# *Modalità di trattamento del bambino con inibitore*

*Angiola Rocino*

**Centro Emofilia e Trombosi**

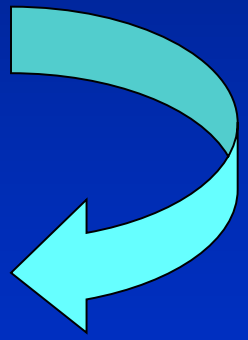
**Ospedale San Giovanni Bosco -Napoli**

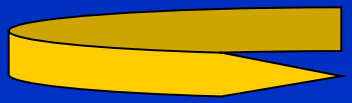
Padova, 13-14 maggio 2016

# *Le emorragie nell' emofilico con inibitore*

- **Non sono più frequenti ma potenzialmente più gravi e difficili da trattare**
- **Ogni episodio emorragico se non adeguatamente gestito può divenire una possibile emergenza clinica**
- **Il trattamento deve essere**

  **il più precoce possibile**





**Regime domiciliare**

**In caso di emorragia grave, è necessario un monitoraggio clinico attento ed assiduo.**

# *Inibitori High Responding / Low Responding*

RECOMMENDATIONS AND GUIDELINES

Definitions in hemophilia: communication from the SSC of the ISTH

V. S. BLANCHETTE,* N. S. KEY,† L. R. LJUNG,‡ M. J. MANCO-JOHNSON,§ H. M. VAN DEN BERG¶ and A. SRIVASTAVA,** FOR THE SUBCOMMITTEE ON FACTOR VIII, FACTOR IX AND RARE COAGULATION DISORDERS

J Thromb Hamost 2014; 12: 1935-39

- **High responding (HR): Picco storico >5 UB**

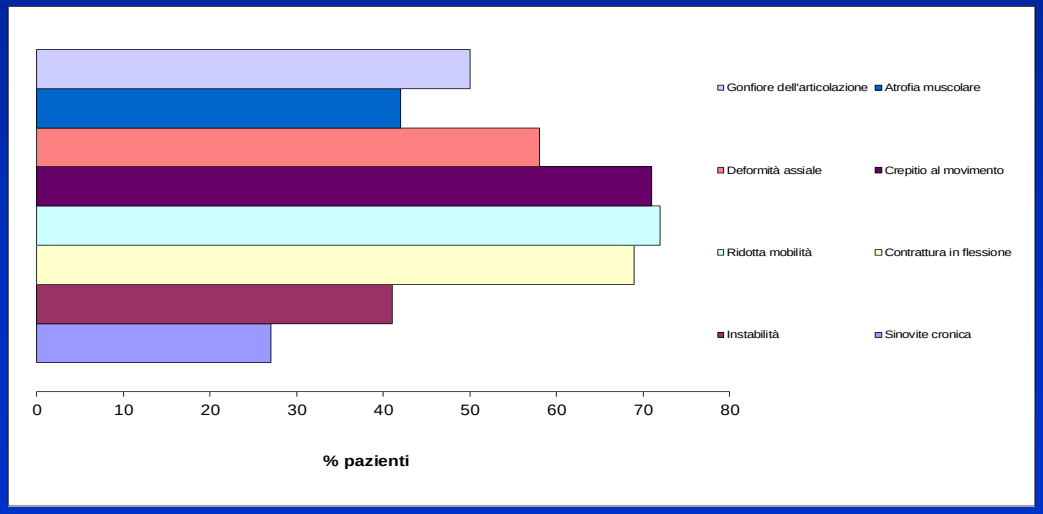
**solo raramente trattabili con FVIII/IX**

**ogni trattamento sostitutivo induce risposta anamnestica.**

- **Low Responding (LR): Picco storico <5 UB**
  **anche dopo stimolazione**
- **Transitori: <5 UB scompaiono spontaneamente entro 6 mesi, nonostante continuino le esposizioni a FVIII/FIX.**

# Gli inibitori High Responding (≥5 UB)

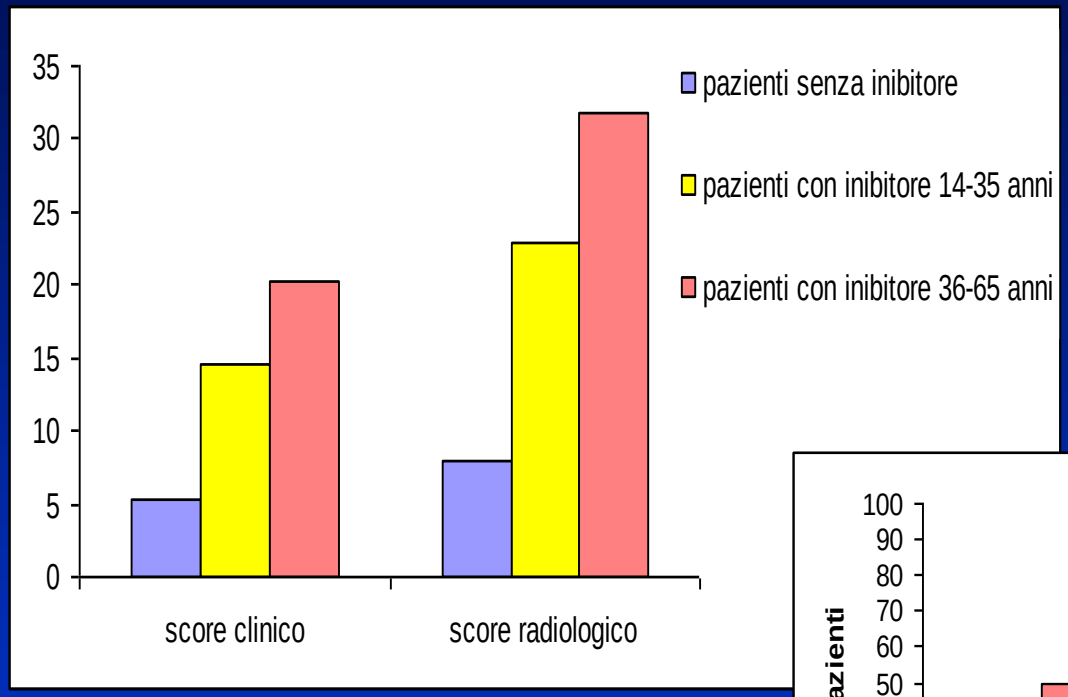
**Impediscono la normale terapia sostitutiva e l'attuazione di regimi di profilassi con FVIII o FIX.**
**Il trattamento degli episodi emorragici richiede l'uso di agenti bypassanti (FEIBA, rFVIIa) la cui efficacia è minore, rispetto alla terapia sostitutiva con FVIII oFIX.**
**E' aumentato il rischio di emorragie gravi e disabilità da artropatia cronica**



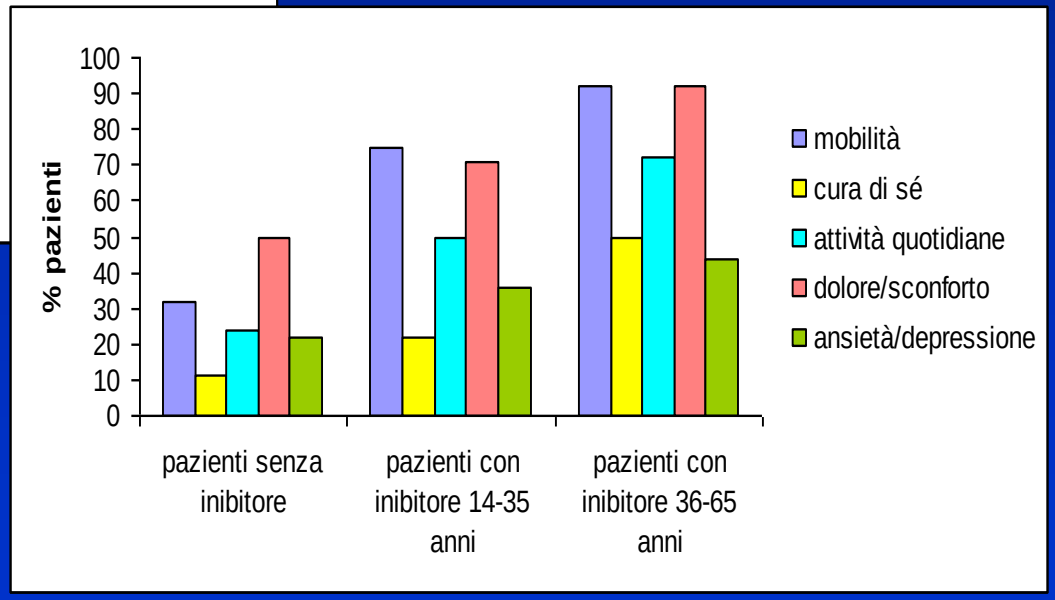

**Il 60-70% presenta problemi di mobilità e dolore cronico**

*Gringeri A et al. Blood 2003; 102: 2358-63*

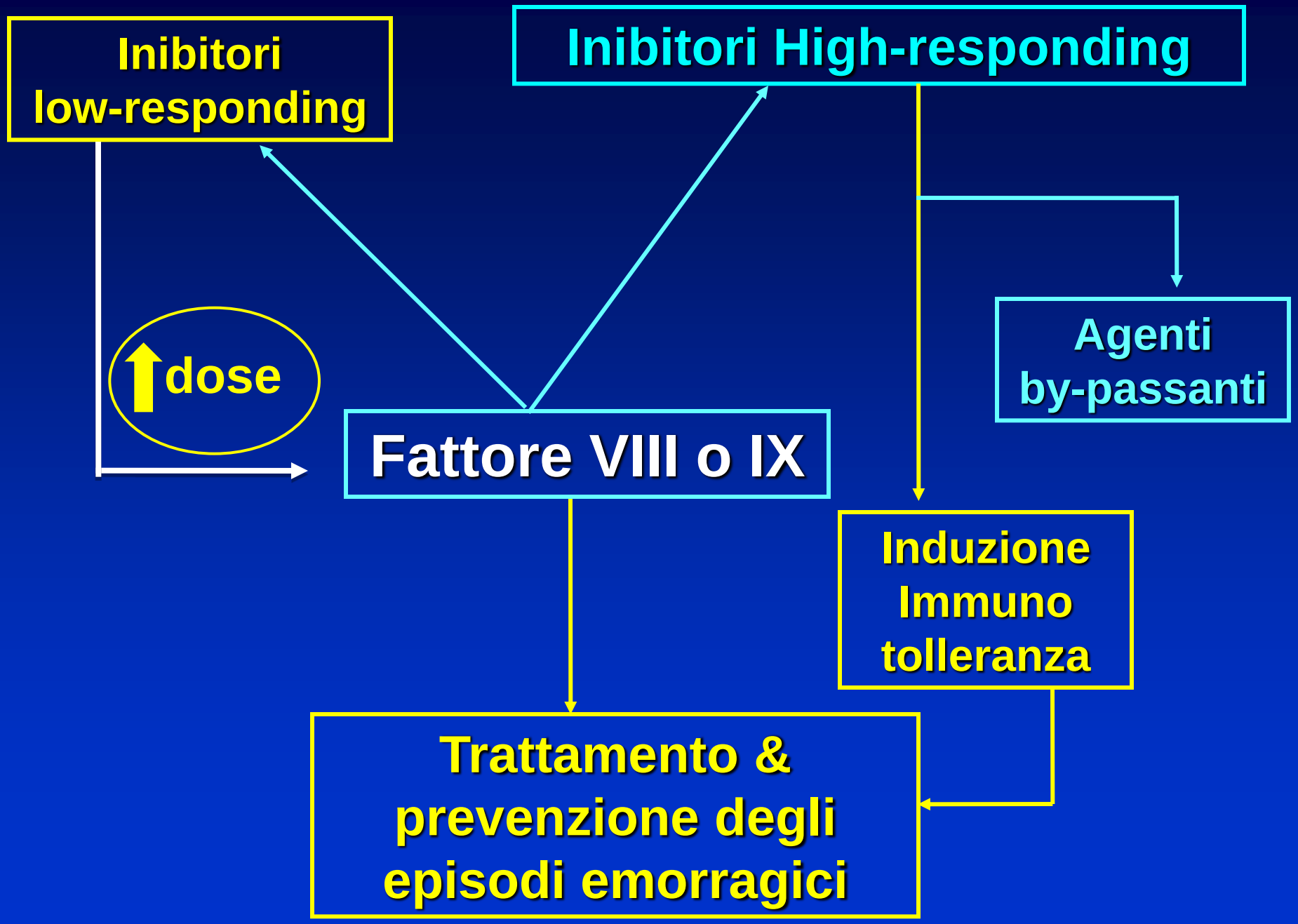
# *Le condizioni ortopediche peggiorano più velocemente*




