

# *Eradicare l'inibitore*

---

**Angiola Rocino**

---

UOC DI EMATOLOGIA-CENTRO EMOFILIA E TROMBOSI  
OSPEDALE S.M.DI LORETO NUOVO ASL NA1  
NAPOLI

# *Haemophilia patients with inhibitors: Bypassing agents treatment*

## **APCC**

### Licensed dosage:

50-100 U/Kg every 6-12 h

**Home treatment**

**Risk of anamnestic response**

**Plasma origin**

**Long dosing interval**

**Thrombotic risk**

**Optimal monitoring?**

APCC licensed for  
prophylactic use

## **rFVIIa**

### Licensed dosages:

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

**Home treatment**

**No anamnestic response**

**Recombinant**

**Short dosing interval**

**Thrombotic risk**

**Optimal monitoring?**

**Both less effective than FVIII prophylaxis in non inhibitor patients**

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

Semin Thromb Hemost 2016; 42:526-32

Pier Mannuccio Mannucci, MD<sup>1</sup> Maria Elisa Mancuso, MD, PhD<sup>1</sup> Elena Santagostino, MD, PhD<sup>1</sup>  
Massimo Franchini, MD<sup>2</sup>

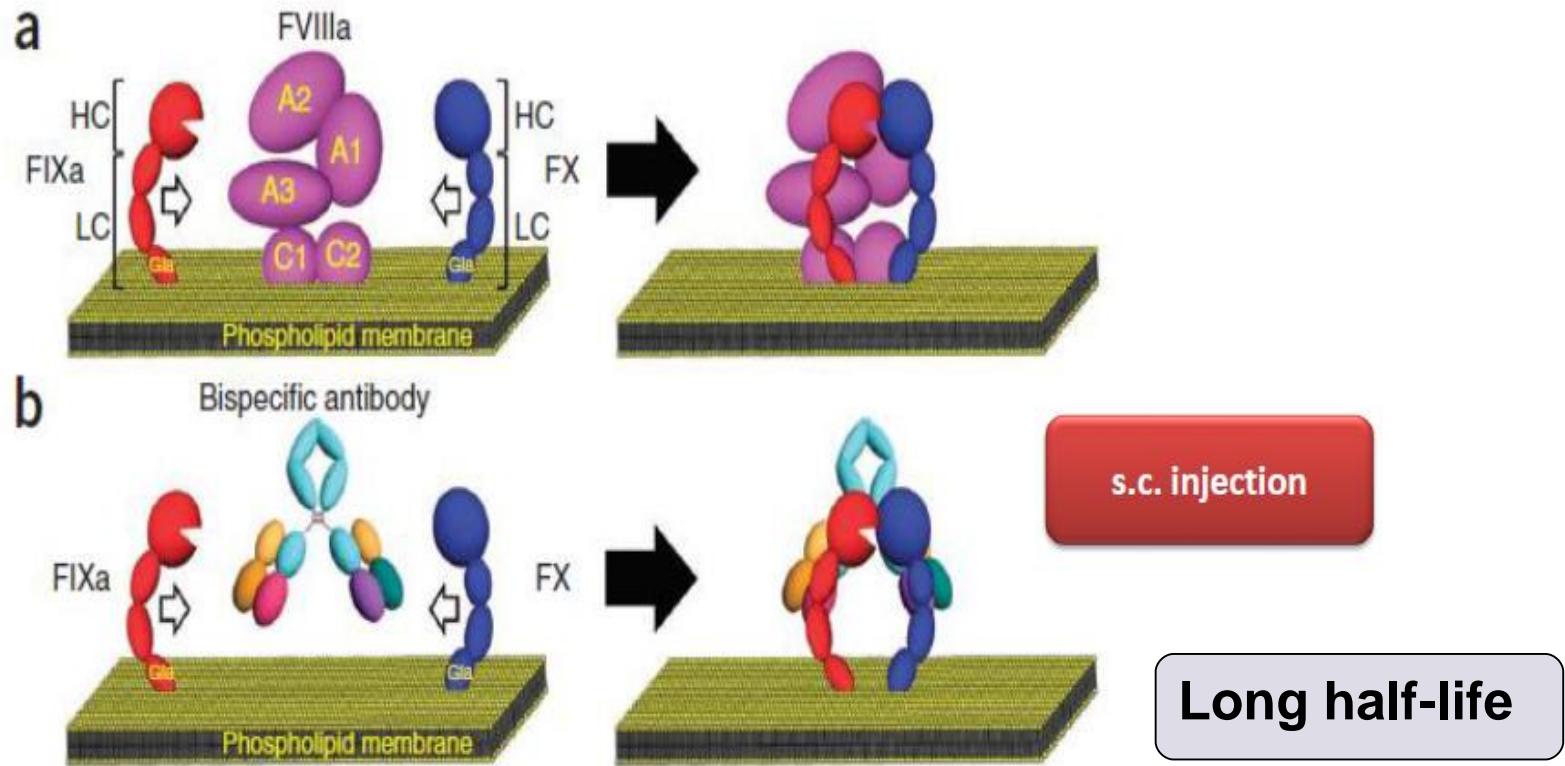
**rFVIIa – FP  
ACE910**

**Anti-TFPI  
(Concizumab)  
Inibitore della  
sintesi di AT  
(ALN-AT3)**

**Aumento  
dell'attività di  
fattori della  
coagulazione:  
Super-FVa  
FXa variant**

**Stabilizzazione del  
coagulo: FXIII**

# Emicizumab: anti-FIXa/FX bispecific antibody (FVIII mimetic agent)

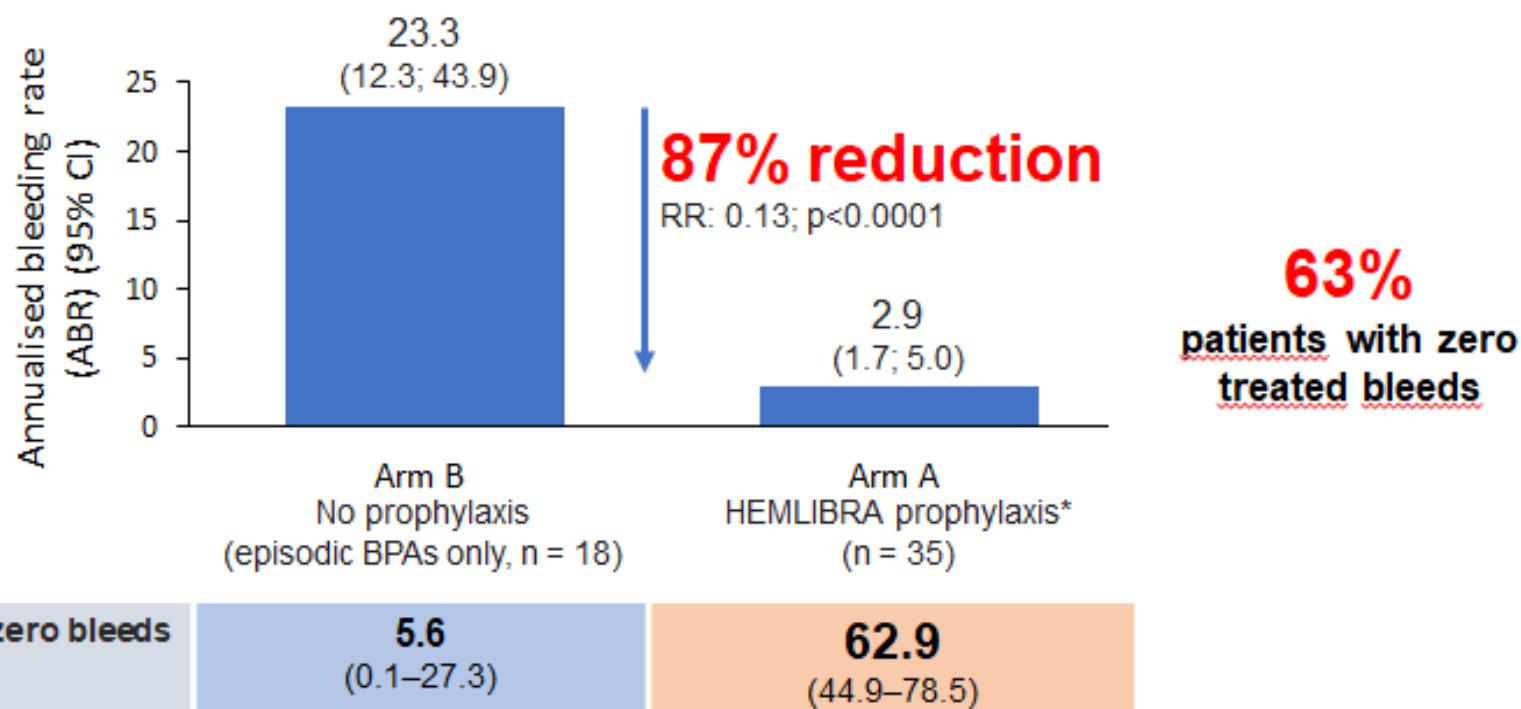


