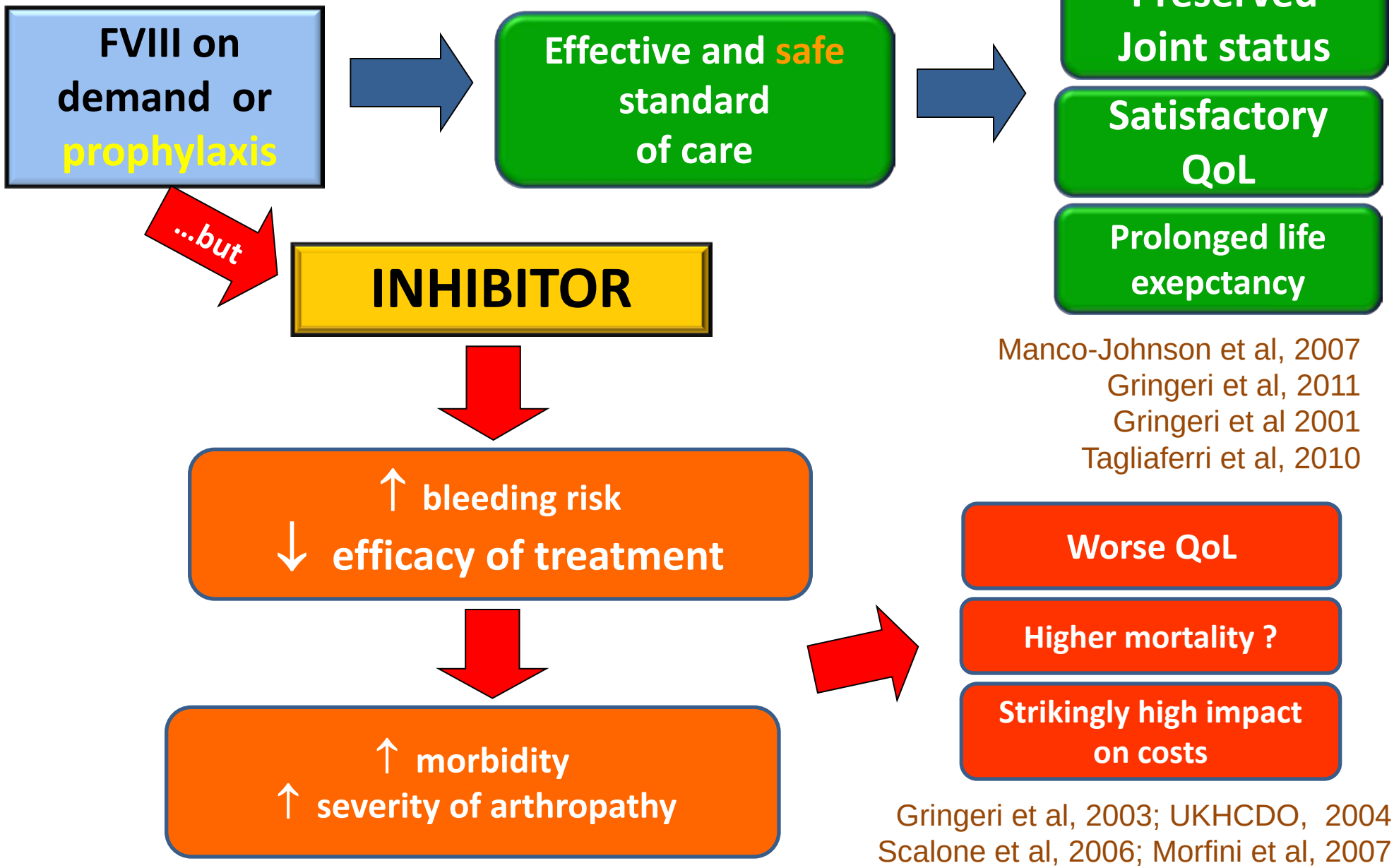
Diffusion of prophylaxis Home Treatment

Minimal joint disease in young generations on **early prophylaxis**

Benefits and improved quality of life even in adults on **late prophy.**

Life expectancy: >70 yrs (Italy, NL)

TREATING HEMOPHILIA IN THE III MILLENNIUM*



Manco-Johnson et al, 2007
Gringeri et al, 2011
Gringeri et al 2001
Tagliaferri et al, 2010

Gringeri et al, 2003; UKHCDO, 2004
Scalone et al, 2006; Morfini et al, 2007
Knight, 2009; Di Minno, 2010

*in high-income countries

Il paziente con inibitore:

compromissione stato articolare

	Group A (n = 38)	Group B (n = 41)	Group C (n = 49)	Group A vs. C	
				95% CI	P
Pain evaluation†					
Major joints	3.13 (±2.76)	4.64 (±4.11)	1.90 (±2.19)	0.45–1.77	*ns*
All joints	3.89 (±3.26)	5.82 (±5.29)	2.27 (±2.67)	0.76–2.68	<0.05
Clinical examination*					
Major joints	14.6 (±12.2)	20.2 (±9.48)	5.27 (±6.20)	4.49–12.18	<0.05
All joints	15.4 (±13.6)	23.2 (±11.6)	5.46 (±7.11)	8.40–14.30	<0.05
Radiological evaluation‡					
Major joints	22.9 (±14.3)	31.8 (±16.2)	8.00 (±10.2)	8.25–24.10	<0.05
All joints	27.8 (±19.6)	35.8 (±26.4)	19.3 (±12.4)	–	*ns*

Morfini et al, ESOS, Haemophilia 2007

A: inibitore HR 14-35 anni

B: inibitore HR 36-65 anni

C: no inibitore

Il paziente con inibitore:

compromissione stato articolare e ↓ qualità di vita

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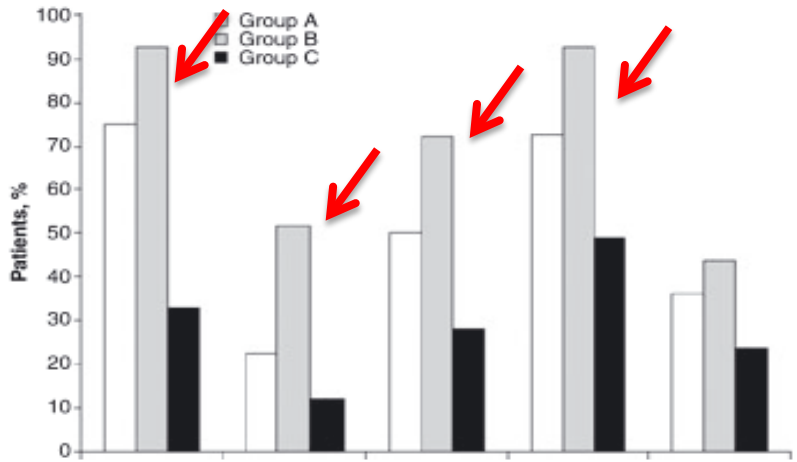
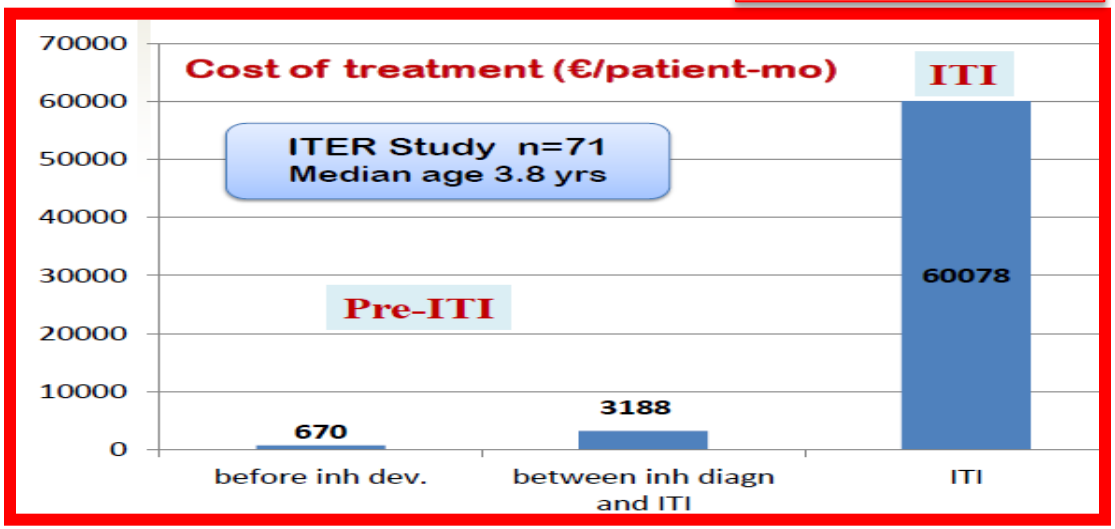
Rocino et al, Haemophilia 2016



EQ-5D



La sfida terapeutica nella gestione del paziente con inibitori

- **Priorità: eradicare l'inibitore**
  - **ITI**

TREATING HEMOPHILIA IN THE III MILLENNIUM

FVIII on demand or prophylaxis

Effective and safe standard of care

Preserved Joint status

Satisfactory QoL

Prolonged life exepctancy

Manco-Johnson et al, 2007
Gringeri et al, 2011
Gringeri et al 2001
Tagliaferri et al, 2010

L'induzione di immuno-tolleranza (ITI) consente di eradicare o ridurre la produzione di alloanticorpi inibitori anti-FVIII, **ripristinando la terapia sostitutiva standard, efficace e sicura, con concentrati di FVIII**

Esposizione ripetuta e protratta nel tempo (a dosi più o meno elevate) **all'antigene** verso il quale gli anticorpi sono diretti

Immune Tolerance Induction (ITI)

- The only approach proven to eradicate/reduce neutralizing inhibitors, in order to restore standard FVIII treatment.
- Heterogeneous regimens of frequent, uninterrupted exposure to FVIII, over a period of months to years, successful in **50-80% of cases**
- 40 years of clinical experience, only one RCT available.