**con non trascurabili ripercussioni sulla QoL**




**Morfini M et al.**
**Haemophilia 2007; 13: 606-12.**


Inibitori low-responding
Inibitori High-responding
dose
Agenti by-passanti
Fattore VIII o IX
Induzione Immuno tolleranza
Trattamento & prevenzione degli episodi emorragici

# *Gli inibitori Low Responding (<5 UB)*

**Possono essere neutralizzati incrementando la dose di FVIII / FIX.**

**Le linee guida AICE prevedono l'uso di una semplice formula che consente di calcolare la dose da somministrare.**

*Gringeri A et al. Blood 2003; 102: 2358-63*

**Dose Neutralizzante =**
**titolo dell'inibitore x volume plasmatico**

**In pratica: titolo in UB x 40 x Kg di peso corporeo**

**Dose da somministrare =**
**Dose neutralizzante + dose incrementante**

# *Trattamento degli episodi emorragici nel paziente con inibitori*

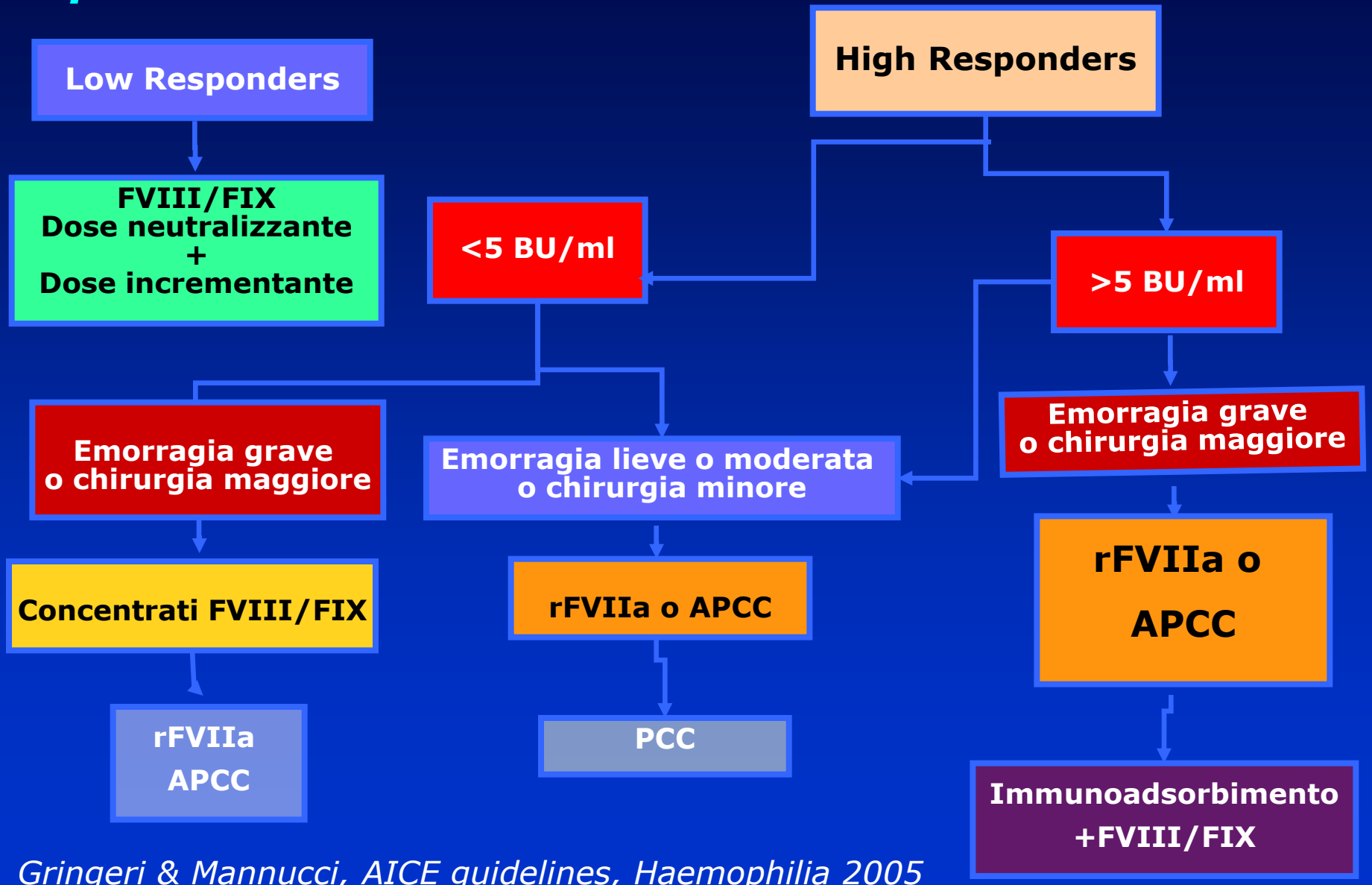
**Agenti bypassanti : mirano a bypassare il FVIII e il FIX nel processo emocoagulativo consentendo la generazione di trombina sulla superficie delle piastrine**

**APCC (FEIBA)**

**rFVIIa (NovoSeven)**

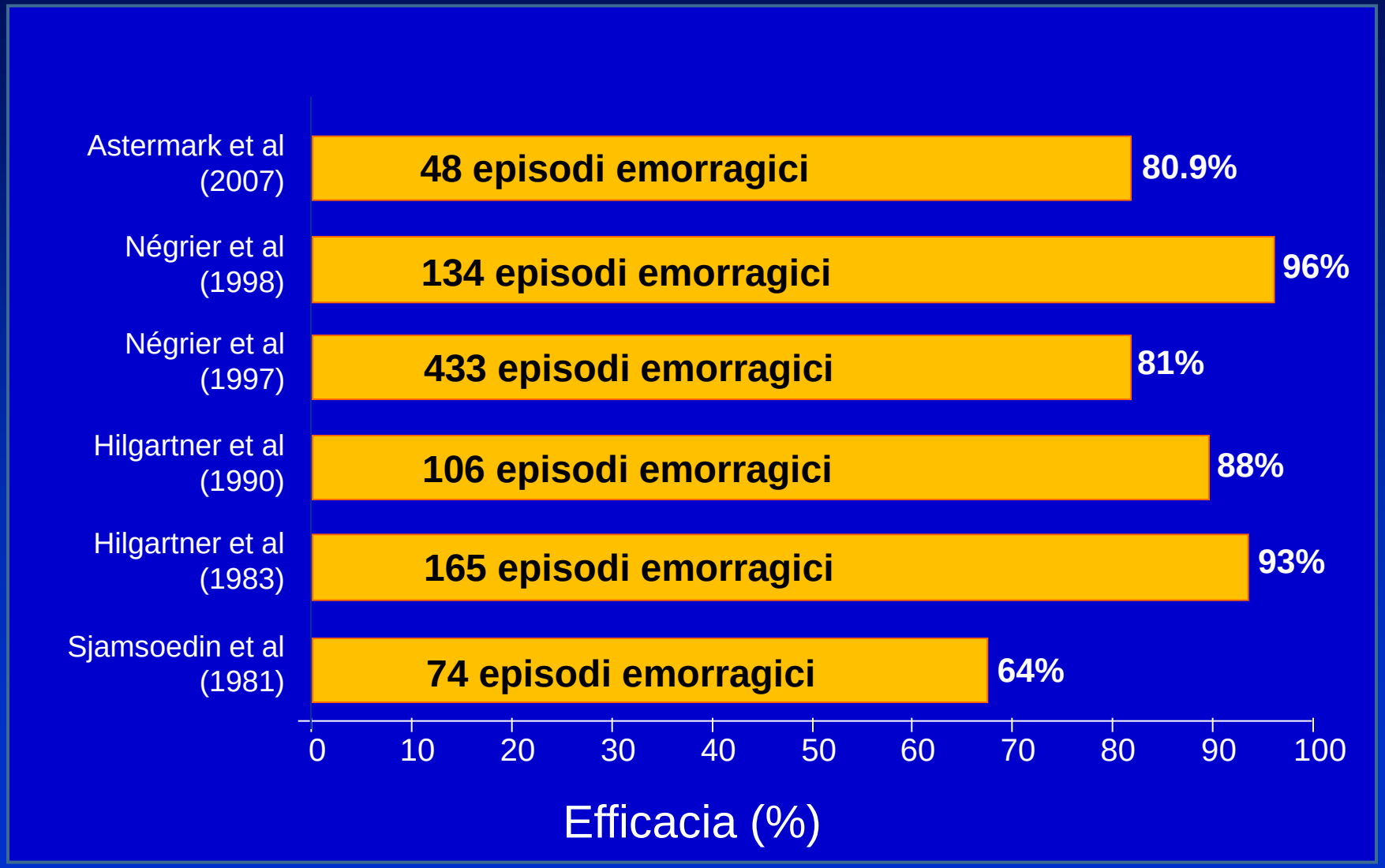
***Entrambi sono efficaci nel controllo delle emorragie (70-80% dei casi) ma non sempre equivalenti.***
***E' possibile possano agire sinergisticamente.***