Muto A et al. J Thromb Haemost 2014; 12: 206-13

Muto A et al. Blood 2014; 124: 3165-71

Shima M et al. NEJM 2016; 374: 2044-53

## In HAVEN 1, treated bleeds were reduced by 87% with Emicizumab prophylaxis vs no prophylaxis



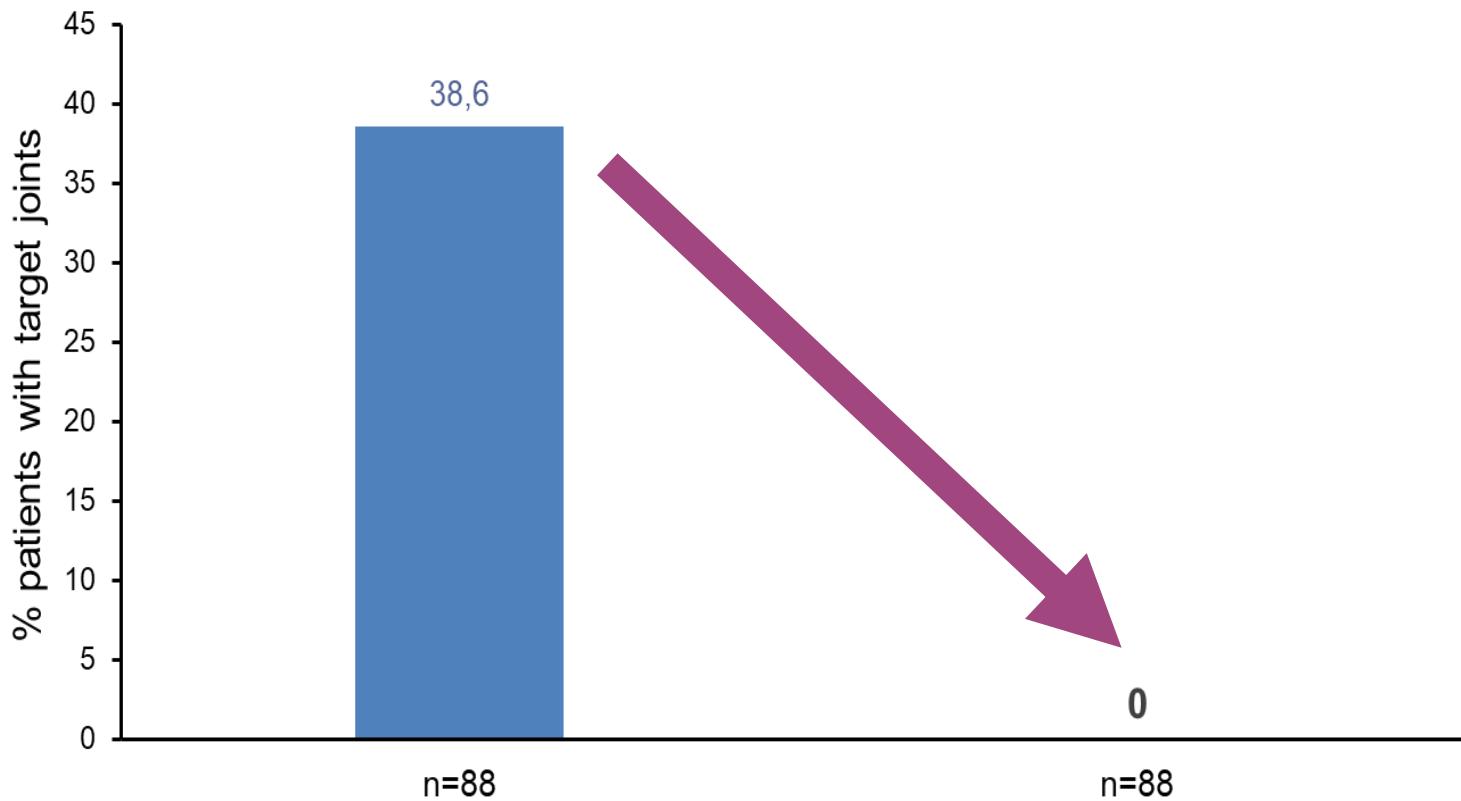
\*Arm A time on treatment: 29.5 weeks (range, 3.3–47.9)

25 October 2016 cut-off

ABR, annualised bleedrate; BPA, bypassing agent; CI, confidence interval; RR, risk ratio

Oldenburg J, et al. N Engl J Med 2017;377:809–18

# Proportion of patients with target joints was reduced with emicizumab



- Incidence of target joints in a post-hoc analysis

# VIVERE CON L'INIBITORE, OGGI

## Mortality rate

AJH

### Impact of inhibitors on hemophilia A mortality in the United States

Christopher E. Walsh,<sup>1\*</sup> J. Michael Soucie,<sup>2</sup> Connie H. Miller,<sup>2</sup> and the United States Hemophilia Treatment Center Network



**TABLE III.** Distribution of Cause of Death Categories by Inhibitor Status for 432 Deaths among 7,386 Males with Severe Hemophilia A, 1998–2011

	With inhibitors		Without inhibitors	
	N (%)		N (%)	P-value <sup>a</sup>
Cause of death category				
Hemophilia related	20 (41.7)		46 (12.0)	<0.001
HIV related	5 (10.4)		71 (18.5)	
Liver disease related	8 (16.7)		123 (32.0)	
Suicide	0		5 (1.3)	
Other	10 (20.8)		104 (27.1)	
Unknown	5 (10.4)		35 (9.1)	

<sup>a</sup> Chi-square test comparing the distributions of death categories by inhibitor status.