Many (±) knowledge gaps

- Who should receive ITI
- When should ITI be started
- What is the appropriate ITI regimen
- **Predictors of ITI outcome**

Blood Transfusion 2014;12:575-98

RECOMMENDATION

Principles of treatment and update of recommendations for the management of haemophilia and congenital bleeding disorders in Italy

Angiola Rocino[1], Antonio Coppola[2], Massimo Franchini[3], Giancarlo Castaman[4,5], Cristina Santoro[6], Ezio Zanon[7], Elena Santagostino[8], Massimo Morfini[9] on behalf of the Italian Association of Haemophilia Centres (AICE) Working Party (see appendix 1)

treatment[138,139]. ITI is recommended in all patients with severe haemophilia A and high-responding inhibitors by the WFH guidelines[8], the European principles of haemophilia care[9], international guidelines and expert panels[76-78,136] and is largely adopted in Italian HTCs[11]. This approach should also be considered in patients with persistent low-responding inhibitors, interfering with standard-dose FVIII prophylaxis or on-demand treatment[76,77]. The main candidates for ITI are children with recent onset high-responding inhibitors in whom early eradication can provide an optimal cost-utility ratio in a long-term perspective[140]. To this purpose, ITI

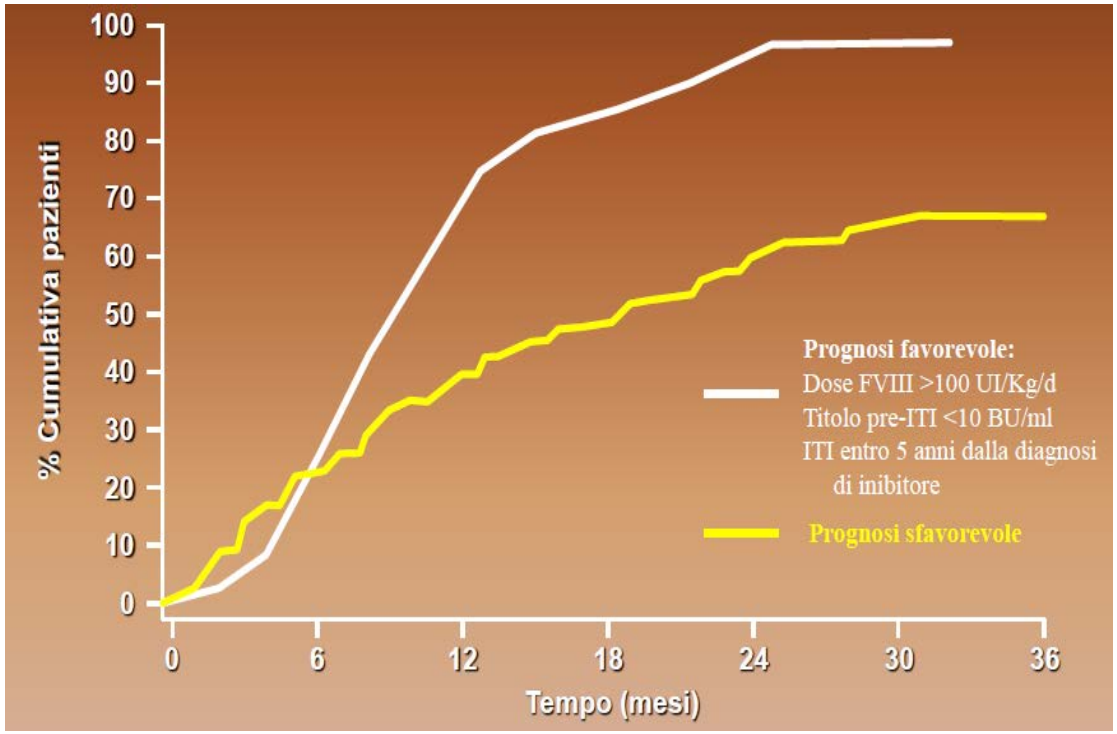
into account this variable[81,141,142]. In addition, ITI should be considered in selected patients with long-standing inhibitors who have severe or recurrent episodes of bleeding, as already reported in the literature[141,142] and in the AICE survey[11], also taking into account that age and time interval between inhibitor diagnosis and starting ITI were not consistently recognised as predictors of success

Adulti: prognosi sfavorevole ?

Registro Internazionale ITI

Fattori associati a successo	p
• **Titolo pre-ITI <10 BU/ml**	**.03**
• **Picco storico <200 BU/ml**	**.01**
• **Tempo tra ITI e diagnosi di inibitore < 5 anni**	**.0001**
• **Dose FVIII > 100 UI/Kg**	**.001**
• **Età < 20 anni**	**. 005**

Mariani & Kroner, Haematologica 2001



Peak historical titer >200 BU/ml
and/or
Pre-ITI titer > 10 BU/ml and/or
> 5 yrs since inh diagnosis

Definizione di
'poor-risk patients'

DiMichele et al, Haemophilia 2007

Fattori prognostici di successo nei Registri ITI

Variabile	IITR	NAITR	GITR	SITR	PROFIT
Successo (%)	50.9	63*	76*	63.4	52
Età all'ITI (range)	13 (1-64) (mediana)	9 (0.1-64) (media)	14 (media)	7 (0.6- 57) (mediana)	6 (0.3-58.5) (mediana)
Età al trattamento	.005 .008	.06	.55	n.s.	n.s.
Intervallo diagnosi inibitore - inizio ITI	.0001 -	.4	.85	n.s.	n.s.
Picco storico inibitore	.01 .04	.05	.0012	.02	.007 .56
Titolo pre-ITI (<10 BU/ml)	.03 .04	.005	n.r.	.03	<0.001
Picco inibitore durante ITI	n.r.	.0001	n.r.	n.r.	<0.001
Dose FVIII	alta .001 .03	bassa .01^	n.r.°	bassa .01	n.s.

IITR: Registro Internazionale; NAITR: Registro Nordamericano; GITR: Registro Tedesco; SITR: Registro Spagnolo; PROFIT: Registro Italiano; *negli emofilici A gravi. **Nelle caselle sono riportate le p univariate (sopra) e/o multivariate**

Late/adult ITI

ORIGINAL ARTICLE *Inhibitors*

Late immune tolerance induction in haemophilia A patients

S. L. MEEKS,* R. L. CHAPMAN,* C. KEMPTON*† and A. L. DUNN*

Haemophilia (2013), 19, 445–448

N=9, median age 18 yrs
Success 4 (44%)
+ 3 partial (25%)

Adult haemophilia A patients with inhibitors: successful immune tolerance induction with a single FVIII/VWF product

S. RANGARAJAN,*† V. JIMÉNEZ-YUSTE‡ and E. SANTAGOSTINO§

Haemophilia (2014), 20, e399–e443

N=20, >18 yrs
Success 13 (65%)
+ 5 partial (25%)

the Italian ITI Registry

AGE AT ITI START (yr.)	≤ 8	8-14	14-25	>25
n	82	14	16	25
SUCCESS, n (%)	43 (52)	7 (50)	7 (44)	13 (52)

<10 BU at ITI start (% of success)	35/43 (81)	6/7 (86)	6/7 (82)	11/13 (85)

No significant impact of age at ITI start on success
The large majority of successful ITI started with low inh titers

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When to start ITI ?

- Immune toleration induction should be started as soon as possible after the inhibitor has been confirmed and when the titre is <10 BU/ml (Grade 1B).
- If the inhibitor titre is >10 BU/ml at diagnosis, the start of ITI should be deferred until it has fallen below 10 BU/ml (Grade 1B). If this has not happened after 1 year, consideration should be given to commencing ITI (Grade 2C).

When should ITI be started?.

1. ITI should be started as soon as possible (see points 2 and 3 below) when a high-titre inhibitor ≥5 to ≤10 BU mL^{-1} is detected and confirmed on ≥1 repeat measurement (1C) [12–15].
2. In patients with a peak inhibitor titre >10 BU mL^{-1}, we recommend postponing ITI until the titre drops to ≤10 BU mL^{-1} (1C) [12–15].
3. In patients with a peak inhibitor titre >10 BU mL^{-1} who experience serious or life-threatening bleeding or have frequent mild to moderate bleeding and are being considered for bypassing agent prophylaxis, an earlier start to ITI is favoured to avoid the morbidity associated with ongoing bleeding (1C) [12,13,46].

ORIGINAL ARTICLE *Clinical haemophilia*

Prompt immune tolerance induction at inhibitor diagnosis regardless of titre may increase overall success in haemophilia A complicated by inhibitors: experience of two US centres

C. NAKAR,* M. J. MANCO-JOHNSON,† A. LAIL,‡ S. DONFIELD,‡ J. MAAHS,* Y. CHONG,* T. BLADES† and A. SHAPIRO*

**The Indiana Hemophilia and Thrombosis Center (IHTC), Indianapolis, IN; †The University of Colorado Hemophilia & Thrombosis Center (UCHTC), Aurora, CO; and ‡Rho, Inc., Chapel Hill, NC, USA*

Table 2. ITI outcome

		All		HRI		
				Time interval from detection to ITI start		
Group	All	LRI*	HRI†	≤1 m	>1–6 m	>6 m
N (%)	58 (100)	19 (33)	39 (67)	23 (59)	5 (13)	11 (28)
Success, *N* (%)	51 (88)	19 (100)	32¶ (82)	22§ (96)	3§ (60)	7§ (64)
Failure, *N* (%)	7 (12)		7 (18)	1 (4)	2 (40)	4 (36)

	HRI ≤1 m	
Group	Pre-ITI <10 BU	Pre-ITI ≥10 BU
N (%)	10 (43)	13 (57)
Success, *N* (%)	9 (90)	13§ (100)
Failure, *N* (%)	1 (10)	

the Italian ITI Registry

TIME INTERVAL INH DIAGN. – ITI (mo.)	≤ 1	1-6	6-12	12-24	>24
n	12	16	22	40	48
SUCCESS, n (%)	4 (33)	12 (75)	11 (50)	14 (35)	29 (61)

<10 BU at ITI start (% of success)	3/4 (75)	9/12 (75)	9/11 (82)	13/14 (93)	26/29 (89)

No significant impact of time between inh diagnosis and ITI start on success

Trend to greater effect of inh titer at ITI start in delayed ITI

International ITI Study - Hay & DiMichele (2002-2009)

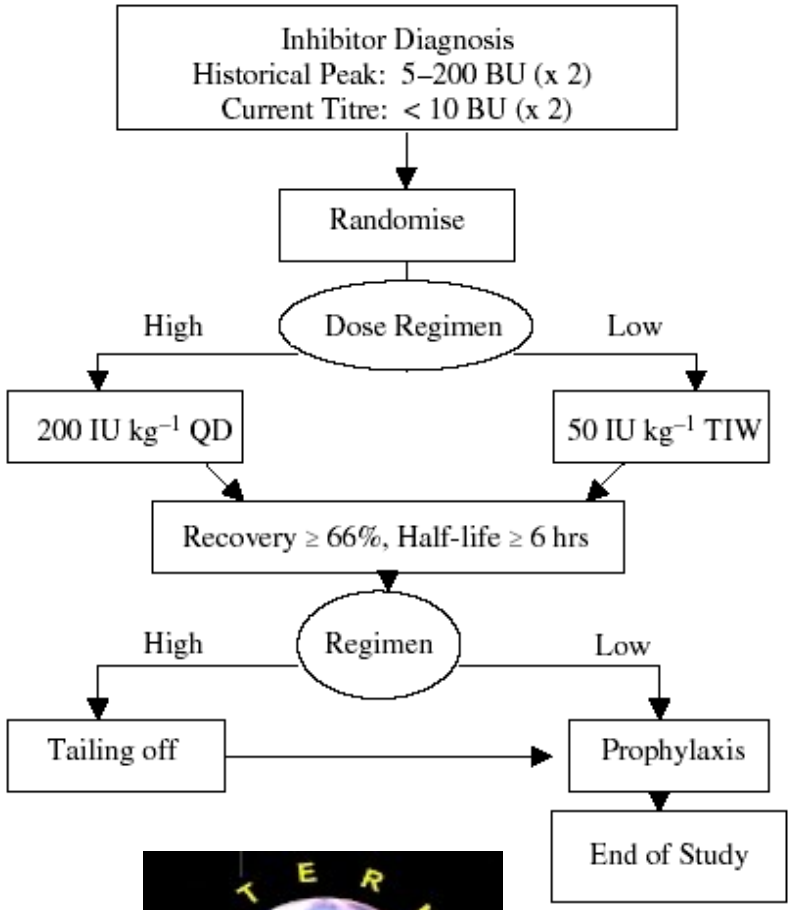
Inclusion Criteria

- ✓ Severe, HR inhibitors
- ✓ age ≤ 8 yrs at ITI start
- ✓ Inhibitor diagnosis ≤ 24 mo. prior to ITI start
- ✓ Inh titer <10 BU at ITI start
- ✓ Historical inh peak ≤ 200 BU

<5 yrs since diagn.