# Trattamento degli episodi emorragici nei pazienti con inibitore

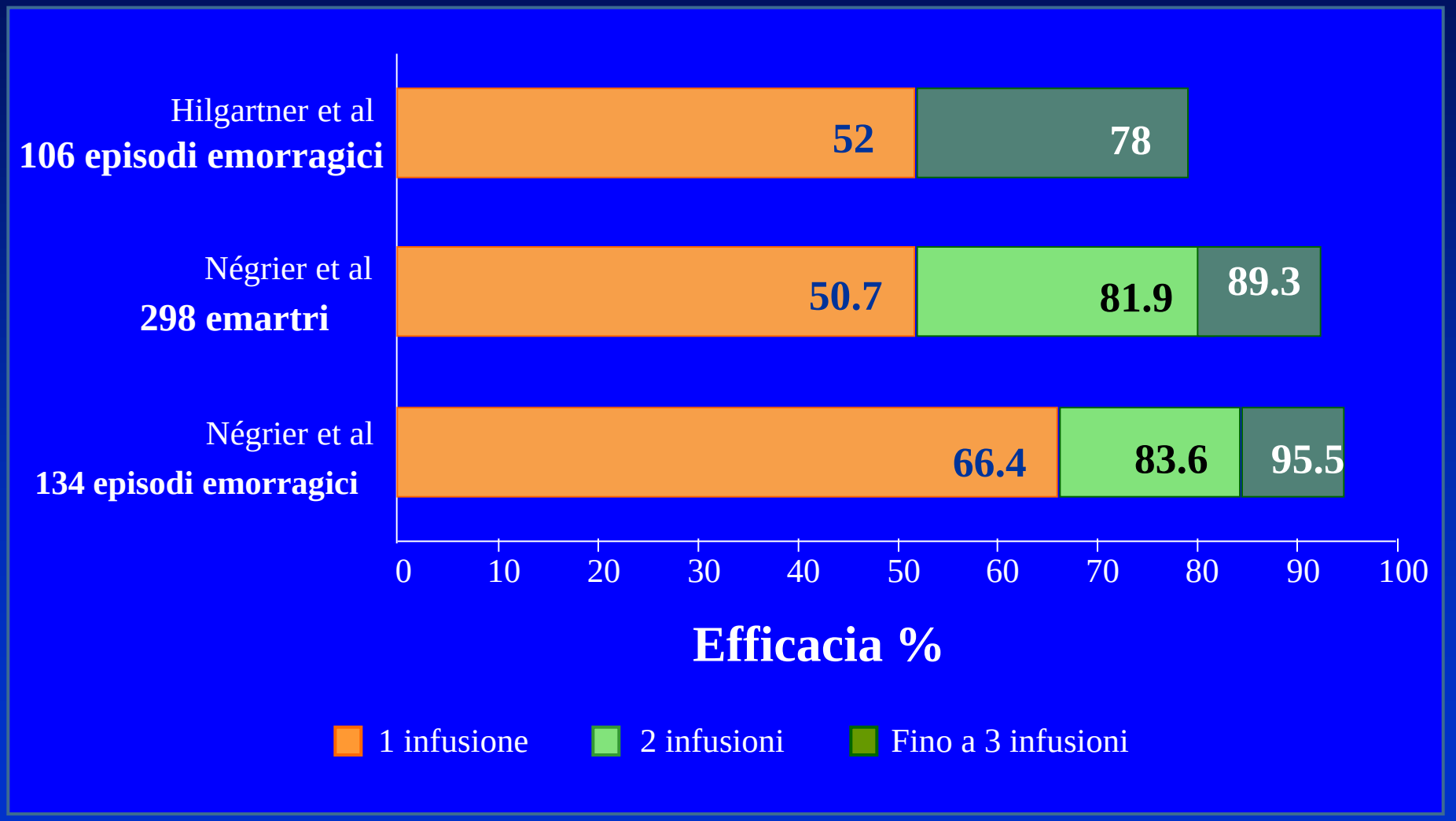



*Gringeri & Mannucci, AICE guidelines, Haemophilia 2005*

# *Efficacia del FEIBA nel trattamento di episodi emorragici acuti*



# *Efficacia del FEIBA nel trattamento di episodi emorragici acuti*



# Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention

*British Journal of Haematology*, 1999, **104**, 22–26

E. SANTAGOSTINO, A. GRINGERI AND P. M. MANNUCCI *Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Hospital and University of Milan, Italy*

**Efficacia:**

**valutata**

**in base a tumefazione, dolore, mobilità**

**Table II.** Response to home treatment with rFVIIa in 53 bleeding episodes.

| Bleeding episode | No. | Response to rFVIIa treatment: Effective | Partially effective | Failure |
|---|---|---|---|---|
| Haemarthroses | 45 | 36 (80%) | 4 (9%) | 5 (11%) |
| In non-target joints | 21 | 18 (86%) | 2 (9%) | 1* (5%) |
| In target joints | 24 | 18 (75%) | 2 (8%) | 4† (17%) |
| Haematomas | 8 | 6 (75%) | 2 (25%) | – |
| Spontaneous haemorrhage | 41 | 34 (83%) | 3 (7%) | 4 (10%) |
| Post-traumatic haemorrhage | 12 | 8 (67%) | 3 (25%) | 1 (8%) |
| Total | 53 | 42 (79%) | 6 (11%) | 5 (10%) |

*Bleeding recurrency at the same site within 48 h of the first rFVIIa injection.

†Three ineffective treatment courses and one bleeding recurrency at the same site within 48 h of the first dose.

**"Effective" trattamento iniziato più precocemente (0.6 ore vs. 2.7 hours; P=0.02)**

# Effect of rFVIIa dose and time to treatment on patients with haemophilia and inhibitors: analysis of HemoRec registry data from the Czech Republic

*Haemophilia* (2009), 15, 752–759

P. SALAJ,* P. BRABEC,† M. PENKA,‡ V. POHLREICHOVA,* P. SMEJKAL,‡ P. CETKOVSKY,* L. DUSEK† and U. HEDNER§

**Rischio di recidiva nella stessa articolazione 4%–5% a 24 ore[1,2]**

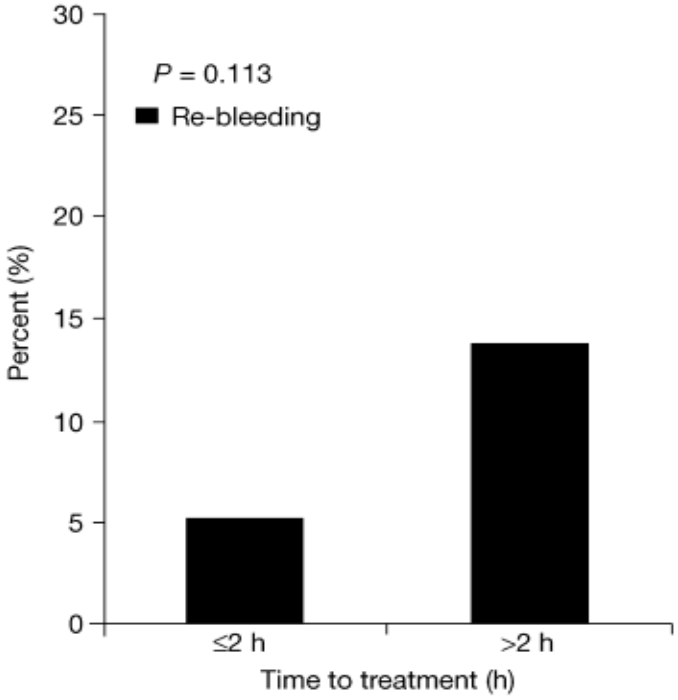



Fig. 1. Incidence of re-bleeding in relation to time to treatment.

(5.2% vs. 13.7% re-bleedings; $P = 0.113$)

**Dati da HemoRec Registry: minor rischio di recidiva se il trattamento del primo emartro viene iniziato entro 2 ore**

1 Croom & McCormack, BioDrugs, 2008. 22:121-36;
2. Key *et al*. Thromb Haemost, 1998. 80(6):912-8;

# *rFVIIa single high dose: trials clinici*

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

## Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors

A multi-centre, randomised, double-blind, cross-over trial

Khan Kavakli[1], Mike Makris[2], Bulent Zulfikar[3], Elizabeth Erhardtsen[4], Zvi S. Abrams[4], Gili Kenet[5] for the NovoSeven® trial (F7HAEM-1510) investigators