**TABLE IV.** Type of Hemorrhage for 66 Hemophilia-Related Deaths by Inhibitor Status

	With inhibitors		Without inhibitors	
	N (%)		N (%)	
Type of hemorrhage				
Intracranial	14 (70)		31 (67)	
Pulmonary	2 (10)		0	
Gastrointestinal	0		4 (9)	
Liver	1 (5)		2 (4)	
Retroperitoneal	1 (5)		0	
Postsurgical	1 (5)		1 (2)	
Shock/sepsis	0		3 (7)	
Unspecified	1 (5)		5 (11)	

# VIVERE CON L'INIBITORE, OGGI

## Intracranial hemorrhage

### Haemophilia

Haemophilia (2012), 18, 39–45



DOI: 10.1111/j.1365-2516.2011.02611.x

ORIGINAL ARTICLE *Clinical haemophilia*

Intracranial haemorrhage in the Italian population of haemophilia patients with and without inhibitors

E. ZANON,<sup>\*</sup> A. IORIO,<sup>†</sup> A. ROCINO,<sup>‡</sup> A. ARTONI,<sup>§</sup> R. SANTORO,<sup>¶</sup> A. TAGLIAFERRI,<sup>\*\*</sup>  
A. COPPOLA,<sup>††</sup> G. CASTAMAN,<sup>‡‡</sup> P. M. MANNUCCI,<sup>§§</sup> and THE ITALIAN ASSOCIATION OF  
HEMOPHILIA CENTERS<sup>1</sup>

Univariate, bivariate (age-adjusted) and multivariate analysis investigating the effects of patient characteristics on ICH occurrence showed that haemophilia severity and inhibitor status were **strongly associated with ICH severe vs. mild, HR 3.96 (2.39 – 6.57); inhibitor vs. non inhibitor.**

Patients with high titer inhibitors have 4-fold higher probability to suffer from ICH. Prophylaxis is not associated to a lower incidence of ICH in patients with inhibitors.

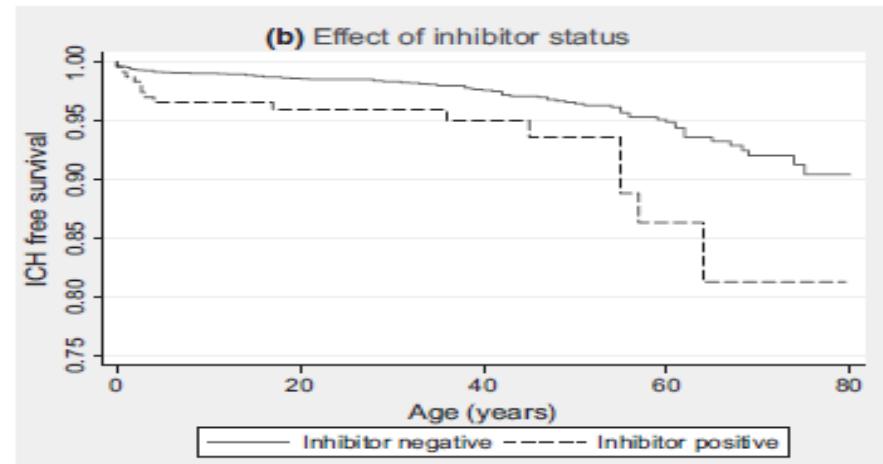
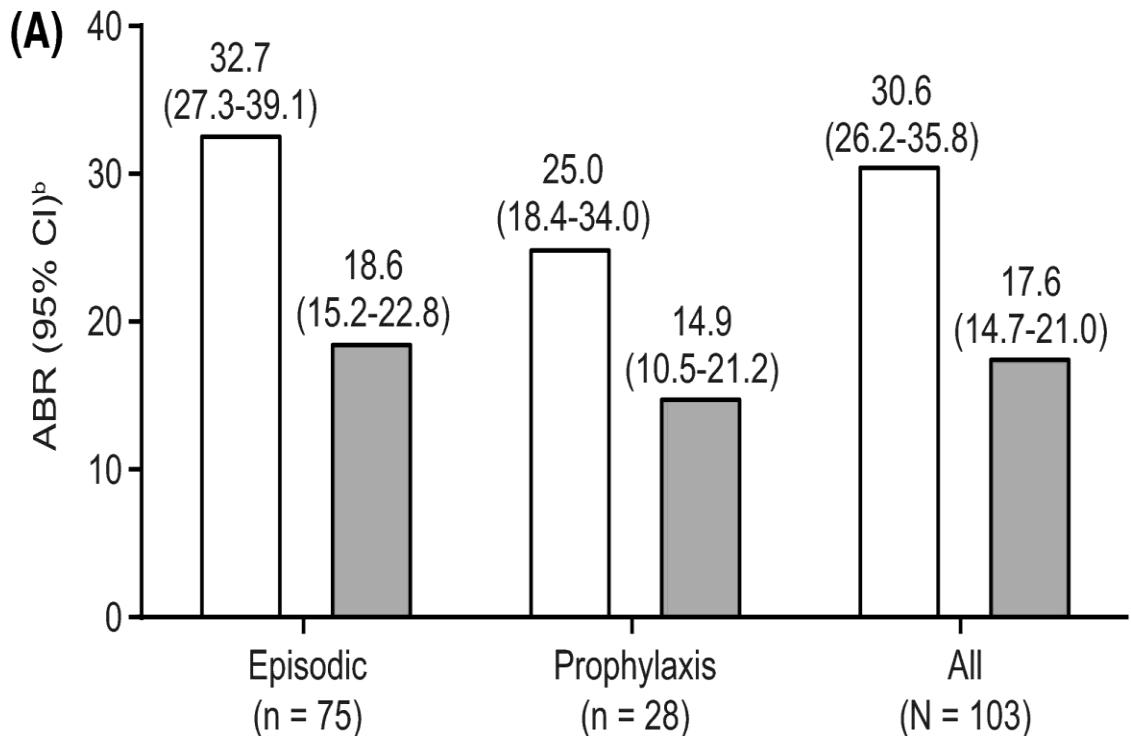


Fig. 2. Kaplan-Meier plots of the role of haemophilia severity and inhibitor status on the occurrence of intracranial haemorrhage (ICH).