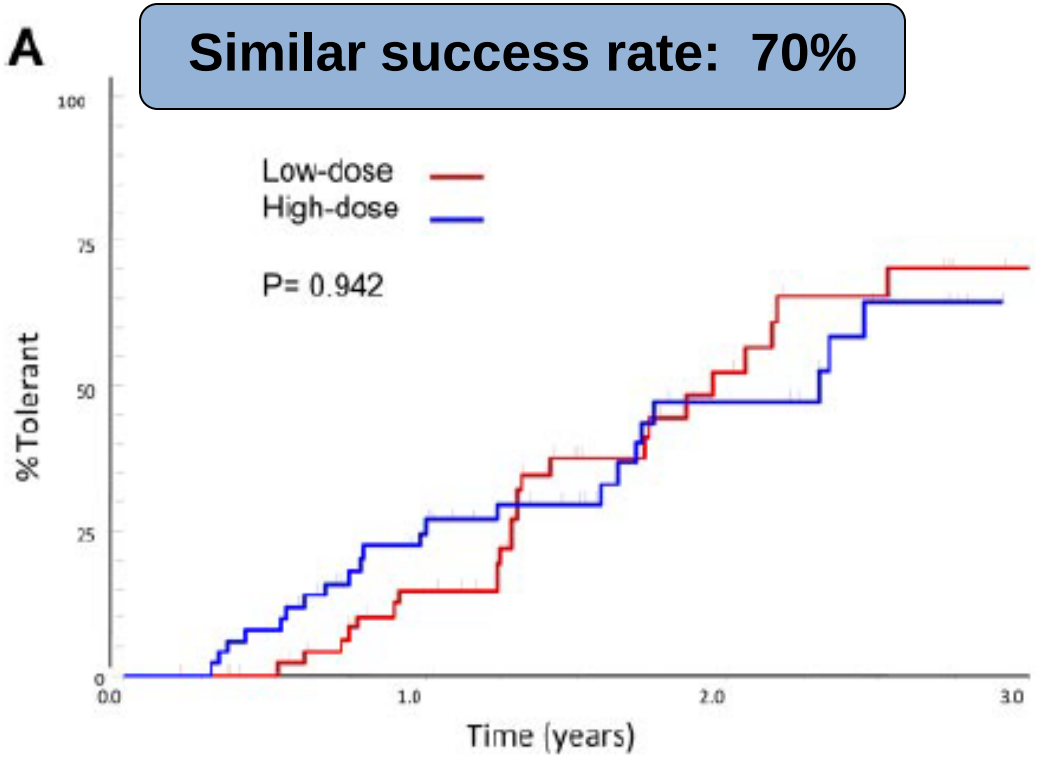
- ✓ First ITI course
- ✓ Stable venous access
- ✓ Informed consent

Good-risk patients, *level IIb*



ITI outcome and predictors of success

Similar success rate: 70%



With the **high-dose regimen**
shorter median time to achieve:
Negative titer (4.6 vs 9.2 mo, p=0.027)
Normal recovery (6.9 vs 13.6 mo, p=0.002)
but not
Tolerance (10.6 vs. 15.5 mo, p=0.116, **ns**)

Predictors of success

Univariate analysis	
Subject variable	***P***
Ethnicity (white/nonwhite)	.71
Age at randomization (ITI)	.83
Peak historical inhibitor titer	.026
Peak titer on ITI	.002
Peak titer on ITI ≤ 250 versus > 250 BU	.0002
Time to titer of < 10 BU pre-ITI	.40
Starting inhibitor titer	.98
Treatment variable	
Randomized treatment arm	.82
Protocol dose compliance	.35
Product type	.58
Total hospital in-patient days	.088
CVAD in place	.58
CVAD infection	.83
Multivariate analysis	
Peak inhibitor titer on ITI	.002

Hay & Di Michele, Blood, 2012

Bleeding episodes during ITI

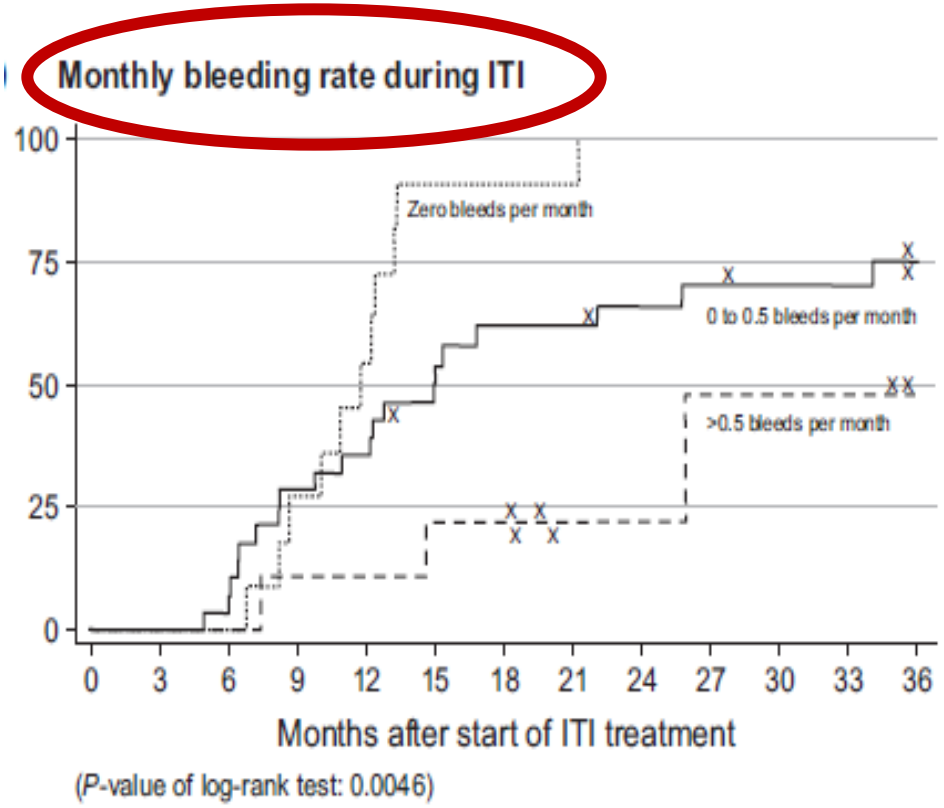
N of bleeds	Low-dose	High-dose	HR (95% CI) , p
All ITI	684 (n=58)	282 (n=57)	**2.2** (1.34-3.62) 0.0019
To neg BU	573 (n=58)	241(n=57)	**2.27** (1.29-4.01) 0.0046
To N IVR	47 (n=27)	4 (n=23)	3.4 (0.84-13.8) 0.088
To N T1/2	9 (n=24)	3 (n=22)	5.18 (0.71-38.0) 0.110
prophylaxis	54 (n=24)	32 (n=22)	1.70 (0.80-3.63) 0.170

Mean bleed rate (bleeds/mo)	Low-dose	High-dose	p
To neg BU	0.623	0.282	**0.00024**
To N IVR	0.127	0.087	0.283
To N T1/2	0.150	0.033	0.552
prophylaxis	0.175	0.102	0.112

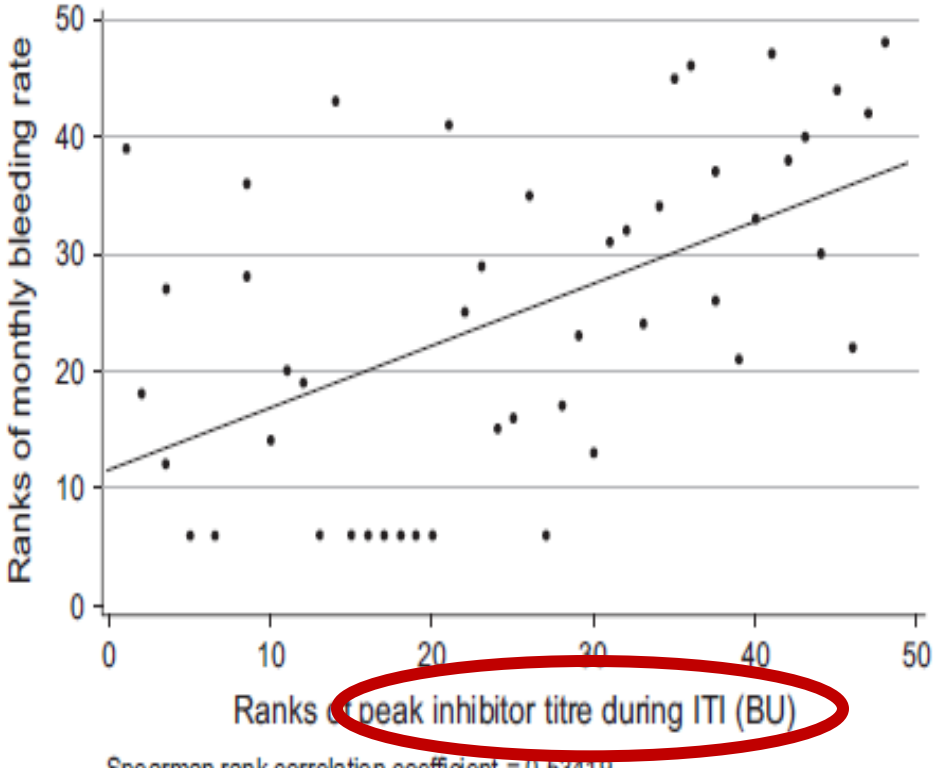
Hay & Di Michele, Blood, 2012

First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/ von Willebrand factor concentrate in an observational immune tolerance induction study