Thromb Haemost 2006;95:600-5

ORIGINAL ARTICLE

## A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors

E. SANTAGOSTINO,* M. E. MANCUSO,* A. ROCINO,† G. MANCUSO,‡ F. SCARAGGI§ and P. M. MANNUCCI*

J Thromb Haemost 2006;4:367-71

# *rFVIIa single high dose: NODOP*

ORIGINAL ARTICLE

A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors

J Thromb Haemost 2006;4:367-71

E. SANTAGOSTINO,* M. E. MANCUSO,* A. ROCINO,† G. MANCUSO,‡ F. SCARAGGI§ and P. M. MANNUCCI*

**20 pazienti arruolati (età 1– 47 anni)**
**18 pazienti trattati per 68 emartri ***

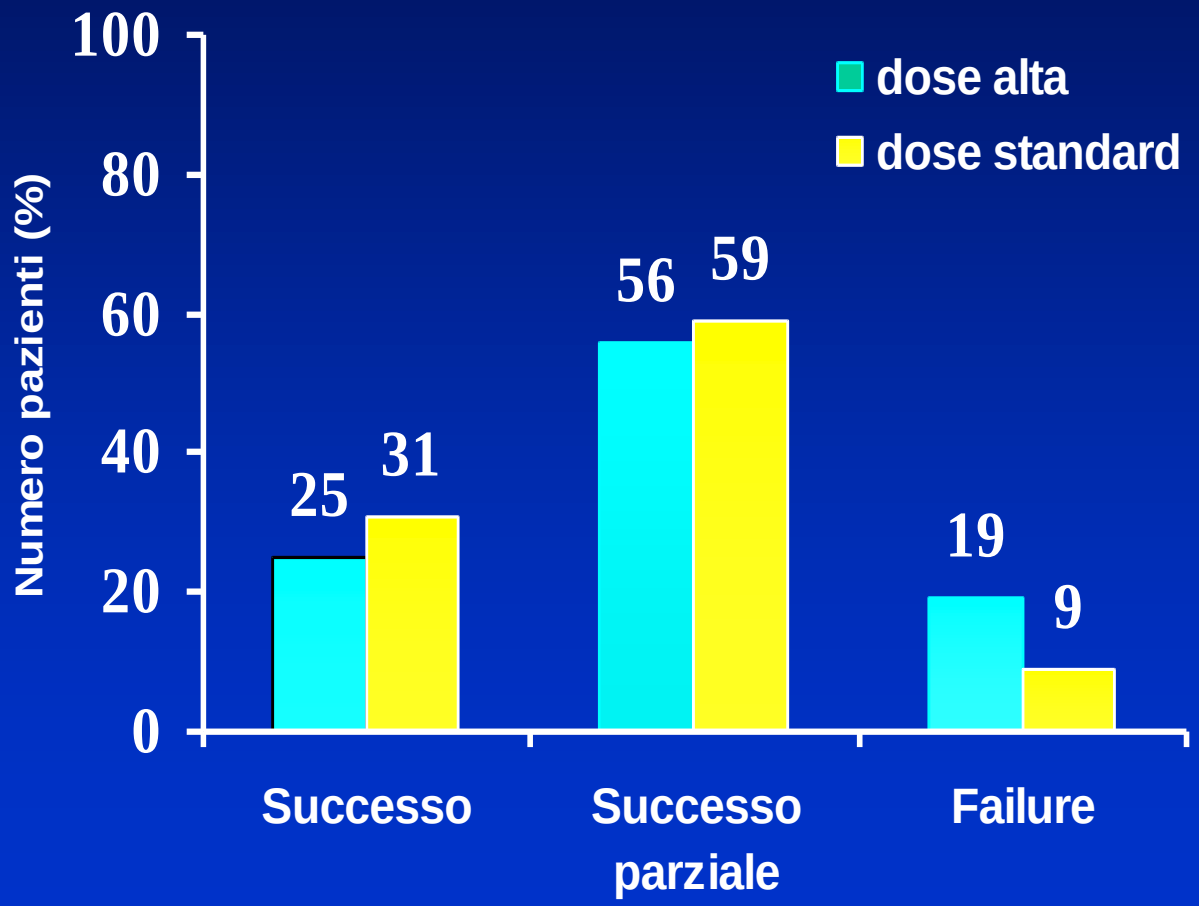
**32 regime a dose standard**

**36 regime ad alta dose iniziale**

**( *48 in articolazioni bersaglio, 71% )**

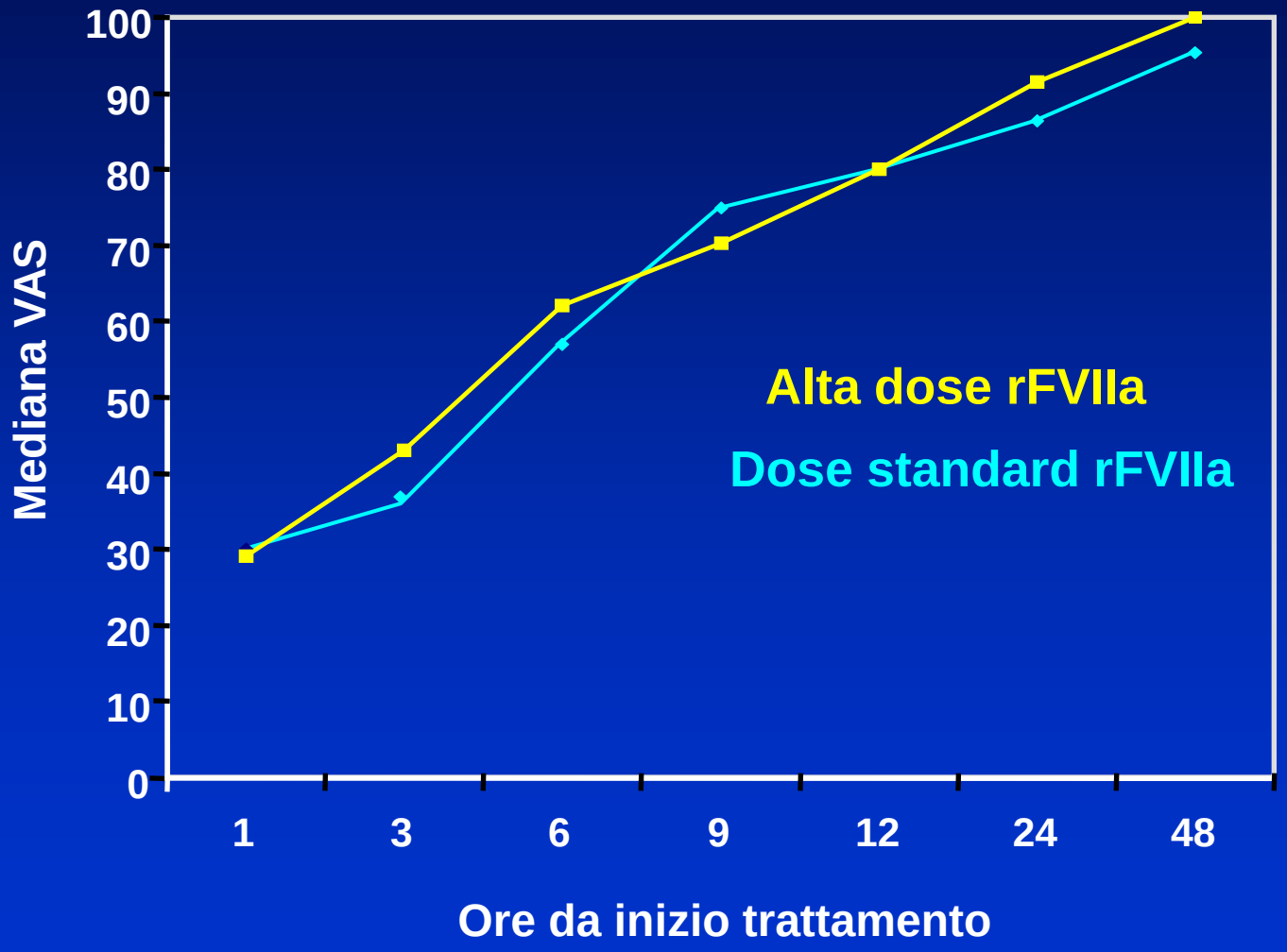
**Rate di recidiva di emartro: 3% con entrambi i regimi di trattamento**

# *Risposta a 9 ore dall'inizio del trattamento*



# NODOP – valutazione efficacia

*Santagostino et al. J Thromb Haemost 2006;4:367-71.*



# *Efficacia del rFVIIa nel trattamento di episodi di emartro*

| | Young *et al.* | Kavakli *et al.* | Santagostino *et al.* | Key *et al.* |
|---|---|---|---|---|
| **Patient population** | 27 patients with ≥2 bleeds in previous 12 months Joint bleeds only | 22 patients with ≥3 bleeds in previous 12 months Joint bleeds only | 20 patients with ≥2 bleeds in previous 6 months Joint bleeds only | 60 patients with ≥2 mild-to-moderate bleeding episodes in previous 12 months All non-severe bleeds |
| **90 µg/kg Bleeding control** at 9 h |   |   |   |   |
| **270 µg/kg Bleeding control** at 9 h |   |   |   | |

**Legend:** Bleeding control defined as (% not requiring rescue medication[1,2] ), as rates of success and partial response as per visual analogue scale and clinical assessment[3], as % of evaluable bleeds for which treatment was rated as "effective" (bleeding ceased or decreased substantially) by the patient.[4]


Young *et al*. Haemophilia, 2008. 14(2):287-94;

Kavakli *et al*. Thromb Haemost, 2006. 95(4):600-5;

Santagostino *et al*. J Thromb Haemost, 2006. 4(2):367-71;

Key *et al*. Thromb Haemost, 1998. 80(6):912-8.

# Studi comparativi head to head

A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study

Jan Astermark,[1] Sharyne M. Donfield,[2] Donna M. DiMichele,[3] Alessandro Gringeri,[4] Steven A. Gilbert,[2] Jennifer Waters,[2] and Erik Berntorp,[1] for the FENOC Study Group

**48 pazienti (età media 27.5 anni; range 3-55)**
**96 emartri (2 per ogni paziente)**

**Table 2. Rates of efficacy by treatment and time point**

| Hours after infusion (N) | FEIBA, % | NovoSeven, % | 90% confidence interval, %* | *P* |
|---|---|---|---|---|
| 2† (48) | 75.0 | 60.4 | −0.73-29.90 | .482 |
| 6 (47) | 80.9 | 78.7 | −11.42-15.67 | .059 |
| 12 (45) | 80.0 | 84.4 | −18.08-9.19 | .101 |
| 24 (42) | 95.2 | 85.7 | −1.29-20.33 | .202 |
| 36 (41) | 100.0 | 90.2 | 2.13-17.38 | .129 |
| 48 (41) | 97.6 | 85.4 | 2.05-22.34 | .325 |

Efficacy is defined as effective or partially effective by patient rating. The 6-hour time point is the primary outcome.

*The 90% confidence interval for the difference in the proportions of patients' rating of efficacy for each of the treatments (columns 2 and 3). Rejecting the null hypothesis at the .05 level is equivalent, in this setting, to showing that the upper and lower limits of the confidence interval for the difference in efficacy fall within plus or minus 15%.

†Prior to the second dose of NovoSeven.

**Differenza mai significativa sia che ricevessero FEIBA (75-100 IU/kg) o 2 dosi di NovoSeven (90-120 μg/kg).**

**Blood 2007;109:546-51**

# FENOC study: implicazioni per la comune pratica clinica

A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study

Jan Astermark,[1] Sharyne M. Donfield,[2] Donna M. DiMichele,[3] Alessandro Gringeri,[4] Steven A. Gilbert,[2] Jennifer Waters,[2] and Erik Berntorp,[1] for the FENOC Study Group

Blood 2007;109:546-51

**Table 4. Proportion of pairs discordant for rating of treatment outcome**

| Hours after infusion | Efficacy of treatment | | Bleeding stopped | |
|---|---|---|---|---|
| | N | % Discordant pairs | N | % Discordant pairs |
| 2* | 48 | 43.8 | 47 | 40.4 |
| 6 | 47 | 31.9 | 46 | 32.6 |
| 12 | 45 | 31.1 | 45 | 33.3 |
| 24 | 42 | 19.1 | 42 | 14.3 |
| 36 | 41 | 9.8 | 41 | 12.2 |
| 48 | 41 | 17.1 | 41 | 7.3 |

Efficacy is defined as effective or partially effective by patient rating.
*Prior to second dose of NovoSeven.

**Notevole discordanza**

**Ciò implica che lo stesso paziente può esibire una differente risposta di efficacia al trattamento con APCC o rFVIIa, sia pur per episodi emorragici simili.**

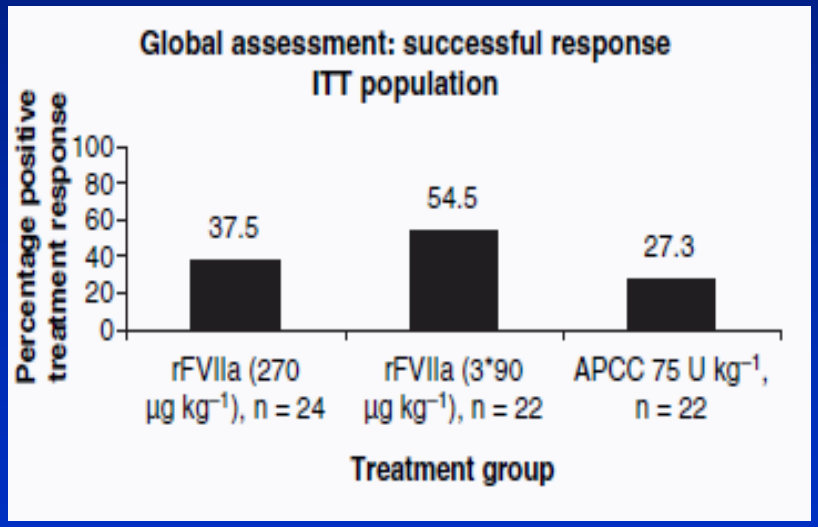
# Studi comparativi head to head

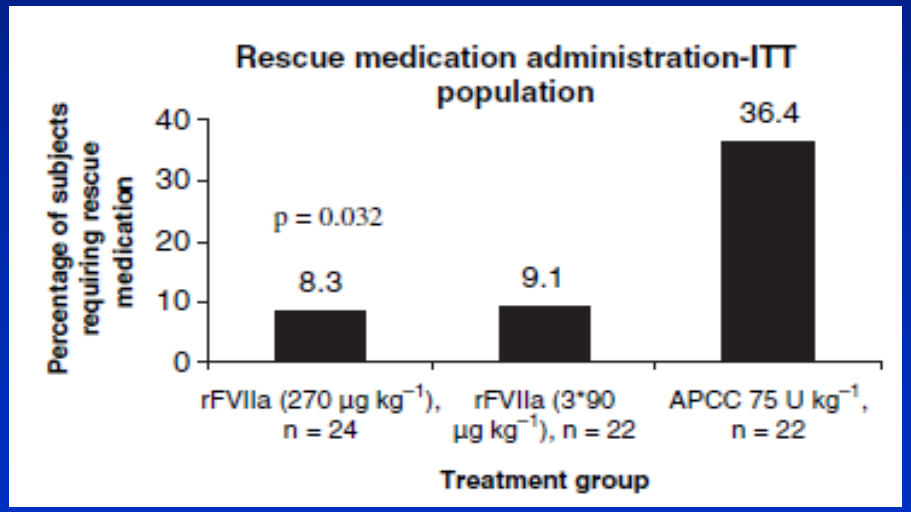
ORIGINAL ARTICLE *Inhibitors*

Single 270 μg $kg^{-1}$-dose rFVIIa vs. standard 90 μg $kg^{-1}$-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison

G. YOUNG,* F. E. SHAFER,† P. ROJAS‡ and S. SEREMETIS§
*Children's Hospital of Orange County, Orange, CA; †St Christopher's Hospital for Children, Philadelphia, PA; ‡Novo Nordisk Inc., Princeton, NJ, USA; and §Novo Nordisk A/S, Bagsværd, Denmark

Haemophilia 2008;14:287-94




**Risultati non significativi tanto che una Crochain Review concludeva che non  vi sono evidenze di maggiore efficacia a vantaggio dell'uno o l'altro bypaassing agent.**

# *Esperienze di profilassi con FEIBA*

| Authors | Year | Total Patients | Patients on ITI | Reduction of Bleeds(mean) |
|---|---|---|---|---|
| Ewenstein B et al. | 2004 | 16 | -- | 53% |
| Ewing N et al. | 2005 | 7 | -- | 68.5% |
| Schino M et al. | 2005 | 4 | -- | 75% |
| DiMichele D, Negrier C. | 2006 | 14 | -- | 53% (10%-85%) |
| Cheng SN et al. | 2006 | 5 | 4 | 90% |
| Leissinger C et al. | 2007 | 5 | -- | 78% |
| Jimenez-Yuste V et al. | 2009 | 5 | -- | 43% |
| Valentino L. | 2009 | 6 | 3 | 84% |
| Lambert T et al. | 2009 | 13 | 5 | 58% |
| Antunes M et al. | 2009 | 2 | -- | 53% (38%-83%) |
| TOTAL | | 77 | 12 | 65.6% |

La profilassi con FEIBA riduce di circa 2/3 il rate di sanguinamento

# Profilassi con rFVIIa (studio retrospettivo):

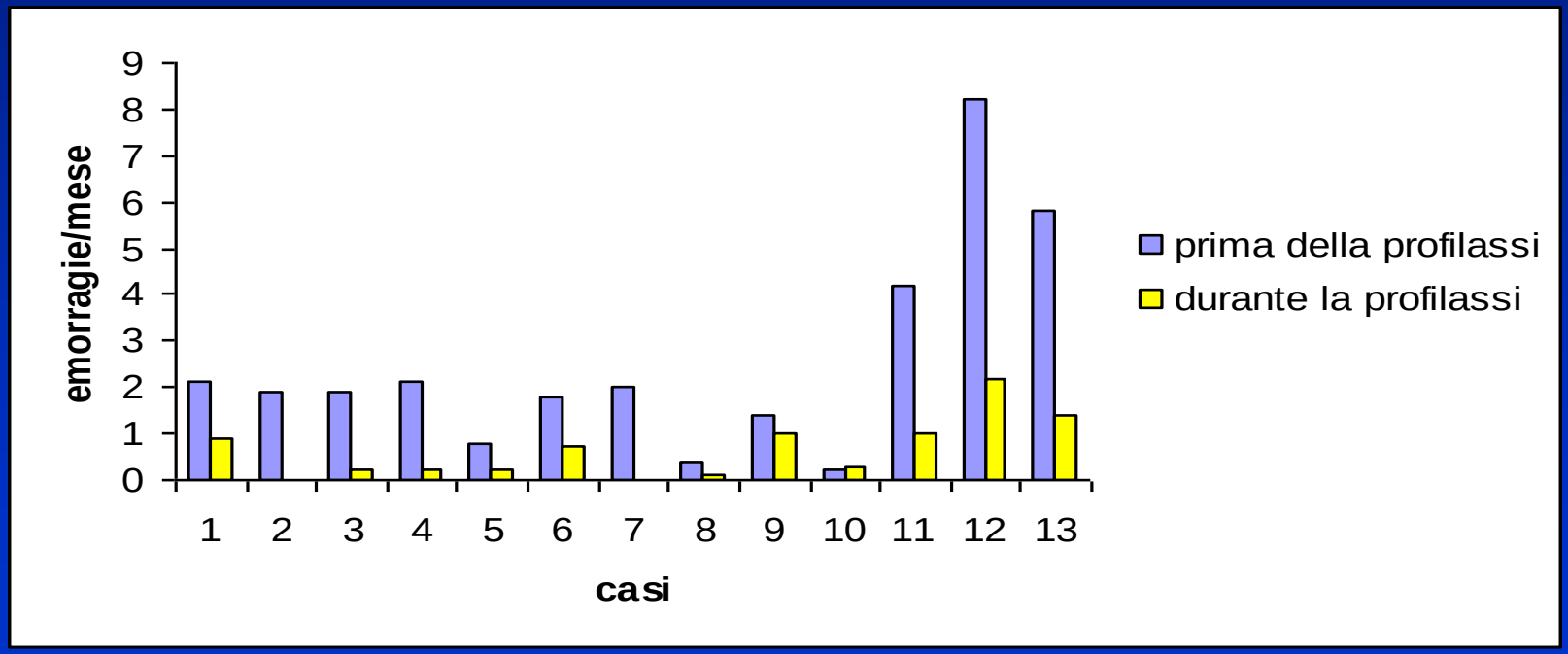
*Haemophilia* (2007), 13, 502–507 DOI: 10.1111/j.1365-2516.2007.01455.x

Prophylactic treatment of haemophilia patients with inhibitors: clinical experience with recombinant factor VIIa in European Haemophilia Centres

M. MORFINI,* G. AUERSWALD,† R. A. KOBELT,‡ G. F. RIVOLTA,§ J. RODRIGUEZ-MARTORELL,¶ F. A. SCARAGGI,** C. ALTISENT,†† J. BLATNY,‡‡ A. BOREL-DERLON§§ and V. ROSSI¶¶

13 pazienti
diversi regimi di trattamento
(200 µg/Kg/sett – 220 µg/Kg/die)

## Numero Emorragie/mese




*Morfini M et al Haemophilia 2007;13: 502-7*

# PRO-PACT: Retrospective observational study on the prophylactic use of recombinant factor VIIa in hemophilia patients with inhibitors

Guy Young [a,*], Guenter Auerswald [b], Victor Jimenez-Yuste [c], Thierry Lambert [d], Massimo Morfini [e], Elena Santagostino [f], Victor Blanchette [g]

| Sub-population | n | Study Period | | |
|---|---|---|---|---|
| | | Pre-Prophylaxis [Bleeds per month (95%CI)] * | Prophylaxis [Bleeds per month (95%CI)] * | Pre vs. Prophylaxis [% change (95%CI)] |
| **Bleeding Population**† | 74 | 1.37 (1.26,1.49) | 0.74 (0.69,0.79) | −45.99 (−54.02,-38.22) |
| Age Categories | | | | |
| Pediatric Patients (<12 Years) | 54 | 1.31 (1.19,1.45) | 0.68 (0.63,0.74) | −48.09 (−57.14,-38.68) |
| Adolescent Patients (12–17 Years) | 7 | 1.1 (0.80,1.46) | 1.09 (0.92,1.33) | −0.91 (−33.01,+35.13) |
| Adult Patients (≥18 Years) | 13 | 1.81 (1.53,2.21) | 0.79 (0.65, 0.95) | −56.35 (−73.74,-40.37) |
| Dosing Categories‡ | | | | |
| Infrequent dosing | 1 | 1.98 (1.02,3.46) | 1.85 (1.26,2.62) | −6.57 (−70.95,+57.90) |
| Dosing 2–4 times/week | 32 | 1.59 (1.41,1.80) | 0.76 (0.68,0.85) | −52.2 (−63.57,-41.28) |
| Daily dosing | 29 | 1.3 (1.14,1.49) | 0.67 (0.60,0.75) | −48.46 (−60.79,-36.22) |
| Frequent Dosing | 11 | 0.94 (0.71,1.23) | 0.77 (0.65,0.92) | −18.09 (−46.30,+10.67) |
| **Frequent Bleeding Population**§ | 36 | 2.1 (1.91,2.31) | 1.01 (0.93,1.10) | −51.9 (−60.74,-43.33) |
| Age Categories | | | | |
| Pediatric Patients (< 12 Years) | 27 | 1.99 (1.78,2.22) | 0.86 (0.78,0.96) | −56.78 (−66.55,-46.78) |
| Adolescent Patients (12–17 Years) | 3 | 1.74 (1.19,2.46) | 1.84 (1.45,2.29) | 5.75 (−36.66,+47.72) |
| Adult Patients (≥18 Years) | 6 | 2.79 (2.31,3.48) | 1.41 (1.13,1.74) | −49.46 (−70.78,-30.19) |
| Dosing Categories‡ | | | | |
| Infrequent dosing | 1 | 1.98 (1.02,3.46) | 1.85 (1.26,2.62) | −6.57 (−70.95,+57.90) |
| Dosing 2–4 times/week | 17 | 2.23 (1.95,2.55) | 0.96 (0.85,1.09) | −56.95 (−68.72,-45.29) |
| Daily dosing | 15 | 2(1.73, 2.32) | 0.81 (0.69,0.94) | −59.5 (−73.10,-46.45) |
| Frequent Dosing | 3 | 1.92 (1.34,2.67) | 2.56 (1.98,3.25) | 33.33 (−13.76,+80.69) |