# VIVERE CON L'INIBITORE, OGGI

## Bleeding rate in inhibitor patients



Bleeding rate is high even in patients on prophylaxis (1.5 bleeds a month). Falls seem to be a common phenomenon in patients with arthropathy

40% of bleeds were traumatic (25% in patients on prophylaxis)<sup>1</sup>

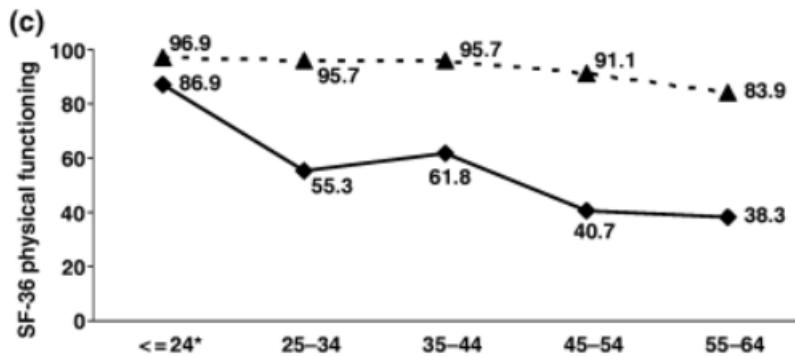
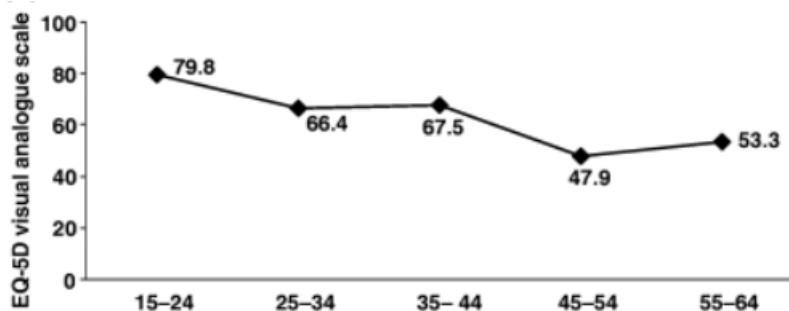
Prophylaxis with emicizumab reduced bleeding rate (79%) but not eliminate bleeding

1. Mahlangu J, et al. *Haemophilia* 2018;00:1-9.

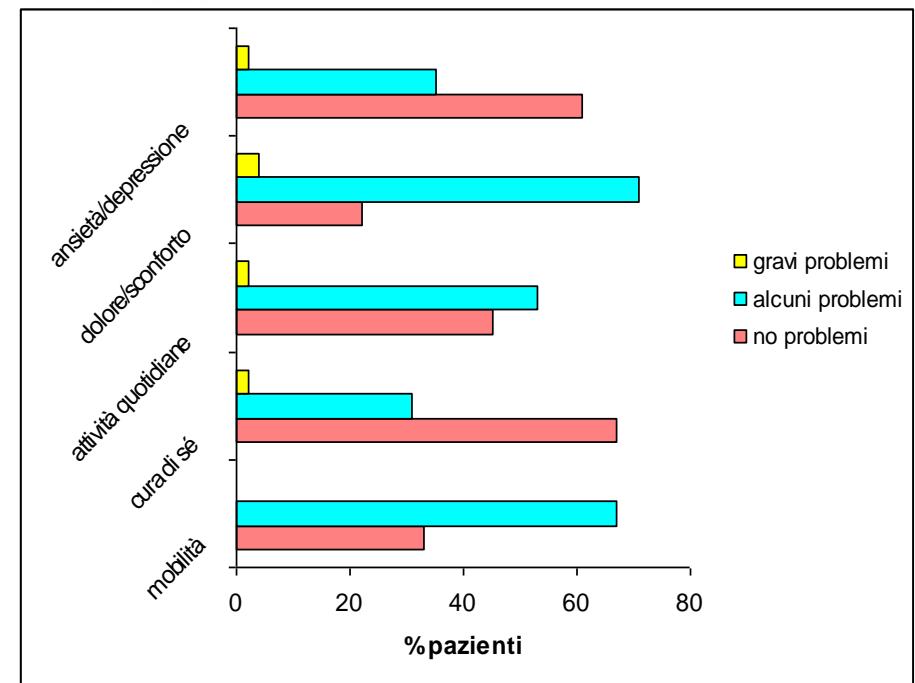
2. Oldenburg J, et al. *N Engl J Med* 2017;377:808-818.

# VIVERE CON L'INIBITORE, OGGI

## Impaired Health-related Quality of Life



Scalone L. et al.; COCIS Study Investigators.  
Haemophilia 2006;12:154-62.



Il 60-70% dei pazienti presenta problemi di mobilità e dolore cronico

Gringeri A et al. Blood 2003;102:2358-2363

# Open issues on ITI

**Which is the rate  
of efficacy of ITI**

**Who should receive ITI**

**When should ITI be started  
Predictors of ITI outcome**



# Similar results with different regimens

ITI protocol	FVIII dose and associated treatment	Success rate (%)	Median time to success, months	Comments
Bonn protocol (high-dose regimen)*	FVIII 100–150 iu/kg every 12 h until inhibitor <1 BU, then FVIII 150 iu/kg until normalization of FVIII recovery and half-life.	92–100	14	Very demanding for patients. High cost
Malmö protocol (high-dose regimen + immune modulation)†	FVIII continuous infusion targeting plasma levels >30 iu/dl until negative inhibitor titre, then 60–90 iu/kg weekly + cyclophosphamide (i.v. 12–15 mg/kg days 1–2, 2–3 mg/kg orally days 3–10) + i.v. immunoglobulins 2·5–5 g/kg day 1, 0·4 g/kg days 4–8.	59–82	1	Rapid response and cost-saving but need for hospitalization and concerns regarding the use of cyclophosphamide in children
Dutch protocol (low-dose regimen)‡	Preliminary protein A sepharose immunoabsorption if initial inhibitor titre >10 BU. Neutralizing dose (25–50 iu/kg twice daily, 1–2 weeks), then tolerizing dose (50–75 iu/kg weekly)	61–88	1–12§	Less demanding for patients and cost-saving
Other low or intermediate dose protocols	Ewing <i>et al</i> , 1988: 50 iu/kg/d Kucharski <i>et al</i> , 1996: 50 iu/kg/week Unuvar <i>et al</i> , 2000: 50–100 iu/kg/d Rocino <i>et al</i> , 2001: 100 iu/kg/d	67 45 57 75	2¶ 10 6 8	Developed for improving cost-effectiveness of treatment

\*Brackmann *et al* (1996) and Oldenburg *et al* (1999); activated prothrombin complex concentrates (aPCC) 40–60 iu/kg every 12 h was included until 1996.