W. KREUZ,* C. ESCURIOLA ETTINGSHAUSEN,* V. VDOVIN,† N. ZOZULYA,‡ O. PLYUSHCH,‡ P. SVIRIN,† T. ANDREEVA,§ E. BUBANSKÁ,¶ M. CAMPOS,** M. BENEDIK-DOLNIČAR,†† V. JIMÉNEZ-YUSTE,‡‡ L. KITANOVSKI,†† A. KLUKOWSKA,§§ A. MOMOT,¶¶ N. OSMULSKAYA,*** M. PRIETO,††† S. Z. ŠALEK,‡‡‡ F. VELASCO,§§§ A. PAVLOVA,¶¶¶ J. OLDENBURG,¶¶¶ S. KNAUB,**** M. JANSEN,†††† L. BELYANSKAYA**** and O. WALTER**** ON BEHALF OF THE OBSITI STUDY GROUP AND THE OBSITI COMMITTEE



n=40

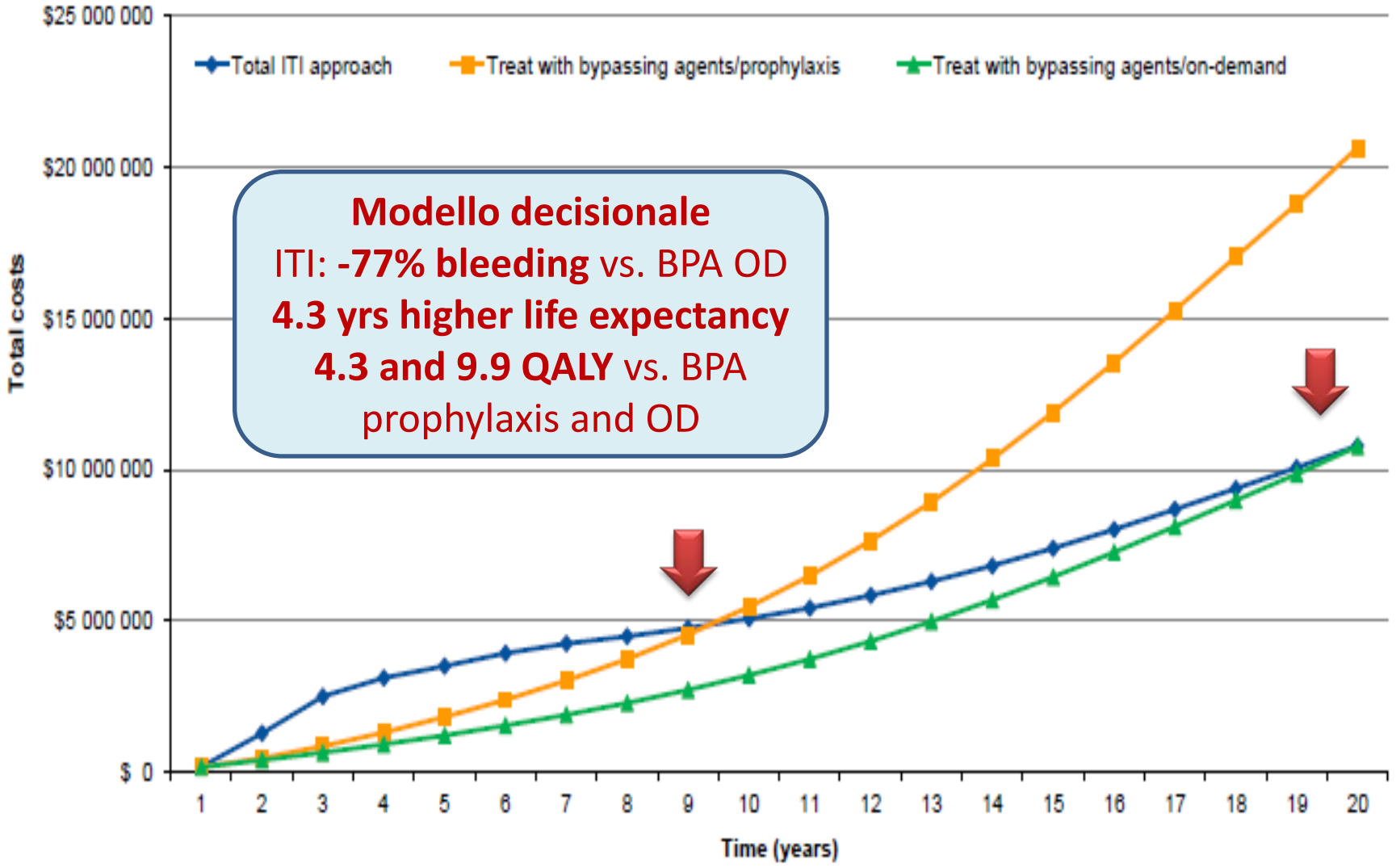


Haemophilia (2015)

Which FVIII dose ?

- **Good prognosis patients:**
  - High-dose regimen should be preferred for safety concern (I-ITI Study)
  - Comparable success with lower dose **(100 IU/Kg/d)** regimens (metanalysis IITR/NAITR, cohort studies), but relative effects on bleeding poorly known; possible adoption in patients who bleed unfrequently and increase of dose if severe/frequent bleeds occur
- **Poor prognosis patients**: Cohort studies and registries suggest better outcomes with high-dose regimens

Cost-utility of inhibitor treatment



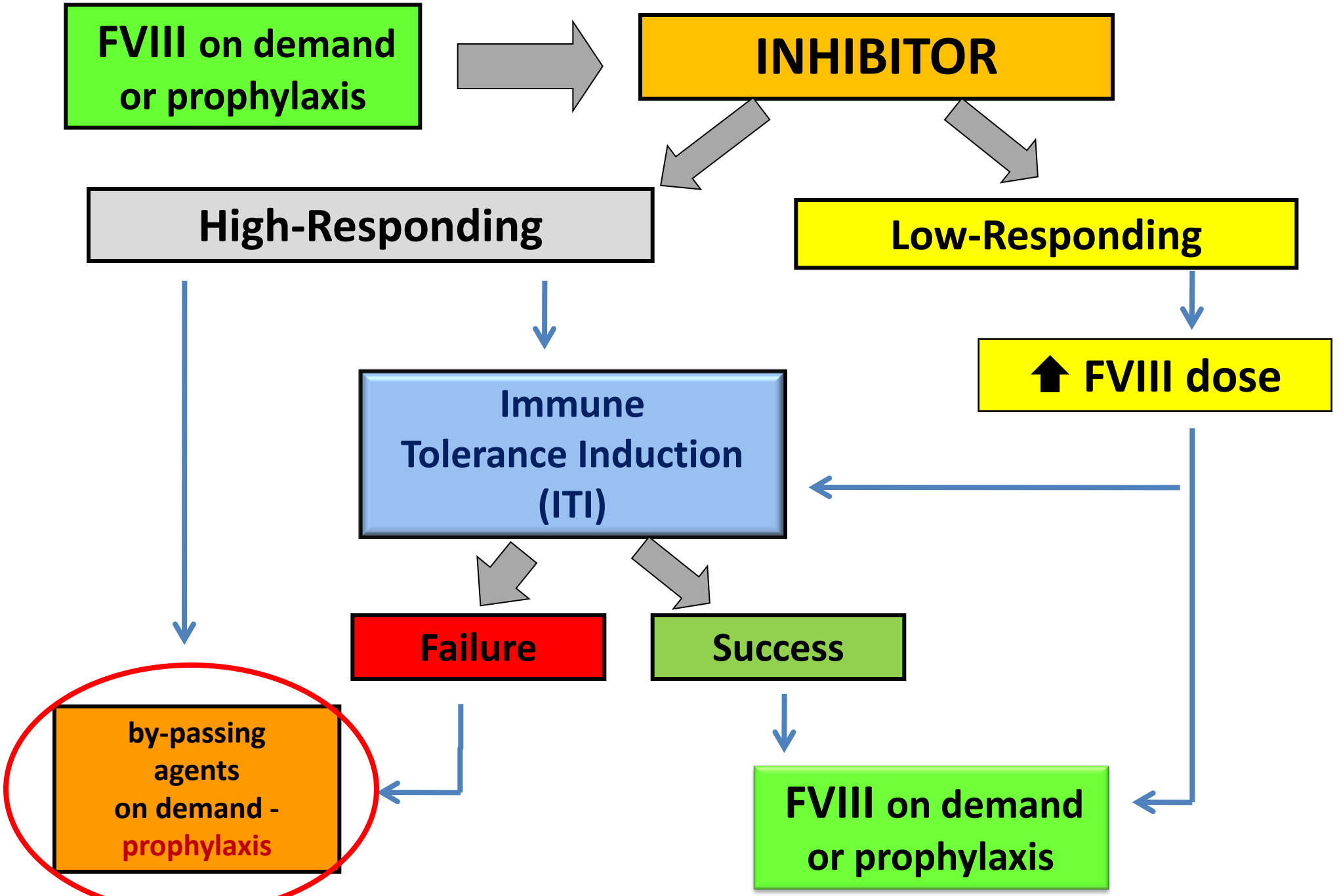
Modello decisionale
ITI: **-77% bleeding** vs. BPA OD
4.3 yrs higher life expectancy
4.3 and 9.9 QALY vs. BPA prophylaxis and OD