*Thrombosis Research 2012; 130:864-70*

# *STUDIO rFVIIa randomizzato: disegno*


**2 bracci di trattamento:**

**10 pazienti trattati con 90 µg/kg/die rFVIIa per 3 mesi**

**10 pazienti trattati con 270 µg/kg/die per 3 mesi**

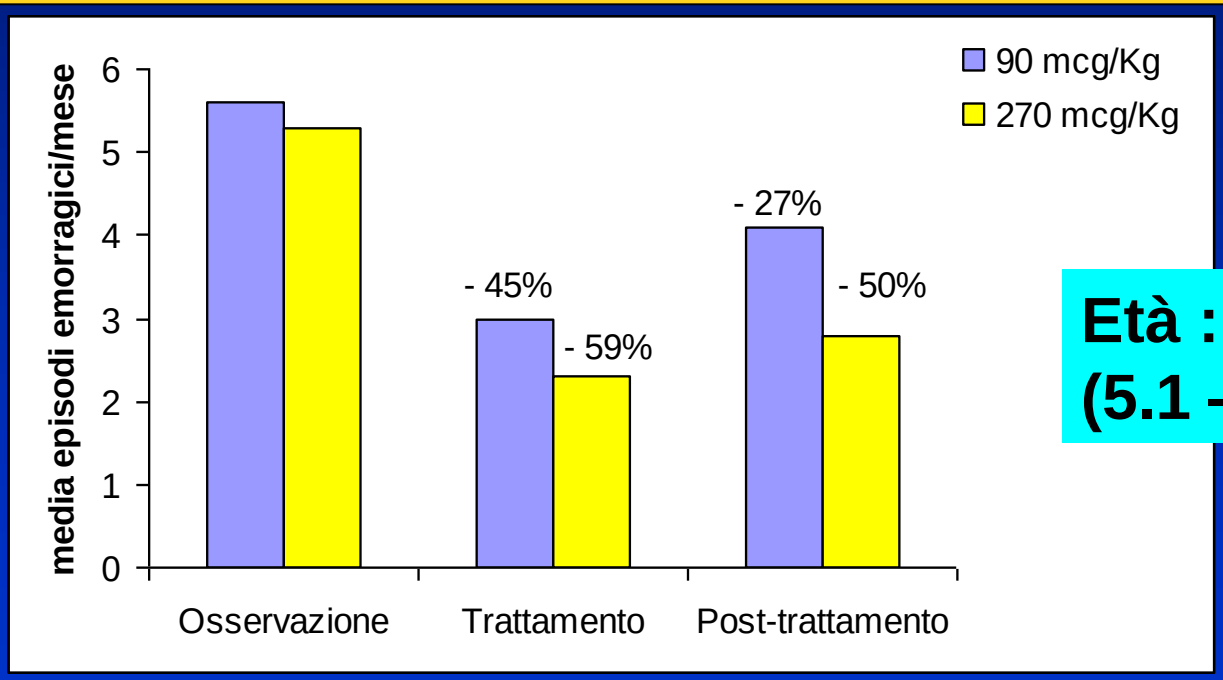
**Età : mediana 15.7 (5.1 – 56.1)**

*Konkle BA et al. J thromb Haemost 2007; 5: 1904-13*

# Profilassi Secondaria con rFVIIa

*Konkle BA et al. J thromb Haemost 2007; 5: 1904-13*

**Criteri di arruolamento:**
**almeno 12 episodi emorragici nei 3 mesi di osservazione pre-profilassi (almeno 2/mese)**




**Età : mediana 15.7 (5.1 – 56.1) anni**

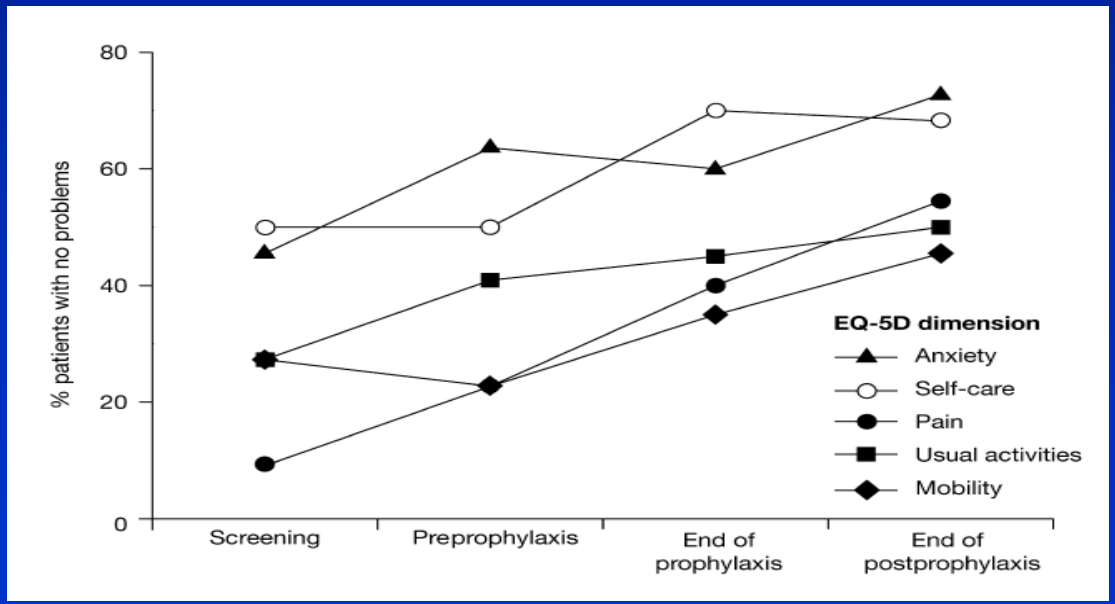
*Significativa riduzione del numero di eventi emorragici anche nei 3 mesi di osservazione post-profilassi*

# STUDIO rFVIIa randomizzato:

*Konkle BA et al. J thromb Haemost 2007; 5: 1904-13*

## Valutazione della QoL

**Screening** **Pre-profilassi** **Post-profilassi** **Termine osservazione Post profilassi**




**Questionario EQ-5D**

*Hoots WK et al. Haemophilia 2008; 14:466-75*

# Pro-FEIBA Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

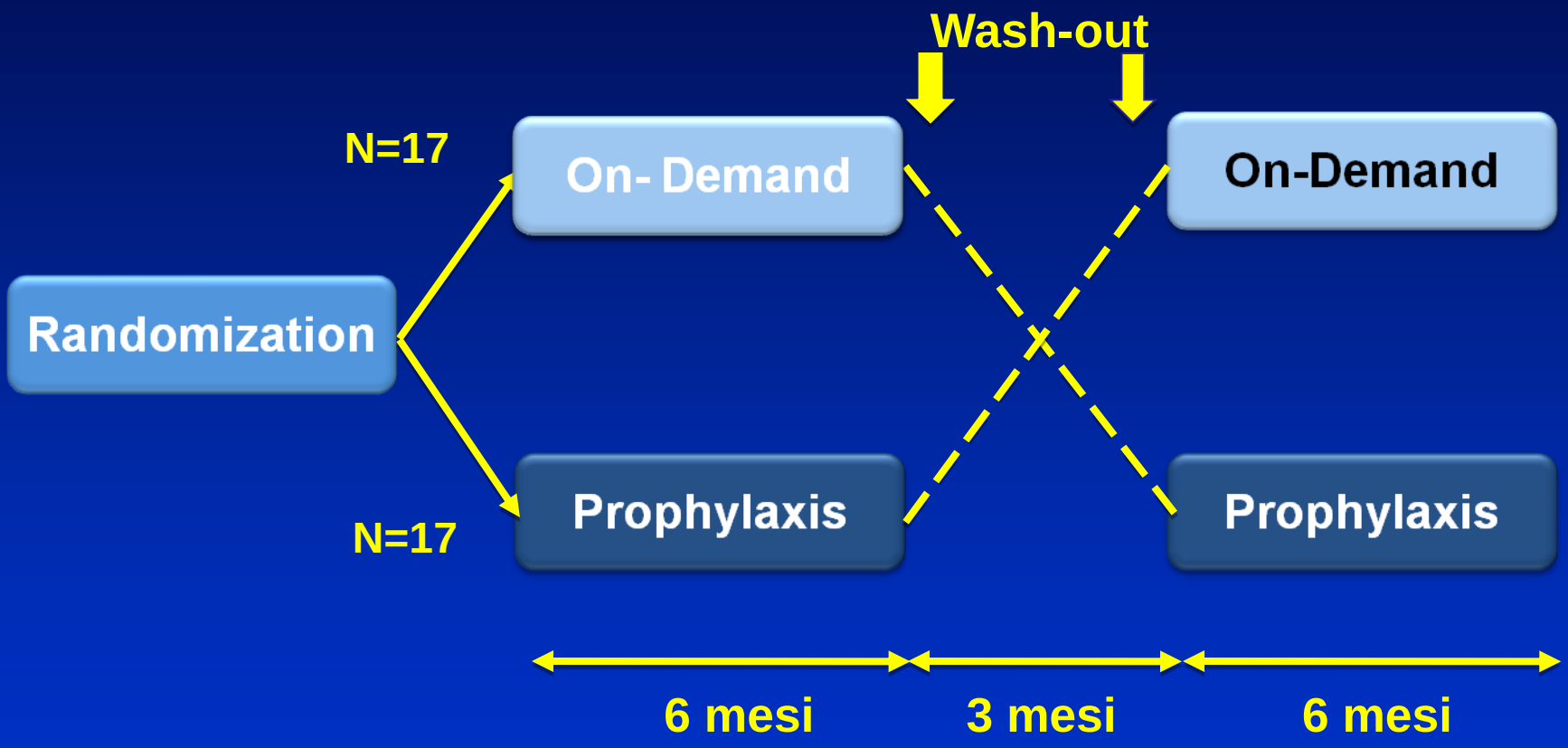
## Anti-Inhibitor Coagulant Complex Prophylaxis in Hemophilia with Inhibitors

Cindy Leissinger, M.D., Alessandro Gringeri, M.D., Bülent Antmen, M.D., Erik Berntorp, M.D., Chiara Biasoli, M.D., Shannon Carpenter, M.D., Paolo Cortesi, M.Sc., Hyejin Jo, M.S., Kaan Kavakli, M.D., Riitta Lassila, M.D., Massimo Morfini, M.D., Claude Négrier, M.D., Angiola Rocino, M.D., Wolfgang Schramm, M.D., Margit Serban, M.D., Marusia Valentina Uscatescu, M.D., Jerzy Windyga, M.D., Bülent Zülfikar, M.D., and Lorenzo Mantovani, D.Sc.