†Nilsson *et al* (1988) and Freiburghaus *et al* (1999).

‡van Leeuwen *et al* (1986) and Mauser-Bunschoten *et al* (1995).

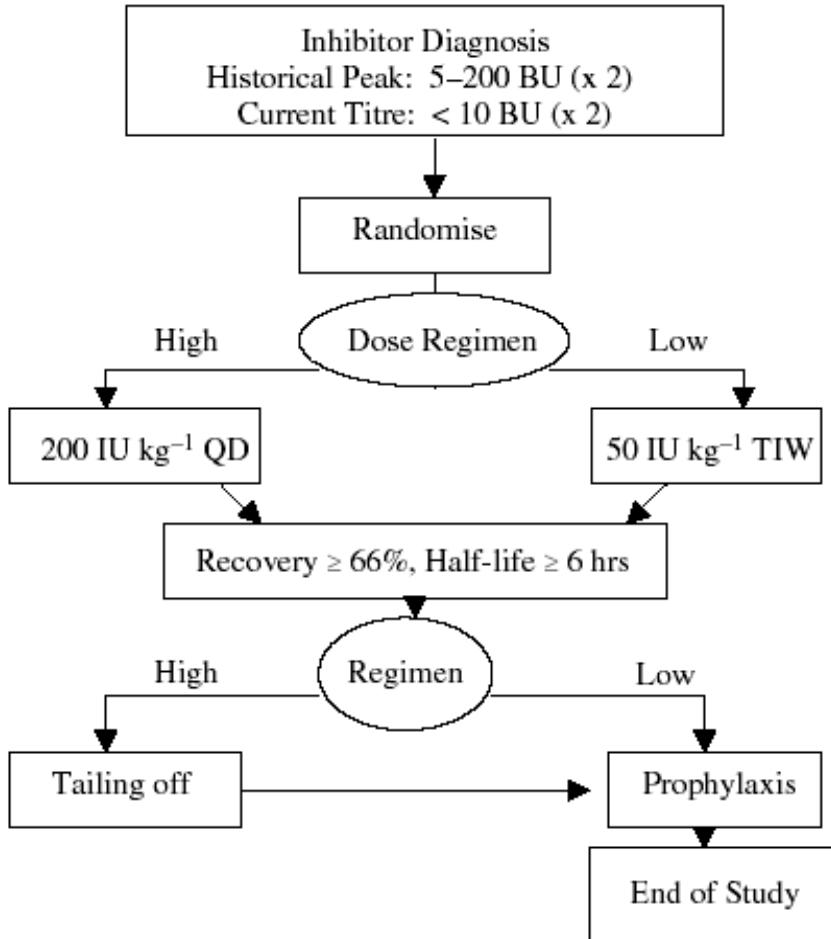
**Coppola *et al*, Br J Haematol,  
2010**

# Similar results with different products

Study	Dose regimen(s)	Type of concentrate ( <i>n</i> <sup>*</sup> )	Success rate (%)
NAITR, DiMichele and Kroner (2002)†	Various	IP and HP pdFVIII (41) Mo/rFVIII (123)	68 71
Mauser-Bunschoten <i>et al</i> (1995)	Dutch protocol	Mostly IP pdFVIII (24)	87
Brackmann <i>et al</i> (1996)	Bonn protocol	Mostly IP pdFVIII (52)	88
Rothschild <i>et al</i> (1998)	Various	rFVIII (8)	25‡
Battle <i>et al</i> (1999)	Various	rFVIII (11)	82§
Smith <i>et al</i> (1999)	High-dose	Mo/rFVIII (11)	91
Rocino <i>et al</i> (2001)	100 iu/kg/d	Mo/rFVIII (12)	83
Orsini <i>et al</i> (2005)	Various	HP pdFVIII (8)	88
Barnes <i>et al</i> (2006)	Various	Mostly rFVIII (29)	79§
Rocino <i>et al</i> (2006)	Various	rFVIII (26)	73
Gringeri <i>et al</i> (2007)	Various	HP pdFVIII (17)	53¶
Kurth <i>et al</i> (2008)	100–200 iu/kg/d	IP and HP pdFVIII (25)	32¶
Grenninger <i>et al</i> (2008)	Various	HP pdFVIII (11)	45¶
Valentino <i>et al</i> (2009)	Various	rFVIII (10)	75

*Coppola et al, Br J Haematol, 2010*

# International ITI Study



## Good-risk patients

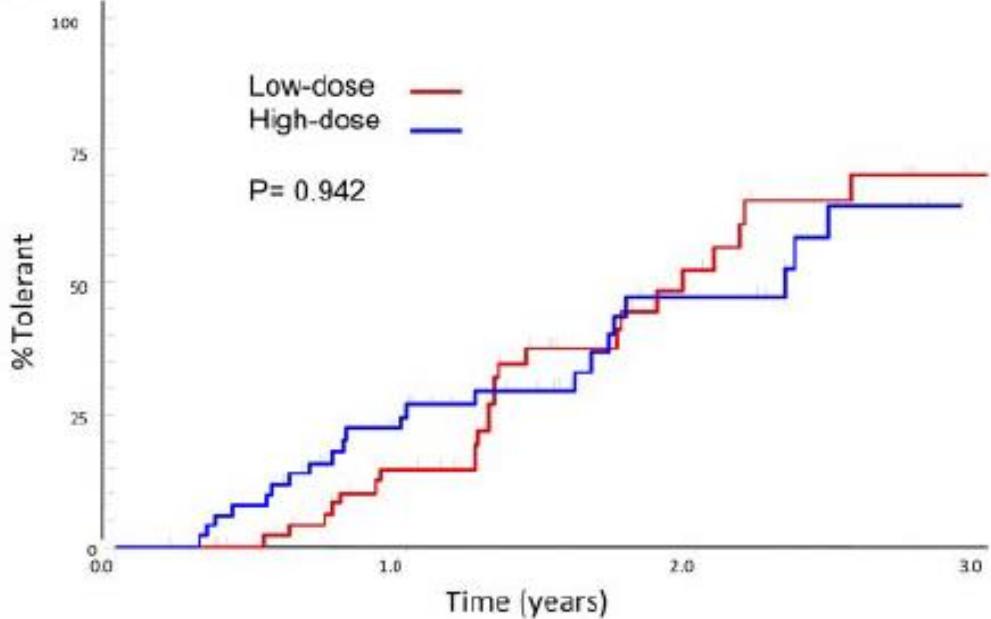
Severe, HR inhibitors  
age  $\leq$  8 yrs at ITI start  
Inhibitor diagnosis  $\leq$  24 mo.  
prior to ITI start  
Inh titer <10 BU at ITI start  
Historical inh peak <200 BU  
First ITI course  
Stable venous access  
Informed consent

# I-ITI study.RESULTS



Similar success rate: 70%

A



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
-----------------------------	------