Earnshaw et al, Haemophilia 2015

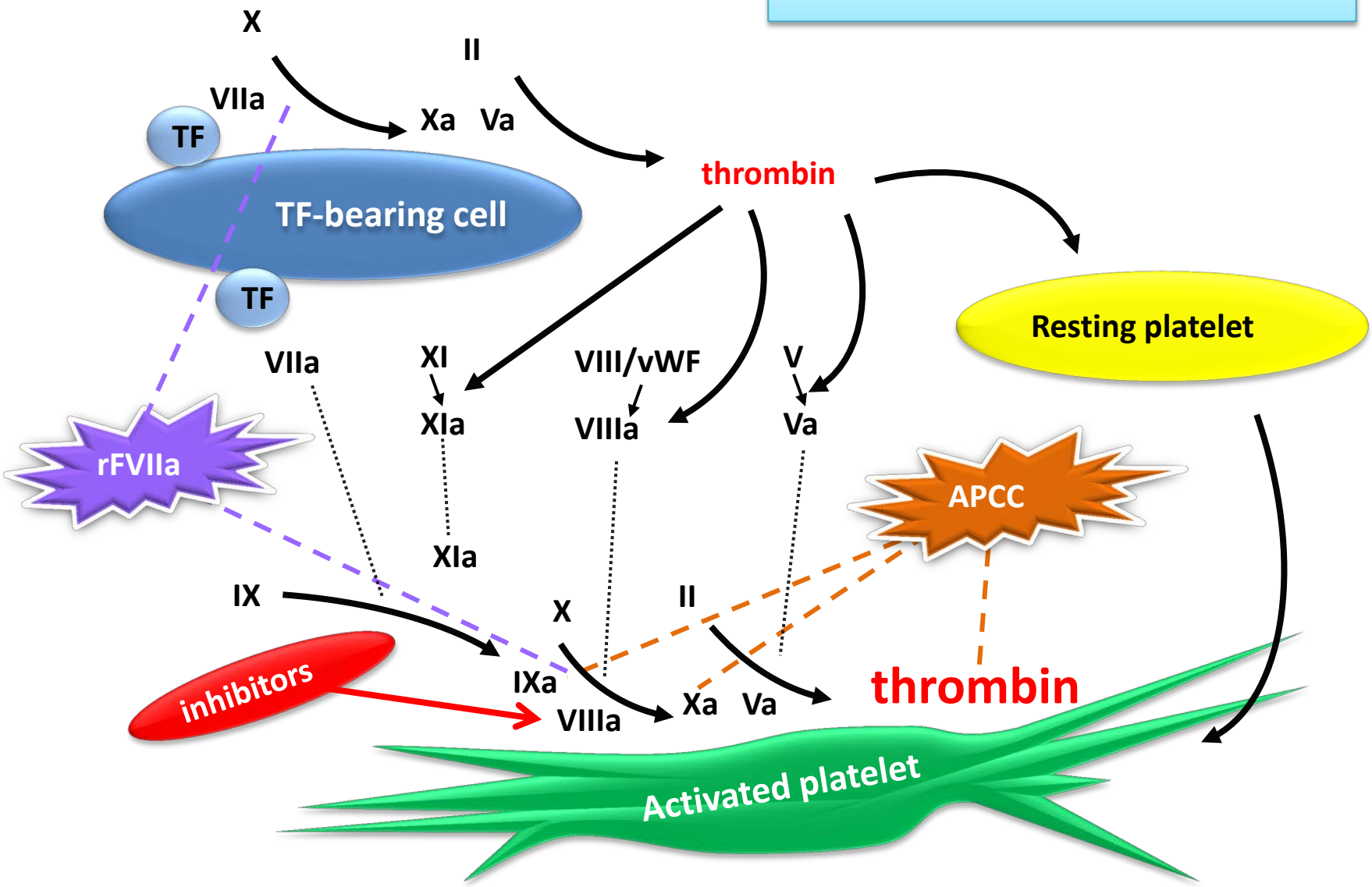
La sfida terapeutica nella gestione del paziente con inibitori

- Priorità: eradicare l'inibitore
  - ITI

- In attesa di eradicare l'inibitore o se insuccesso dell'ITI: limitare i danni e migliorare la QoL
  - Ottimizzare il trattamento e la prevenzione delle emorragie


FVIII on demand or prophylaxis
INHIBITOR
High-Responding
Low-Responding
FVIII dose
Immune Tolerance Induction (ITI)
Failure
Success
by-passing agents on demand - prophylaxis
FVIII on demand or prophylaxis

BYPASSING AGENTS



Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors (Review)

Iorio A, Matino D, D'Amico R, Makris M

antibody (immunotolerance induction) and for acute bleeding episodes. Treatment for bleeding episodes is with one of two available bypassing agents, recombinant activated factor VIIa (Novoseven) or human activated prothrombin complex concentrate (FEIBA). It is not known if one of these products is better than the other. We searched for trials comparing the effectiveness (time until bleeding stops, effect on joint motion, need for re-treatment) and safety of Novoseven and FEIBA in people with haemophilia with inhibitors during episodes of acute bleeding. We found two clinical trials comparing Novoseven and FEIBA. The trials did not show a difference in the effectiveness of the two products and both were equally safe in terms of tolerability and the absence of clotting complications. We conclude that both recombinant factor VIIa and plasma derived concentrates can be used to treat bleeds in individuals with haemophilia and inhibitors.

Cochrane Database Syst Rev. 2010 Aug 4;(8):CD004449

THE COCHRANE COLLABORATION®

FENOC Study

aPCC 75-100 IU/kg (target 85 IU/kg), single IV bolus *vs.*
rFVIIa 90-120 μg/kg (target 105 μg/kg) IV bolus repeated after 2 hours

48 patients, age > 2 yrs, treated within 4 hrs from onset of symptoms
2 episodes differently treated in each patient

Effective or partially effective

	2 h	6 h	12 h	24 h	36 h	48 h
FEIBA	75.0%	80.9%	80.0%	95.3%	100%	97.6%
rFVIIa	60.4%	78.7%	84.4%	85.7%	90.2%	85.4%
Discordant Episodes	43.8%	31.9%	31.9%	19.1%	9.8%	17.1%

Statistical requirements for equivalence not satisfied

Higher than expected discordant outcomes with the different treatment

Astermark et al, Blood 2007

Bypassing agents

APCC

Licensed dosage:
50-100 U/Kg every 6-12 h
(Max. 200 U/Kg/day)

- Home treatment (large volume, 30-45 min to administer)
- Risk of anamnestic response
- Plasma origin
- Long dosing interval
- Thrombotic risk
- Optimal monitoring?
- Can be associated with tranexamic acid

rFVIIa

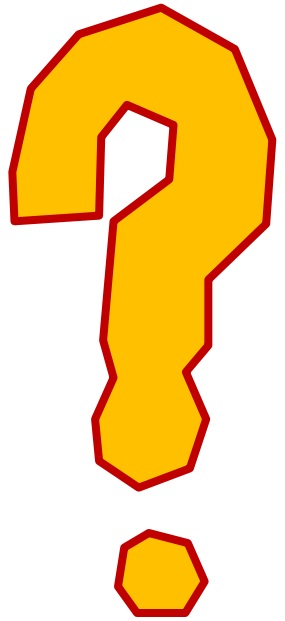
Licensed dosages:
90-120 µg/Kg every 2-3 h
270 µg/Kg single dose

- Home treatment
- No anamnestic response
- Recombinant product
- Short dosing interval
- Thrombotic risk
- Optimal monitoring?
- Association with tranexamic acid ?

INDIVIDUAL RESPONSE TO TREATMENT

Open issues in the management of bleeding in inhibitor patients…

- 10-20% of bleeds not satisfactorily treated
- 20-40% discordant clinical responses



- Optimization of first-line treatment
  - Early
  - Intensive
  - Patient general education

- **Prophylactic regimens…**
  - Reduce bleeding frequency and severity
  - Reduce / delay joint damage ???

Prophylaxis with bypassing agents
Prospective randomized studies

	rFVIIa Konkle et al, 2007 n=22	APCC PRO-FEIBA, 2011 n=26	APCC PROOF, 2013 n=36
Design	**Double-blind**, parallel group trial	Open-label, cross-over trial (**intra-individual** comparison	Open-label, 2-arm, parallel trial (**inter-individual** compar.)
Treatment	90 µg/Kg /d vs. 270 µg/Kg/d	85 ± 15 IU/Kg x3/wk vs. on demand	85 ± 15 IU/Kg e.o.d. (n=17) vs. on demand (n=19)
Follow-up	3 mo (vs. 3 mo pre and post-prophyl.)	6 mo each treatment (3 mo wash-out)	12 mo
Age, yrs (range)	**15.7 (5.1-56.5)**	**28.7 (2.8-62.8)**	**23.5 (7-56)**
Bleeding criteria for enrolment	≥ 12/3 mo	≥ 6 / 6 mo	≥ 12 /12 mo

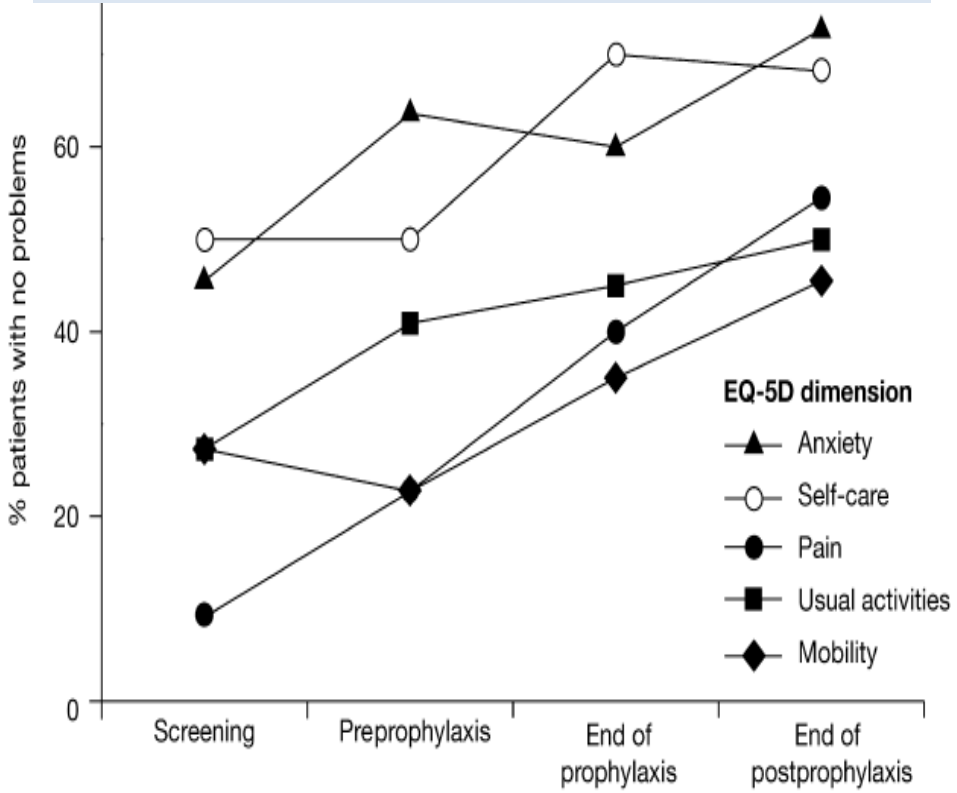
Results from randomized studies

	rFVIIa Konkle et al, 2007 n=22	APCC PRO-FEIBA, 2011 n=26	APCC PROOF, 2013 n=36
Bleeding rate on demand (/mo)	5.6 / 5.3	13.1	28.7
Bleeding rate on prophylaxis (/mo)	3 / 2.2	5.0	7.9
Reduction on prophyl %	**45% 59%**	**62%**	**72.5%**
↓ bleeding rate in target joints	**43% 61%**	**72%**	**75%**
Other results	**Benefit lasting during 3 mo post-prophyl**	62% of patients with ↓ of bleeding rate >50% (overall 84%); in 23% 0 bleeds	↓ New target joints **26% additional reduction** last 6 mo vs first 6 mo

LACK OF DATA ABOUT LONG-TERM OUTCOMES!!!