ABSTRACT

*N Engl J Med 2011; 365: 1684-92*

# *Disegno dello studio Pro-FEIBA*

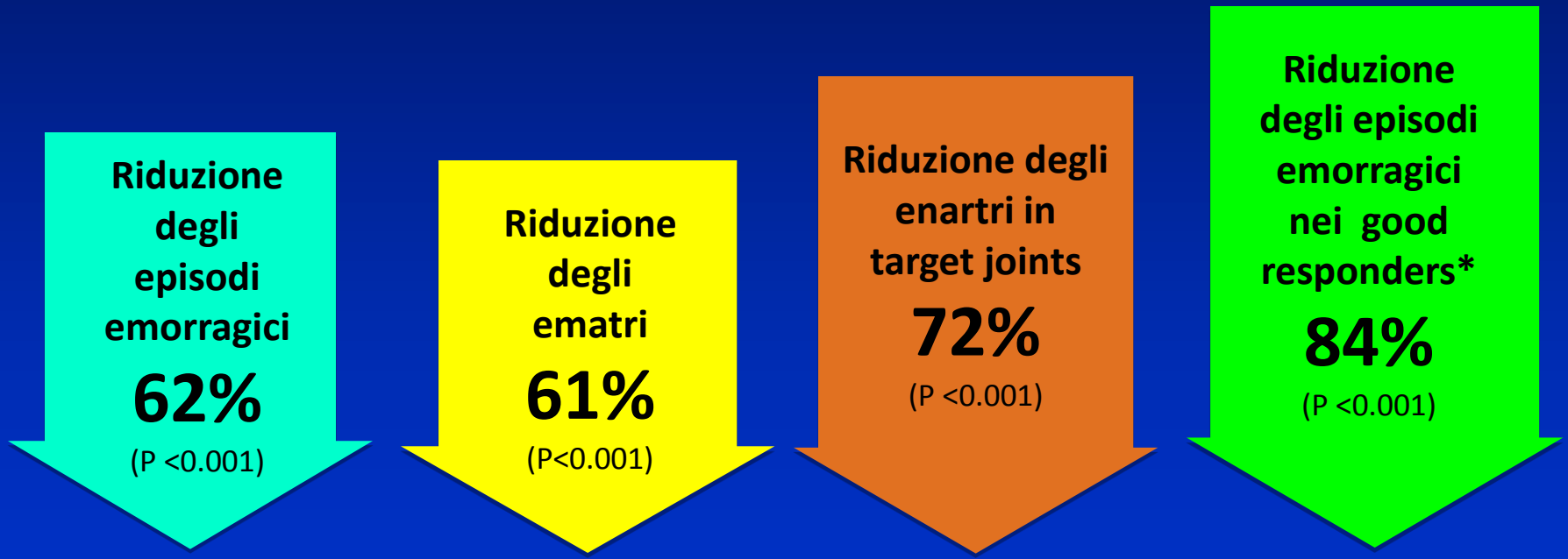



Profilassi: FEIBA 85 U/Kg ± 15% 3 giorni non consecutivi per settimana
On-demand : FEIBA 85U/Kg ± 15%

# Pro-FEIBA: Risultati

26 pazienti valutabili; età mediana 28.7 anni (3-63); 6 pazienti (23%) età <12 anni.

In confronto a trattamento a domanda con FEIBA




*Good responders mostravano una riduzione ≥50% del numero di episodi emorragici.

*Leissinger C et al. N Engl J Med. 2011;365:1684-1692.*

# Pro-FEIBA Study - QoL

Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study

A. GRINGERI,* C. LEISSINGER,† P. A. CORTESI,‡ H. JO,§ F. FUSCO,¶ S. RIVA,**
B. ANTMEN,†† E. BERNTORP,‡‡ C. BIASOLI,§§ S. CARPENTER,¶¶ K. KAVAKLI,***
M. MORFINI,††† C. NÉGRIER,‡‡‡ A. ROCINO,§§§ W. SCHRAMM,¶¶¶ J. WINDYGA,****
B. ZÜLFIKAR†††† and L. G. MANTOVANI‡‡‡‡

Haemophilia *2013; 19: 736-43*

**Valutata mediante SF-36 e EQ-52 in 18/19 pazienti di età >14 anni.**

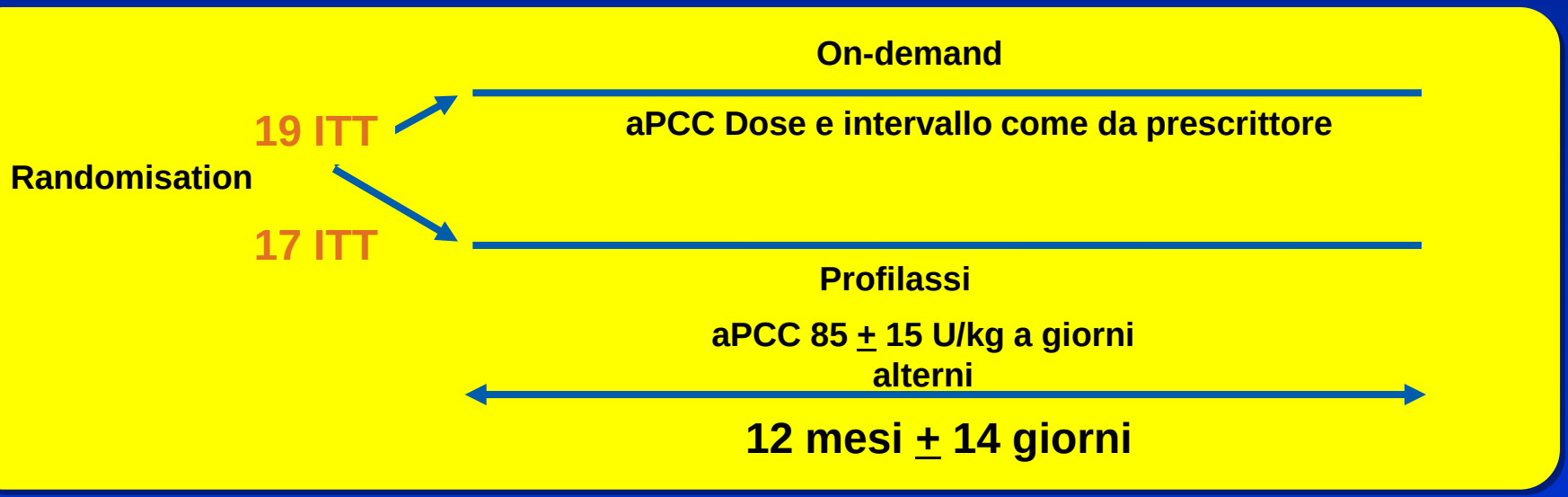
**Dopo aver ricevuto 6 mesi di profilassi con APCC, i pazienti 'good responders', definiti come coloro che manifestavano una riduzione del 50% degli episodi emorragici, manifestavano una riduzione significativa del dolore cronico (P = 0.015) e della capacità di partecipazione sociale (P = 0.036).**

# PROOF-Study
## (randomizzato a gruppi paralleli)

ORIGINAL ARTICLE *Clinical haemophilia*

### Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors

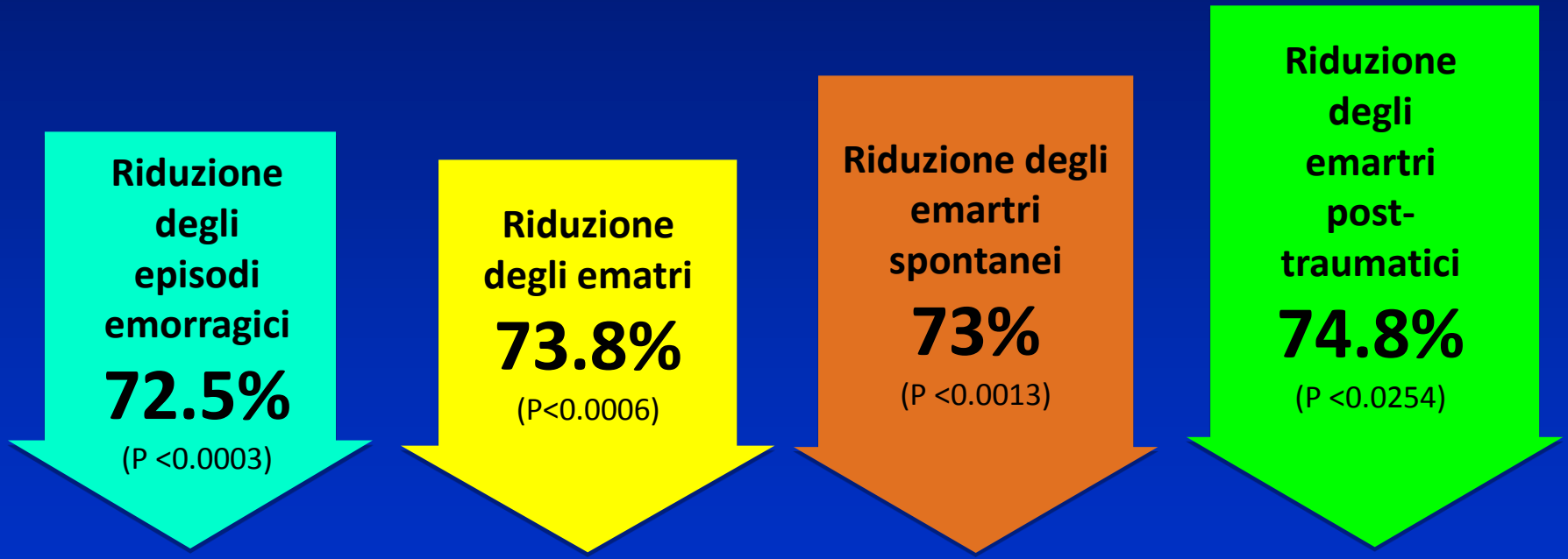
S. V. ANTUNES,* S. TANGADA,† O. STASYSHYN,‡ V. MAMONOV,§ J. PHILLIPS,¶ N. GUZMAN-BECERRA,† A. GRIGORIAN,† B. EWENSTEIN† and W.-Y. WONG†
*UNIFESP, São Paulo, Brazil; †Baxter Healthcare Corporation, Westlake Village, CA, USA; ‡Institute of Blood Pathology and Transfusion Medicine under the Ukrainian National Academy of Medical Sciences, Lviv, Ukraine; §Department of Reconstructive Orthopedic Surgery for Hemophilia Patients, Moscow, Russia; and ¶Wellington Hospital, Wellington South, New Zealand




*Haemophilia 2014; 20: 65-72*

# ***Proof: Risultati***

## In confronto a trattamento a domanda con FEIBA




Antunes SV et al. ***Haemophilia 2014; 20: 65-72***

# *Proof: altri risultati*

**Nel gruppo di trattamento in profilassi**

**l'ABR nel secondo semestre di trattamento è del 26% più basso (5.9 vs 8) anche se la differenza non raggiunge la significatività statistica**

**Comparsa di nuove articolazioni bersaglio**

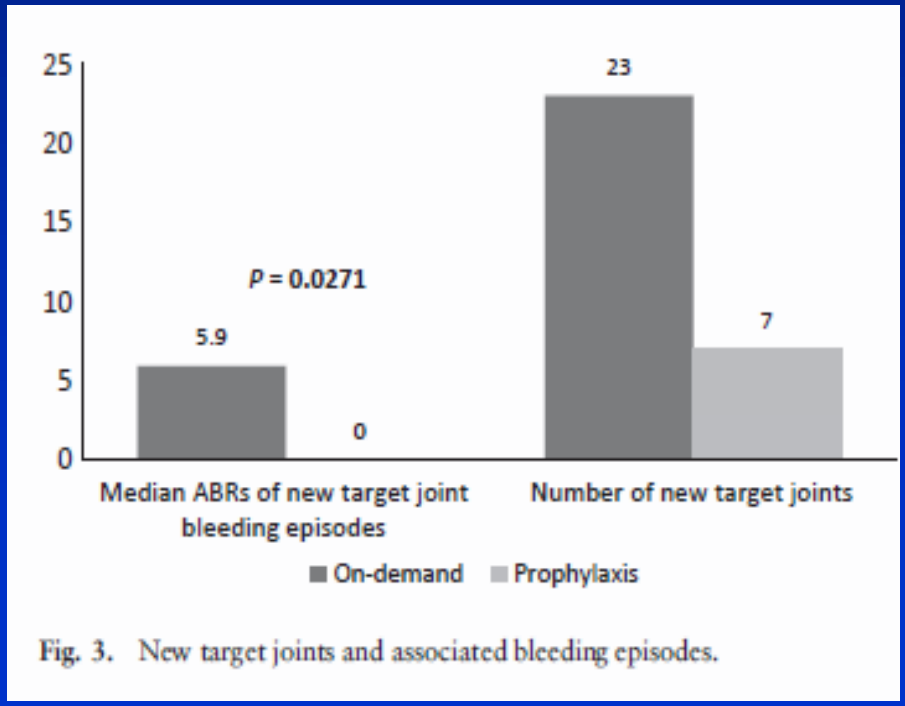



Fig. 3. New target joints and associated bleeding episodes.