# Bleeding episodes during

The principal results of the International Immune Tolerance Study: a randomized dose comparison

Charles R. M. Hay<sup>1</sup> and Donna M. DiMichele,<sup>2</sup> on behalf of the International Immune Tolerance Study



**Table 7. All intercurrent bleeding by treatment arm and phase of ITI**

	Regimen	Bleeds, n	HR	95% CI	P
All ITI (n = 58 vs 57)	LD	684	2.2	1.34-3.62	.0019
	HD	282			
Phase 1 (n = 58 vs 57)	LD	573	2.27	1.29-4.01	.0046
	HD	241			
Phase 2 (n = 27 vs 23)	LD	47	3.4	0.84-13.8	.088
	HD	4			
Phase 3 (n = 24 vs 22)	LD	9	5.18	0.71-38.0	.110
	HD	3			
Phase 4 (n = 24 vs 22)	LD	54	1.70	0.80-3.63	.170
	HD	32			

Phase 1 indicates the time from the start of ITI until the Bethesda titer is negative; phase 2, from phase 1 until the FVIII recovery is normal; phase 3, from phase 2 to normal half-life; and phase 4, 12-month prophylactic phase after the half-life has normalized.

# 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

71 pazienti (età: 0.4-41  
anni)

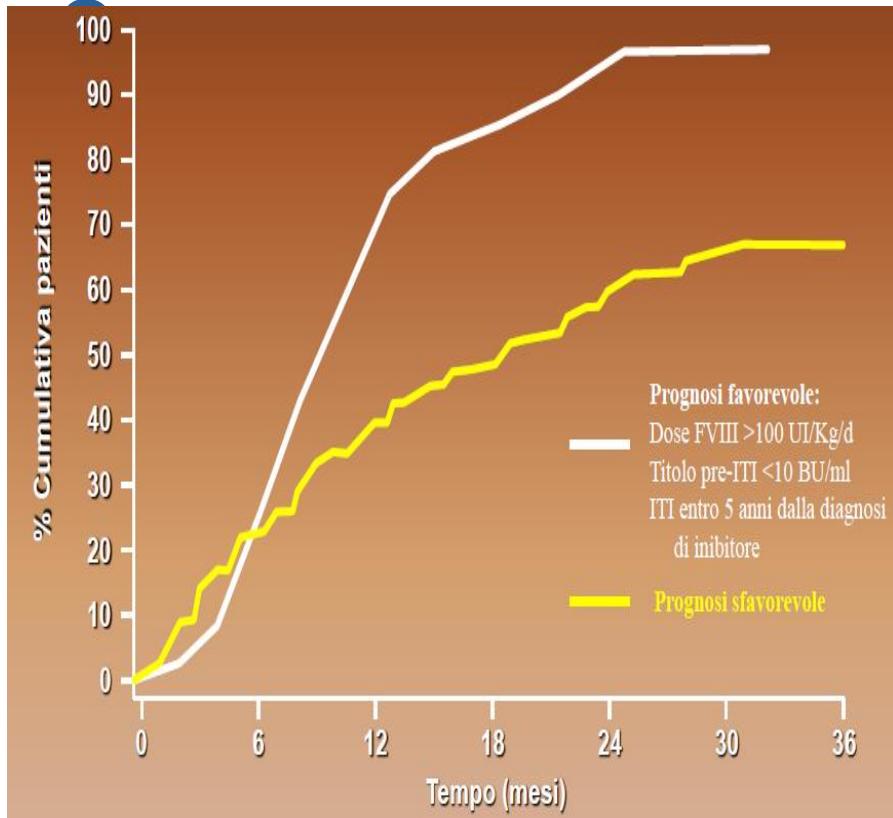
**Undetectable inhibitor was achieved in 84.5% of patients  
inhibitor eradication with normal FVIII PK in 74.2%.**

**Median time to successful tolerance was 10.7 months  
(range 2.0–90.0 months).**

**No significant influence of inhibitor titer at ITI start.  
Peak inhibitor level on ITI was a significant predictor of ITI  
success.**

**Breakthrough bleeding event incidence during ITI was  
associated with time to success.**

# Adulti: prognosi sfavorevole



Mariani & Kroner, Haematologica 2001

## Registro Internazionale ITI

### Fattori associati a successo

- | Fattore  | p            |
|--|--------------|
| • Titolo pre-ITI <10 BU/ml                                 | .03          |
| • Picco storico <200 BU/ml                                 | .01          |
| • <b>Tempo tra ITI e diagnosi di inibitore &lt; 5 anni</b> | <b>.0001</b> |
| • Dose FVIII > 100 UI/Kg                                   | .001         |
| • <b>Età &lt; 20 anni</b>                                  | <b>.005</b>  |

# Fattori prognostici: Registri ITI

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

# ITI tardiva – in età adulta

ORIGINAL ARTICLE *Inhibitors*

## Late immune tolerance induction in haemophilia A patients

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

**N=9, median age 18 yrs**

**Success 4 (44%)+ 3 partial (25%)**

**Haemophilia 2013; 19:445-48**

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**

**N=20, >18 yrs**

**Success 13 (65%)  
+ 5 partial (25%)**

# Searching for new predictors of ITI outcome



ORIGINAL ARTICLE

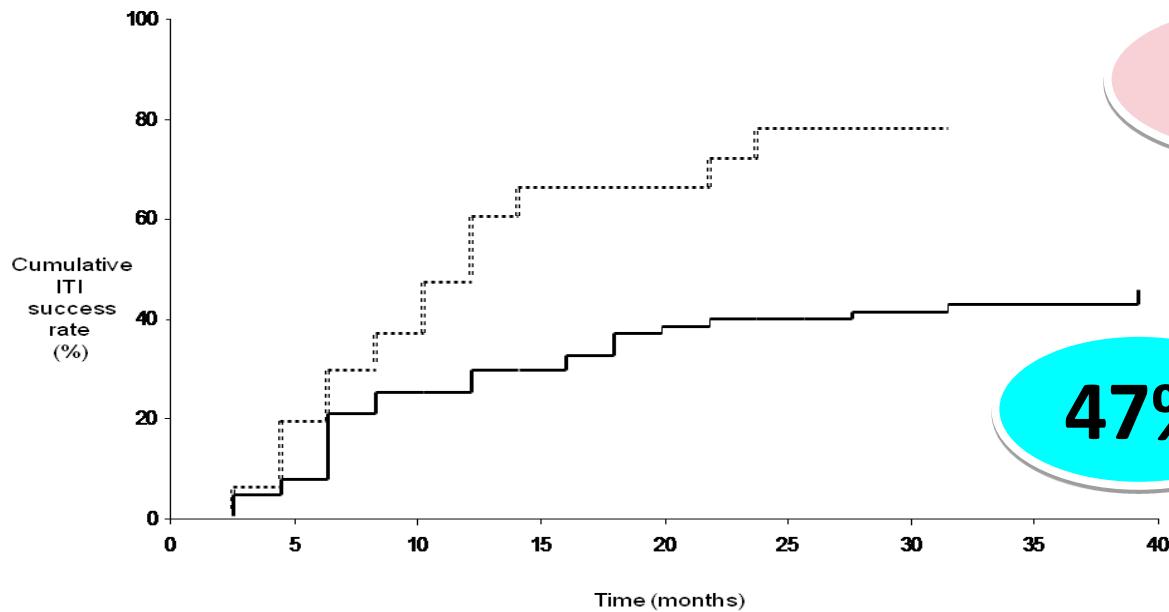
## Factor VIII gene (*F8*) mutations as predictors of outcome in immune tolerance induction of hemophilia A patients with high-responding inhibitors