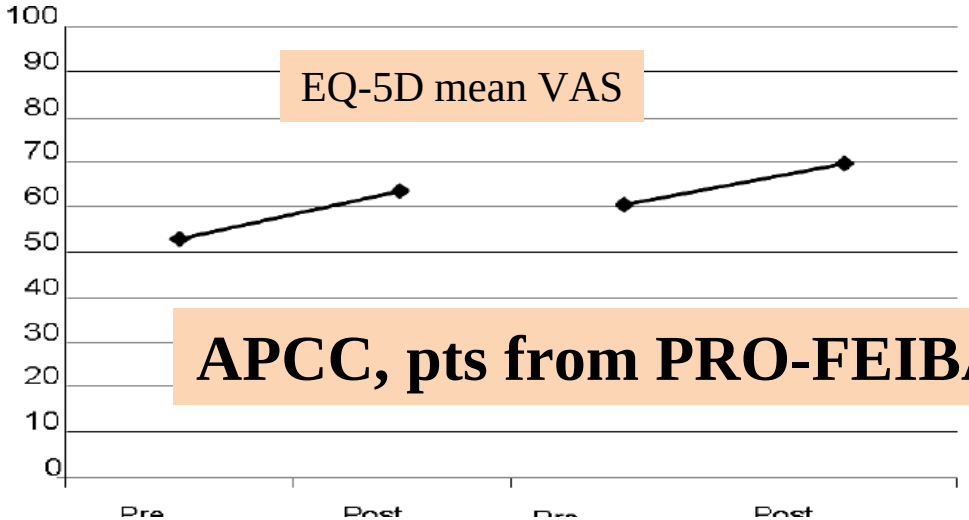
Improvement of HRQoL

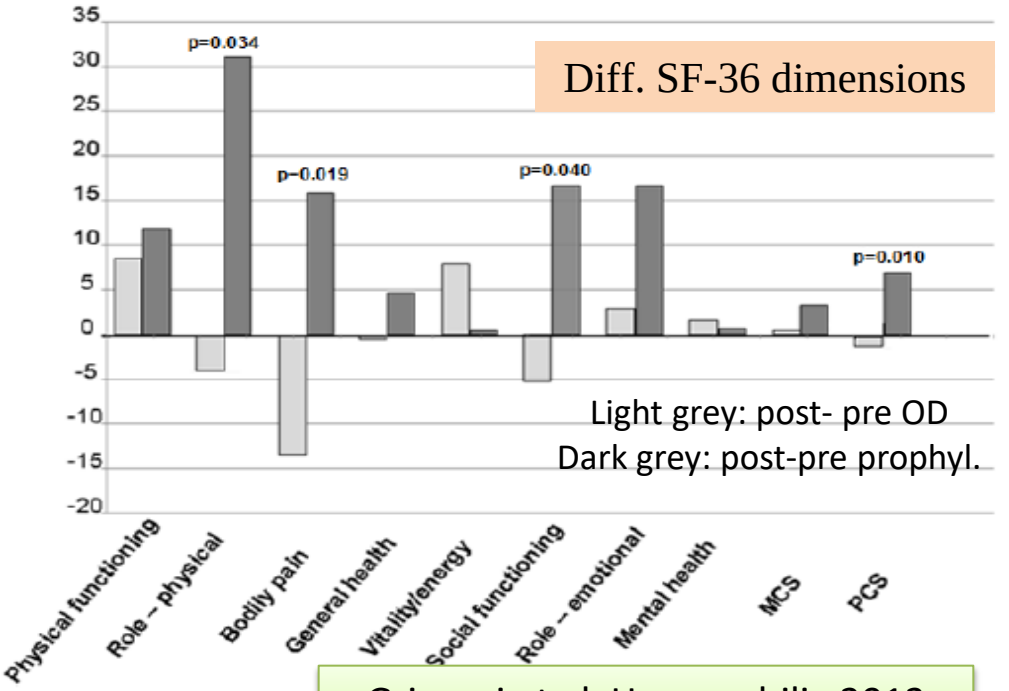
rFVIIa, pts from Konkle Study



Hoots et al, Haemophilia 2008

APCC, pts from PRO-FEIBA





Gringeri et al, Haemophilia 2013

La sfida terapeutica nella gestione del paziente con inibitori

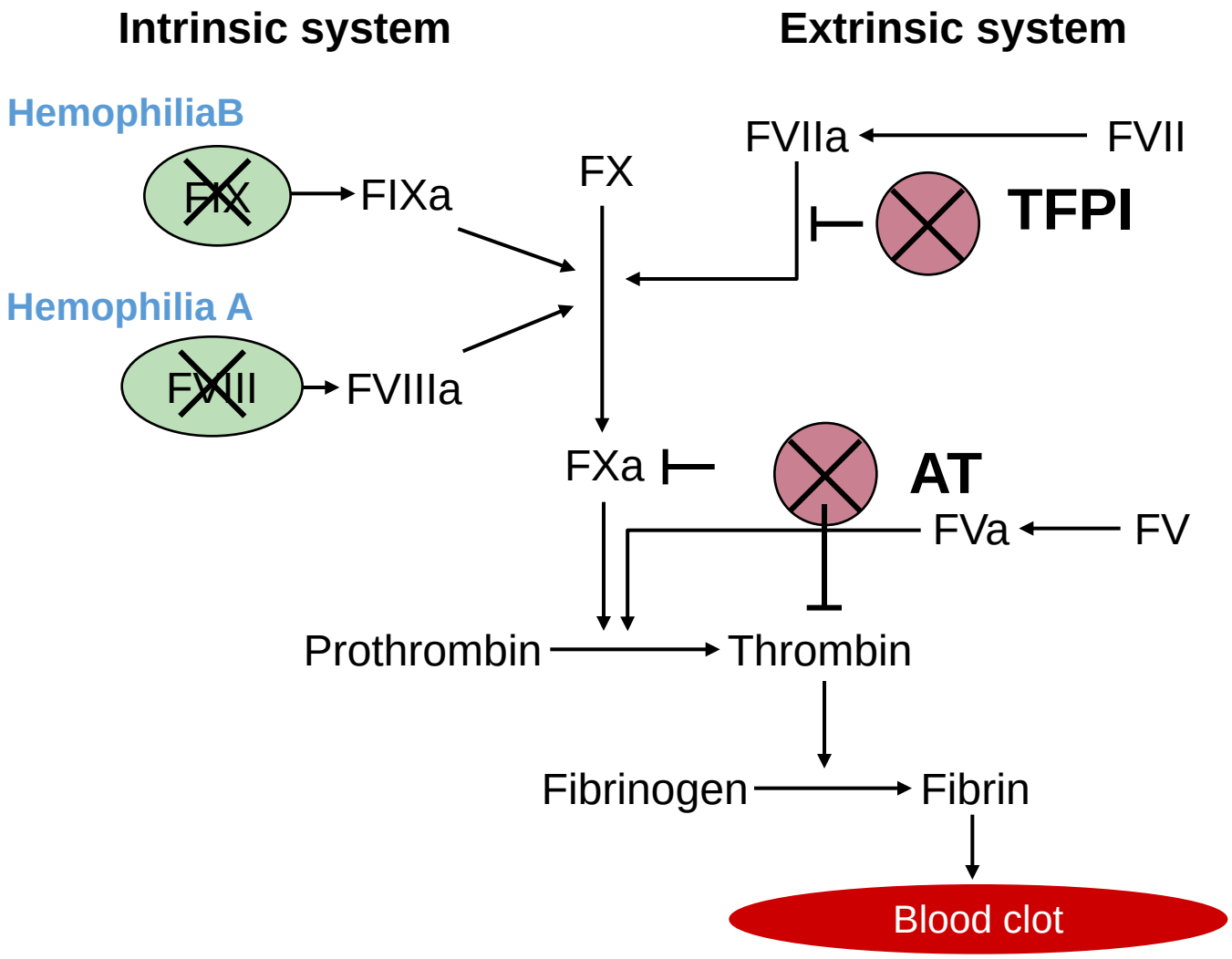
- Priorità: eradicare l'inibitore
  - ITI
- In attesa di eradicare l'inibitore o se insuccesso dell'ITI: limitare i danni e migliorare la QoL
  - Ottimizzare il trattamento e la prevenzione delle emorragie
- **Nuove strategie ?**

Innovative Pharmacological Therapies for the Hemophilias Not Based on Deficient Factor Replacement

Pier Mannuccio Mannucci, MD[1] Maria Elisa Mancuso, MD, PhD[1] Elena Santagostino, MD, PhD[1]
Massimo Franchini, MD[2]