# Proof Study - QoL

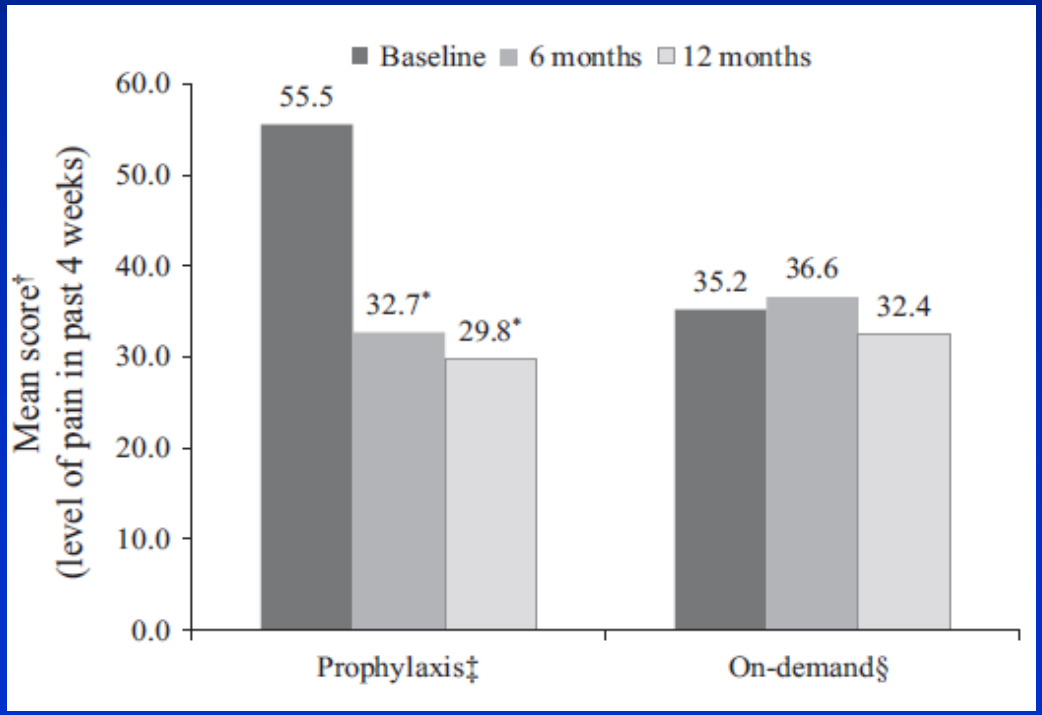
Prophylaxis with anti-inhibitor coagulant complex improves health-related quality of life in haemophilia patients with inhibitors: results from FEIBA NF Prophylaxis Study

O. STASYSHYN,* S. ANTUNES,† V. MAMONOV,‡ X. YE,§ J. EPSTEIN,¶ Y. XIONG¶ and S. TANGADA¶

Haemophilia *2014; 20: 644-50*

**17 pazienti in profilassi**
**15 on demand**

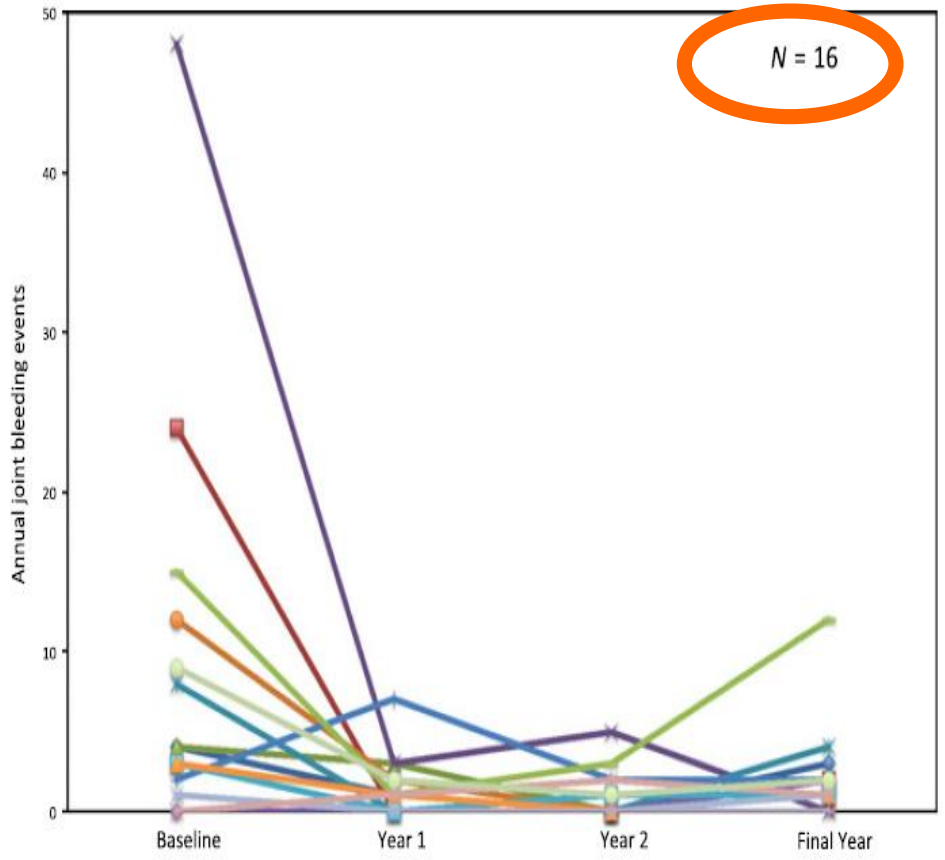
**Media VAS per general pain scores**



# Prophylaxis with FEIBA in paediatric patients with haemophilia A and inhibitors

N. EWING,* C. ESCURIOLA-ETTINGSHAUSEN† and W. KREUZ†
*City of Hope National Medical Center, Duarte, CA, USA; and †HZRM - Hemophilia Centre Rhein Main, Moerfelden-Waldorf, Germany

**Età media: 7.5 ± 3.6 anni**




**Joint status score**

| Patient ID | US1 | US2 | US3 | US4 | US5 | US6 | US7 |
|---|---|---|---|---|---|---|---|
| | United States | | | | | | |
| Baseline joint status | 6 | 5 | 0 | 7 | 11 | 12 | 11 |
| Joint status at last evaluation* | 5 | 3 | 0 | 5 | 6 | 3 | 2 |

| Patient ID | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 |
|---|---|---|---|---|---|---|---|---|---|
| | Germany | | | | | | | | |
| Baseline joint status | 0 | 0 | 0 | 0 | 0 | 17 | 0 | 10 | 0 |
| Joint status at last evaluation* | 1 | 0 | 4 | 0 | 1 | 15 | 3 | 8 | 1 |

*Haemophilia, 2015*

# *Profilassi nei pazienti con inibitore? Chi, quando, perchè*

**Quando?**

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

**Chi?**

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

**Perchè?**

**Migliorare la QoL**

# Raccomandazioni all'uso della profilassi

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

**Haemophilia, 2007**

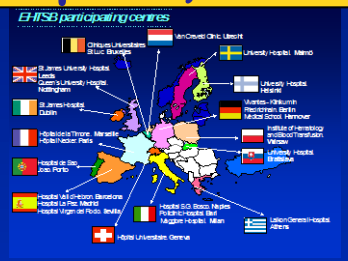
International workshop on immune tolerance induction: consensus recommendations[1]

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

**Haemophilia, 2007**

Current use of by-passing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors

J. ASTERMARK,* A. ROCINO,† M. VON DEPKA,‡ H. M. VAN DEN BERG,§ A. GRINGERI,¶ L. G. MANTOVANI,** M. MORADO,†† R. P. GARRIDO,‡‡ M. SCHIAVONI,§§ A. VILLAR†† and J. WINDYGA,¶¶ ON BEHALF OF THE EHTSB[1]




**Haemophilia, 2010**

FEIBA prophylaxis in haemophilia patients: a clinical update and treatment recommendations

D. PERRY,* E. BERNTORP,† C. TAIT,‡ G. DOLAN,§ P. A. HOLME,¶ M. LAFFAN,** R. LASSILA,†† A. MUMFORD,‡‡ J. PASI,§§ J. WILDE,¶¶ A. WILL*** and T. T. YEE†††

**Haemophilia, 2011**

When should prophylaxis therapy in inhibitor patients be considered?

G. YOUNG,* G. AUERSWALD,† V. JIMENEZ-YUSTE,‡ B. A. KONKLE,§ T. LAMBERT,¶ M. MORFINI,** E. SANTAGOSTINO†† and V. BLANCHETTE‡‡

bjh guideline

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

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

*[1]School of Medicine, Cardiff University, University Hospital of Wales, Wales, [2]Royal Hospital for Sick Children, Glasgow, [3]The London School of Medicine and Dentistry, Royal London Hospital, Barts, Queen Mary University, London, [4]Great Ormond Street NHS Trust, London, [5]Hampshire Hospital NHS Foundation Trust, Basingstoke & North Hampshire Hospital, Basingstoke, [6]Royal Victoria Infirmary, Newcastle upon Tyne, [7]Birmingham Childrens' Hospital NHS Foundation Trust, Birmingham and [8]Central Manchester University Hospitals, Manchester, UK*

*Br J Haematol 2013;160: 153-70*

# 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

*Rush University Medical Center, Chicago, IL; †Emory University School of Medicine, Atlanta, GA; ‡Puget Sound Blood Center/University of Washington, Seattle, WA; §University of New Mexico, Albuquerque, NM; ¶Aflac Cancer and Blood Disorders Center, Emory University/Children's Healthcare of Atlanta, Atlanta, GA; and **St. Jude Children's Research Hospital, Memphis, TN, USA*

**Haemophilia, 2015**

**Before initiating ITI in patients with an inhibitor titre >5 BU/mL who bleed frequently, bypassing agent prophylaxis may be considered (1A).**

**In patients who bleed frequently during ITI, bypassing agent prophylaxis can be used concomitantly with FVIII (even at doses of 200 IU/kg/day) until the inhibitor titre is <1 BU/mL (2C).**

## *Problemi aperti:*

**E’ possibile prevenire l’insorgenza di artropatia cronica in bambini con inibitore**

**Come modulare la profilassi con agenti bypassanti negli emofilici con inibitore**

**Quale dose utilizzare inizialmente**

**E' possibile prevenire la comparsa dell'inibitore ?**

## *Profilassi nel paziente con inibitore: la scelta terapeutica*

***deve tenere in conto:***

- **Evidenze di efficacia**
- **Caratteristiche del prodotto**
- **Risposta individuale del paziente**
- **Costo-efficacia**
- **Esperienza personale del clinico**
- **Preferenze del paziente**