A. COPPOLA,\* M. MARGAGLIONE,†‡ E. SANTAGOSTINO,§ A. ROCINO,¶ E. GRANDONE,‡  
P. M. MANNUCCI§ and G. DI MINNO\* FOR THE AICE PROFIT STUDY GROUP\*\*

\*Regional Reference Centre for Coagulation Disorders, Department of Clinical and Experimental Medicine, Federico II University, Naples;

†Medical Genetics, University of Foggia, Foggia; ‡Haemostasis and Thrombosis Unit, IRCCS ‘Casa Sollievo della Sofferenza’, S. Giovanni Rotondo (FG); §A. Bianchi Bonomi Haemophilia and Thrombosis Centre, Department of Medicine and Medical Specialties, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation and University of Milan, Milan; ¶Haemophilia and Thrombosis Centre, S. Giovanni Bosco Hospital, Naples; Italy; and \*\*AICE: the Italian Association of Haemophilia Centres, PROFIT: PROgnostic Factors in Immune Tolerance<sup>1</sup>

n=86



RR (95% CI)  
2.4 (1.2-4.9)  
p=0.01

# Raccomandazioni da LG

## Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition)



Peter W. Collins,<sup>1</sup> Elizabeth Chalmers,<sup>2</sup> Daniel P. Hart,<sup>3</sup> Ri Liesner,<sup>4</sup> Savita Rangarajan,<sup>5</sup> Kate Talks,<sup>6</sup> Mike Williams<sup>7</sup> and Charles R. Hay<sup>8</sup>

### Irrespective of age and inhibitor titer

- Immune toleration induction is recommended for patients with severe haemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (Grade 1B).



### US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors

L. A. VALENTINO, \* C. L. KEMPTON, † R. KRUSE-JARRES, ‡ P. MATHEW, § S. L. MEEKS ¶ and U. M. REISS \*\* ON BEHALF OF THE INTERNATIONAL IMMUNE TOLERANCE INDUCTION STUDY INVESTIGATORS

- Children with severe haemophilia A and persistent inhibitors  $>5 \text{ BU mL}^{-1}$  (confirmed on  $\geq 1$  repeat measurement) with a peak historical inhibitor titre  $<200 \text{ BU mL}^{-1}$  and other good-risk characteristics (Table 2) should receive ITI (Grade 1A) [2].
- Children with severe haemophilia A and inhibitors  $>5 \text{ BU mL}^{-1}$  (confirmed on  $\geq 1$  repeat measurement) with a peak historical inhibitor titre  $>200 \text{ BU mL}^{-1}$ , regardless of poor-risk characteristics (Table 2), should receive ITI (1A) [12–15]. Higher doses are needed, and consideration should be given to initiating ITI with a VWF-containing product (2C) [42].
- Adults with severe haemophilia A and inhibitors  $>5 \text{ BU mL}^{-1}$  (confirmed on  $\geq 1$  repeat measurement), regardless of inhibitor duration, should be considered for ITI (2C), particularly those with frequent bleeding or a poor response to bypass therapy (1C) [12–15,43,44].



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

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

## *Inhibitor eradication*

Treatment of patients with inhibitors should be primarily aimed at inhibitor eradication, in order to prevent, or at least reduce, the negative impact of persistent inhibitors on patients' morbidity and quality of life<sup>34,35,137</sup>. ITI through regular, prolonged, often high-dose FVIII administration is the only therapeutic approach proven to eradicate or reduce the neutralising inhibitor activity and restore the efficacy of FVIII replacement treatment<sup>138,139</sup>. ITI is recommended in all patients with severe haemophilia A and high-responding inhibitors

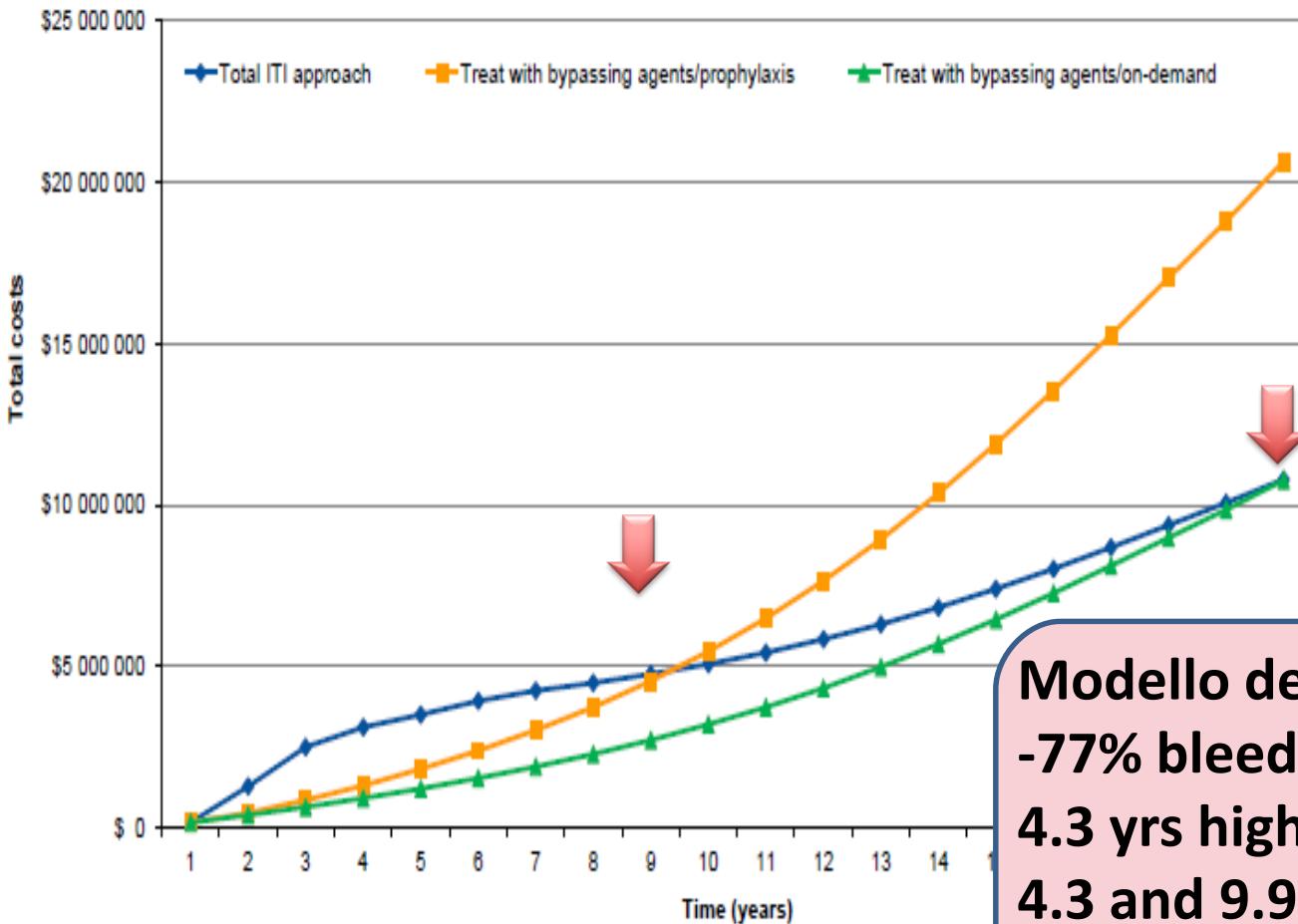
treatment<sup>76,77</sup>. The main candidates for ITI are children with recent onset high-responding inhibitors in whom early eradication can provide an optimal cost-utility ratio in a long-term perspective<sup>140</sup>. To this purpose, ITI should be started early after inhibitor detection, possibly as soon as titres <10 BU/mL are measured. Such a low