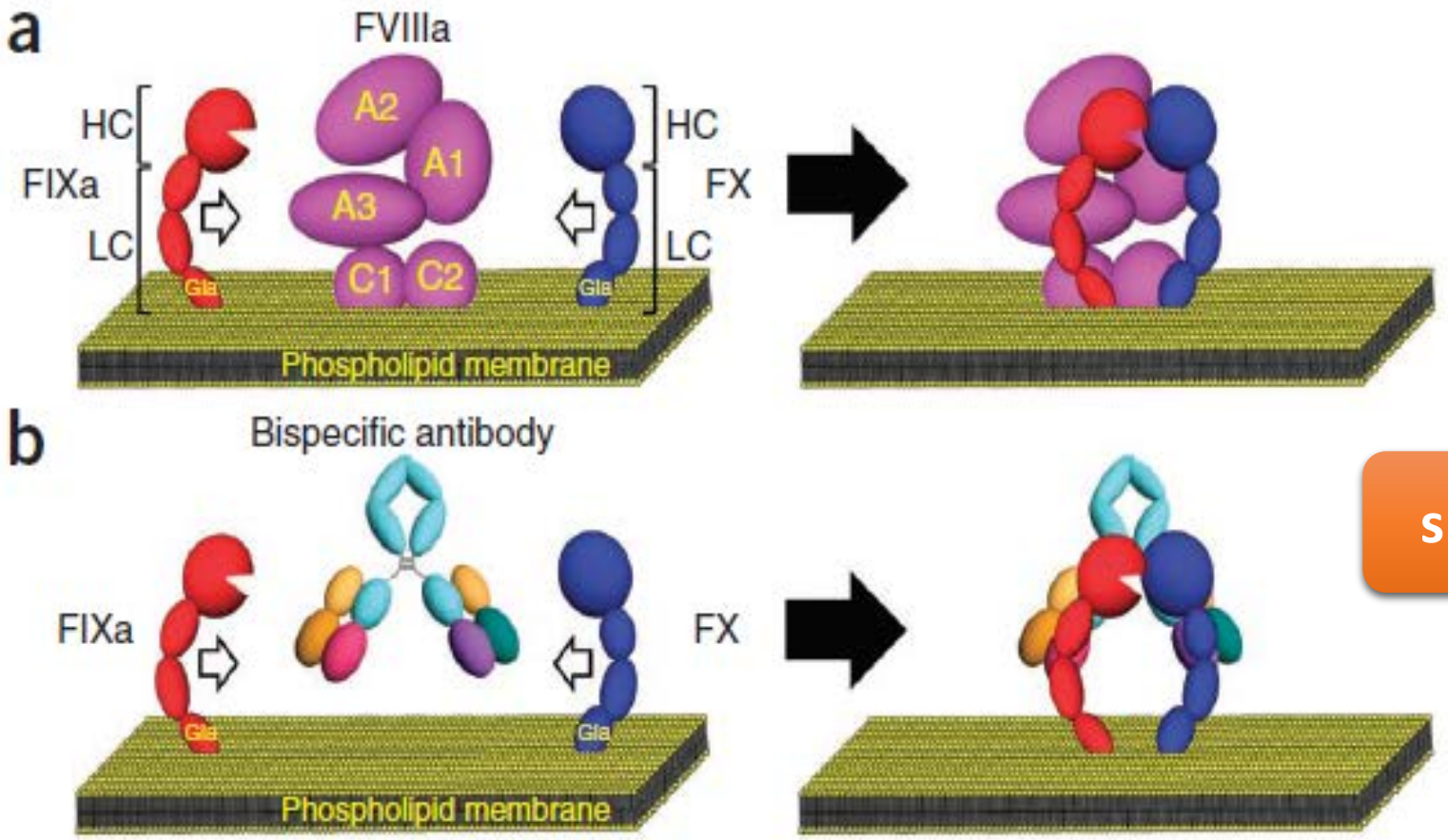
Semin Thromb Hemost 2016, in press

Non-replacement strategies



Sehgal A et al, *Nature Med.* 2015; 21: 492-7

The bispecific FVIII-mimetic antibody

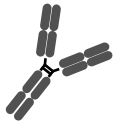


s.c. injection

Long half-life

hBS23, Kitazawa et al, Nat Med 2012
Improved variant, **ACE910**, Muto et al, J Thromb Haemost 2014

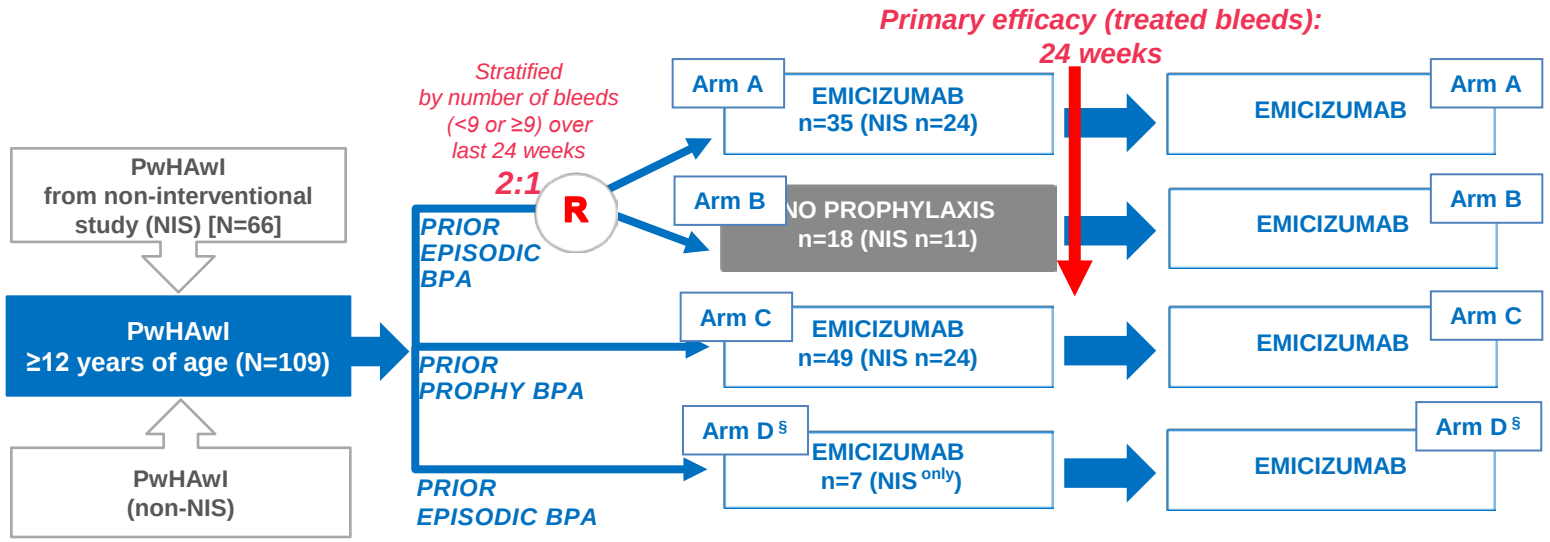
New targets to restore clotting

	Tissue factor pathway inhibitor	Antithrombin	FIXa–FX interaction
	Concizumab	**Fitusiran**	**Emicizumab**
			
Company	**NovoNordisk**	**Alnylam Pharmaceuticals/ Sanofi Genzyme**	**Chugai Pharmaceuticals/ La Roche Hoffman**
Stage of development	**Phase II/III**	**Phase III**	**FDA, EMA Approved**
Main characteristic	**SC administration**	**SC administration**	**SC administration**

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

N Engl J Med 2017;377:809-18.



Primary Endpoint:

Emicizumab prophylaxis (Arm A) vs no prophylaxis (Arm B) → Reduction in treated bleed rate at 24 weeks

Secondary Endpoints:

Emicizumab prophylaxis (Arm A) vs no prophylaxis (Arm B) → **(1)** Reduction in bleed rates all bleeds (both treated and not treated with BPAs), treated spontaneous, joint, and target joint bleeds at 24 weeks **(2)** Haem-A-QoL (adults) at 25 weeks **(3)** EQ-5D-5L score at 25 weeks

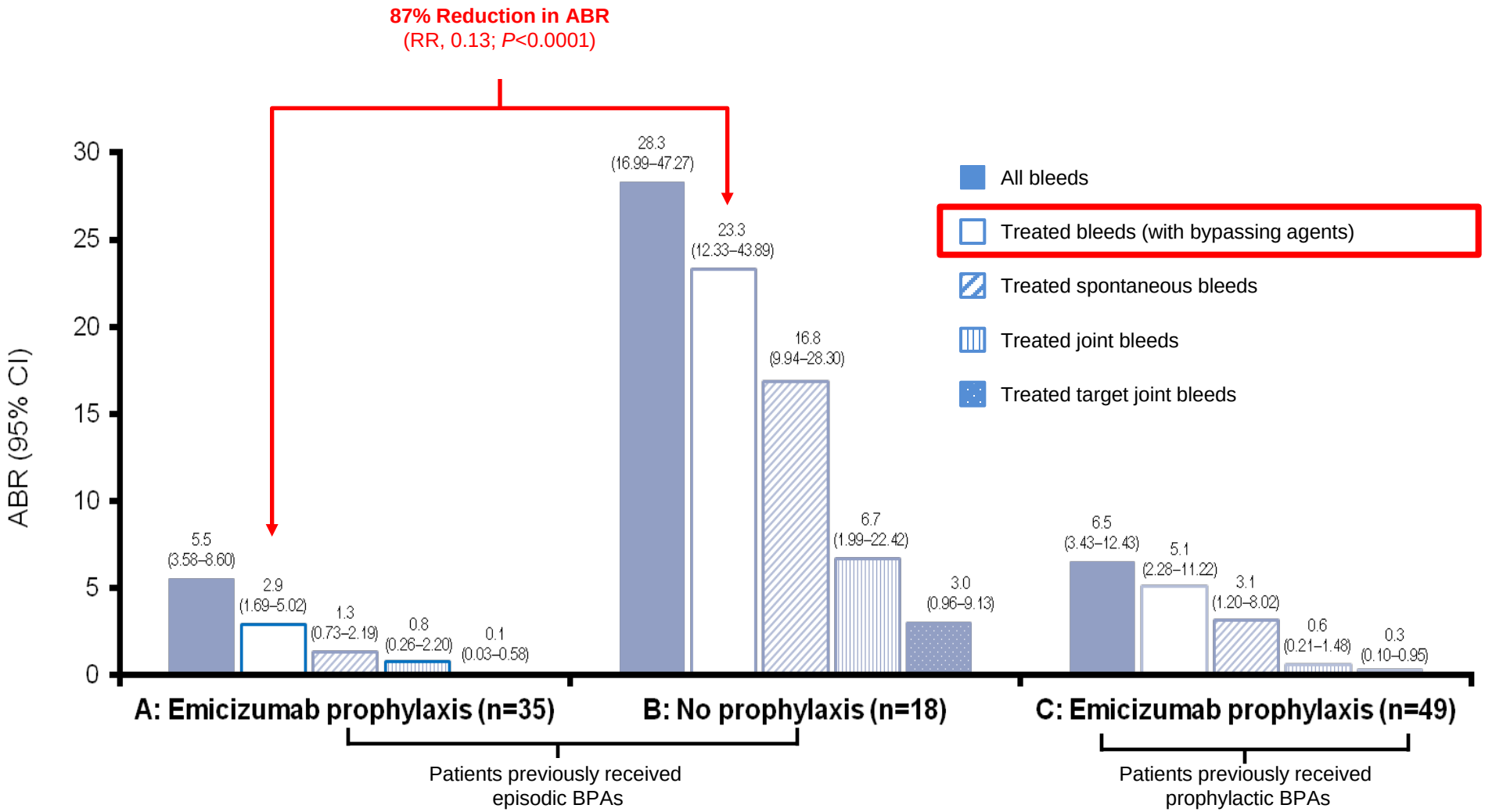
Emicizumab prophylaxis (Arms A, C) → Reduction in treated bleed rates compared with patient's historical bleed rate (last 24 weeks prior to study entry)

HAVEN 1: phase III https://clinicaltrials.gov/ct2/show/NCT02622321

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

N Engl J Med 2017;377:809-18.

Annualized Bleeding Rate* for Study Arms A, B, and C



*Calculated using negative binomial regression model.

Thromboembolic SAE in HAVEN 1

Event	Received BPA prior to event?	Anti-coagulation	Resolution	Additional treatment	Restarted emicizumab
Thrombosis #1*	aPCC	**No**	**Resolved**	Supportive care only	**Yes**
Thrombosis #2**	aPCC	**No**	Resolving	Supportive care only	No
TMA #1	aPCC/rFVIIa	N/A	**Resolved**	Plasmapheresis	No
TMA #2	aPCC	N/A	**Resolved**	Supportive care only	**Yes**
TMA #3	aPCC/rFVIIa	N/A	Resolving***	Plasmapheresis	No

* Cavernous sinus thrombosis

** Skin necrosis-superficial thrombophelebitis

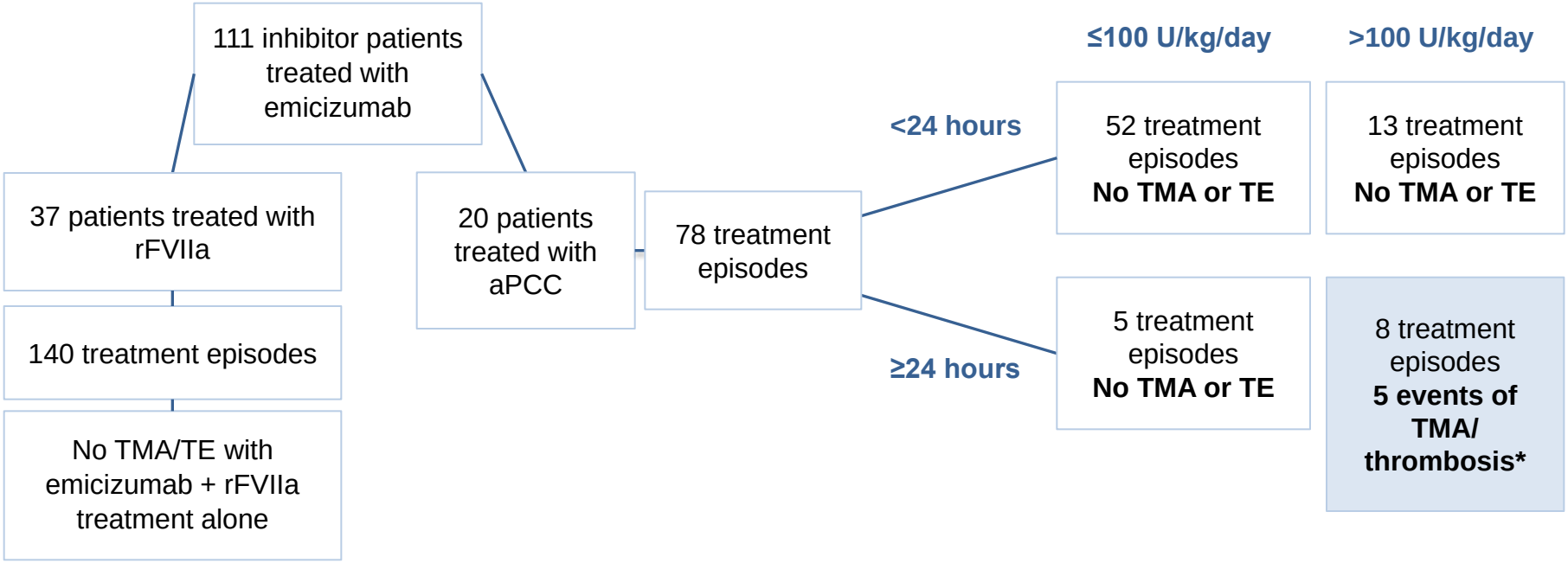
***Patient treated for rectal hemorrhage, which was eventually fatal; death was deemed unrelated to emicizumab

■ Serious thrombotic and TMA events were seen when aPCC was administered at repeated doses (>100 U/kg/day on average for ≥24 hours) to treat breakthrough bleeds during emicizumab prophylaxis.

■ No serious TE or TMA events occurred with emicizumab alone or when rFVIIa alone was used for breakthrough bleed treatment.

Oldenburg J et al. NEJM 2017

HAVEN 1: *Assessment of interaction between emicizumab and aPCC*



- Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal hemorrhage, considered unrelated to emicizumab, patient refused blood products and TMA was resolving at the time of aPCC cessation.

*Two patients also received rFVIIa prior to/during the event
Updated data cutoff – April 21, 2017, including 8 additional patients

Oldenburg J et al. ISTH 2017

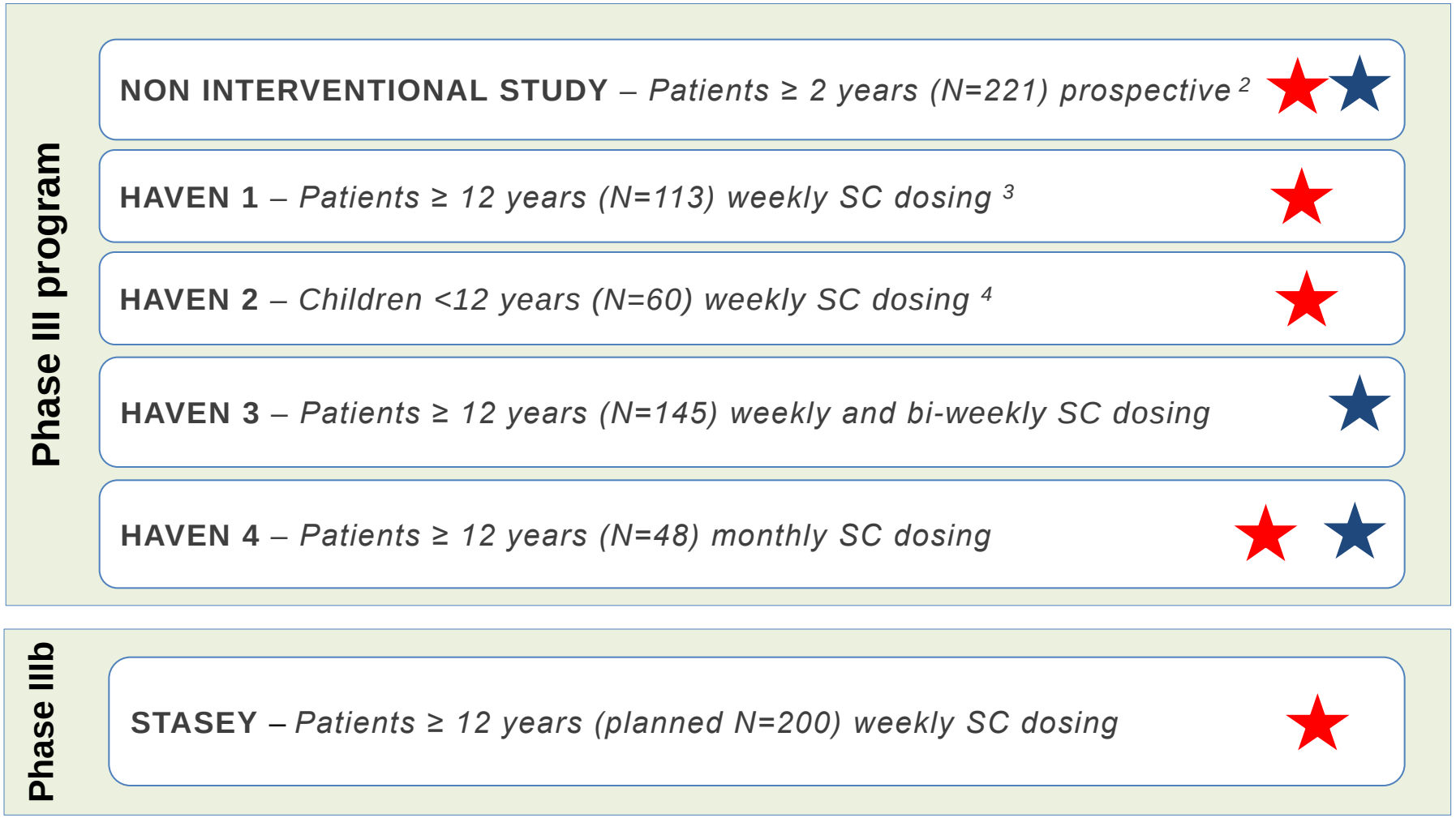
Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII?

Peter J. Lenting[1], Cécile V. Denis[1], and Olivier D. Christophe[1]

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

Blood First Edition Paper, prepublished online October 17, 2017

Emicizumab: Clinical Development Plan in PwHA[1]



[1]https://clinicaltrials.gov/ct2/results?cond=&term=emicizumab&cntry1=&state1=&recrs=;
[2]https://clinicaltrials.gov/ct2/show/study/NCT02476942?term=non+interventional&type=Obsr&cond=Hemophilia+A&fund=2&draw=1&rank=3;
[3]Oldenburg J et al NEJM 2017, [4]Young et al ISTH 2017

★ Inhibitor Patients
★ **Non - Inhibitor Patients**

EMA/67076/2018
EMEA/H/C/004406

Hemlibra (*emicizumab*)

An overview of Hemlibra and why it is authorised in the EU

Part VI: Summary of the risk management plan

Summary of risk management plan for Hemlibra (emicizumab)

Information on neutralising anti-drug antibody to Hemlibra

We recently learned that a patient in our phase III HAVEN 2 clinical trial developed a neutralising anti-drug antibody to Hemlibra. As with all therapeutic proteins, there is a potential for the development of anti-drug antibodies with Hemlibra, as indicated in the US and EU Hemlibra product labels. For this patient, the anti-drug antibody resulted in reduced efficacy of Hemlibra. The patient and his family have decided to discontinue treatment with Hemlibra, and he will resume treatment with his previous medicine.

24 April 2018

Perspectives and drawbacks

SC prophylaxis in inhibitor patients

SC prophylaxis in patients without inhibitors

- HA: all these agents (inhibitor prevention?)
- HB: anti-TFPI & fitusiran

Potential drawbacks

- Thrombotic risk
- Need for multiple agents available at home
- Training for IV and SC administration
- Laboratory monitoring
- Neutralizing antibodies
- Costs

Limited experience with newly approved therapeutic options

Expanded access protocols – fast-tracked approval

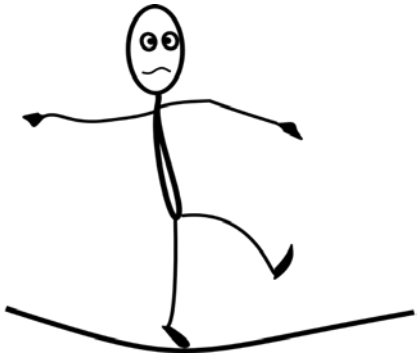
To facilitate access to promising therapies in rare diseases

Safety and efficacy data from limited number of subjects with limited follow-up period

Enrolment of selected patients in clinical trials

Patients who are least likely to be disadvantaged by participation; most likely to provide good data

Implications for patients with characteristics and comorbidities not seen in clinical trials



Sfide aperte … al momento

… interessantissime prospettive

Grazie