into account this variable<sup>81,141,142</sup>. 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<sup>141,142</sup> and in the AICE survey<sup>11</sup>, also taking into account that age and time interval between inhibitor diagnosis and starting ITI were not consistently recognised as predictors of success

# ITI: Costo-utilità

*Earnshaw et al, Haemophilia 2015*



**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.

# ITI: Costo-utilità



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)¶

**Cost of inhibitor patient: 18000/yr  
Cost of ITI buffered in 3.3 to 13.2**

**yrs**

Description	Cost per patient-month (€)		Cost per Kg patient-month (€) Mean (SD)
	Mean (SD)	Range	
Cost of FVIII given for ITI	46 143.9 (42,511.1)	1994.6–222 096.9	1692.1 (1328.7)
Cost of FVIII used for the treatment of breakthrough bleedings treatment during ITI	11 644.8 (52,125.8)	0–376 920.8	427.0 (1381.1)
Cost of bypassing agents used for the treatment of breakthrough bleeds during ITI	2289.9 (5,308.5)	0–28 082.6	84.0 (432.3)
Total costs	60 078.5 (80,452.0)	2334.3–506 818.2	2203.1 (2302.3)

\*Cost calculation includes the cost of the overall factor consumption for bleeding episodes in the whole study population, including those that did not bleed.

**ITER Study n=71  
Success rate: 84.5%  
Median age 3.8 yrs**

# ITI and prevention of bleeds

Prophylaxis using bypassing agents ?  
New agents  
(EMICIZUMAB) ?



**Ogni paziente ha proprie caratteristiche e proprie esigenze di vita;  
anche il paziente con inibitore ha diritto a vivere una vita normale e operare una scelta terapeutica che lo protegga dalla comparsa di emorragie invalidanti e gli consenta di prevenire lo sviluppo di artropatia cronica (profilassi)**



# The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab

Manuel Carcao<sup>1</sup>  | Carmen Escuriola-Ettingshausen<sup>2</sup> | Elena Santagostino<sup>3</sup> |  
Johannes Oldenburg<sup>4</sup>  | Ri Liesner<sup>5</sup> | Beatrice Nolan<sup>6</sup> | Angelika Bátorová<sup>7</sup> |  
Saturnino Haya<sup>8</sup> | Guy Young<sup>9</sup>  Future of Immunotolerance Treatment Group

**TABLE 1** Questions regarding ITI facing the haemophilia community with the advent of non-factor therapies

Should patients with inhibitors still undergo one or multiple ITI attempts to eradicate their inhibitors?

Should emicizumab be given concurrently with ITI to prevent bleeds?

Given that now with emicizumab low-dose ITI regimens may no longer be handicapped by higher bleeding rates in comparison with high-dose ITI regimens (which are associated with much higher cost and burden) will ITI regimens change?

Will government and insurance payers support the cost of concomitant emicizumab with ITI?

Will there be any role for prophylaxis with traditional bypassing agents (rFVIIIa and FEIBA)?

If patients undergo ITI (particularly patients receiving concomitant emicizumab) and achieve success, will they continue on emicizumab?

If patients remain on emicizumab post inhibitor eradication, must they continue on some regular exposure to FVIII to maintain tolerance to FVIII?

Haemophilia. 2019 Apr 29. doi:10.1111/hae.13762. [Epub ahead of print]

**TABLE 2** Key conclusions and recommendations

Eradication of inhibitors is still a desirable goal and ITI is the only approach that currently offers this potential.

Patients with inhibitors should be offered at least one attempt at ITI.

Although inhibitor eradication is still a laudable goal, for those patients who for various reasons must delay or are unable to undertake ITI, emicizumab alone is now an option.

The likelihood of successful ITI is mainly on the basis of historical pre-ITI peak titre and peak titre during ITI. ITI dose/regimen may be chosen according to patients' risk group.

Monitoring should be done frequently (suggest monthly), and ITI dose/frequency can be adjusted depending on how the patient is doing (based on changes in inhibitor titre and bleeding phenotype).

For patients who are not appearing to be successful with ITI, adjustments to the ITI regimen can be undertaken. This includes switching FVIII products or intensifying the regimen. With the availability of emicizumab, the FIT group would in general not be supportive of adding immunosuppressive therapy.

In the future, patients are likely to undertake fewer courses of ITI making the initial course so much more important and making decisions regarding what FVIII product to use and what ITI regimen to use even more important.

Emicizumab can almost certainly be used concomitantly with FVIII during ITI to prevent bleeds. This may impact on the decision of what ITI regimen to use.

Many questions remain as to what to do with patients after successful ITI; can tolerance to FVIII be maintained without ongoing exposure to FVIII?



# *Profilassi nei pazienti con inibitore?*

## *Chi, quando, perché*

**Chi?**

Tutti i pazienti ad alto rischio  
per lo sviluppo di artropatia cronica

**Quando?**

**Prima di iniziare l'ITI**  
**Durante l'ITI**  
**In caso di fallimento ad ITI**  
**In presenza di articolazioni bersaglio**  
**In caso di pregresse emorragie gravi**  
**In preparazione e dopo chirurgia ortopedica**

**Perchè?**

**Migliorare la QoL Impedire/rallentare lo  
sviluppo di artropatia cronica.**