

Refinements in the use and dosage of rVIIa to improve patient care

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Declaration of conflict

- I received air fare support from Novo Nordisk Malaysia to attend and present at the AHF/Malaysian Society of Haematology meeting
- My acknowledgements and thanks to medical affairs departments at Novo Nordisk Malaysia and Denmark for their support in slide preparation

Topics for Discussion

- Background to Inhibitors
 - Treatment of Inhibitors
 - Difficulties in delivery of care
 - Recent studies in refinements of use of r FVIIa
 - Practice Guidelines
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- Questions and Comments

Haemophilia facts

- Estimates suggest haemophilia A and B affect approximately 400,000 males worldwide¹
- A considerable proportion of patients develop inhibitors (neutralising antibodies) of factors VIII (FVIII) or IX (FIX) after exposure to factor concentrates²
 - 15–30% of patients with haemophilia A (FVIII)
 - 3–5% of patients with haemophilia B (FIX)
- Approximately 10% of all patients with treated haemophilia in have inhibitors (prevalence)³

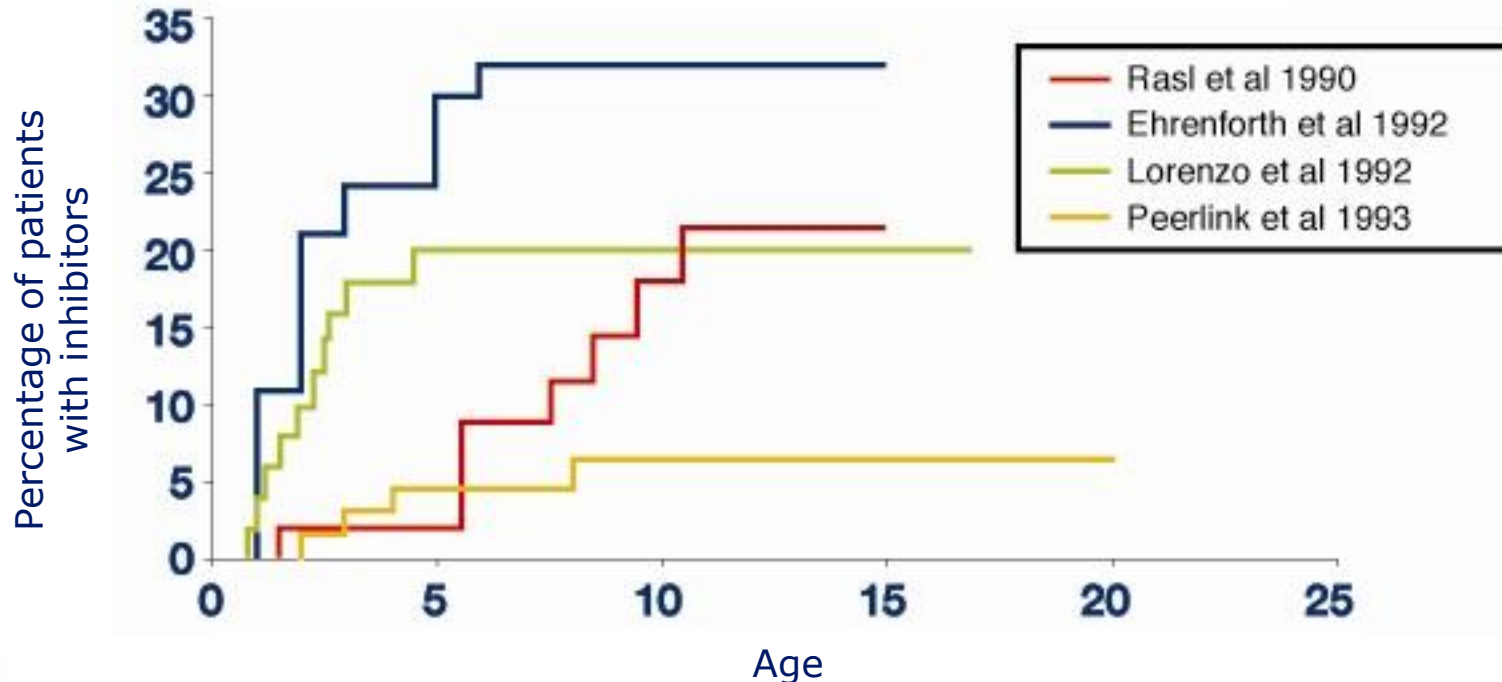
The problem of inhibitors

- Patients with severe mutations in the hemophilia gene, such as deletions or inversions, are most likely to develop inhibitors
- Development of low titre inhibitors (<5 BU) may indicate transient formation, but high titres (≥ 5 BU) tend to be persistent and recur with rechallenge in the absence of an immune tolerance program
- Antibodies (inhibitors) against FVIII or FIX render clotting factors ineffective and make the management of bleeding episodes more difficult

Inhibitors develop at an early age

- Typically, inhibitors develop in early childhood within 10–20 exposure days to FVIII or FIX¹
 - Rarely, treated adults can develop inhibitors (<3%)

Cumulative risk of inhibitor development²



Treatment of Inhibitors

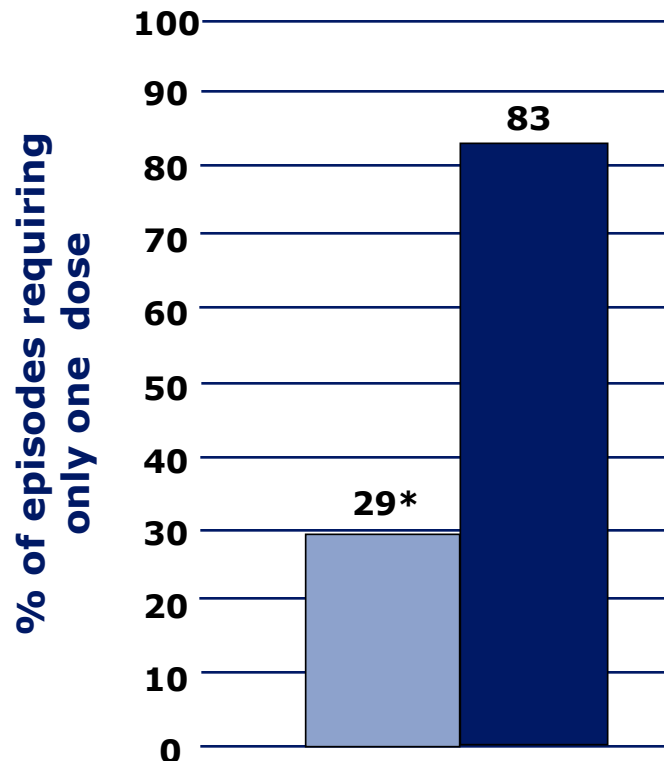
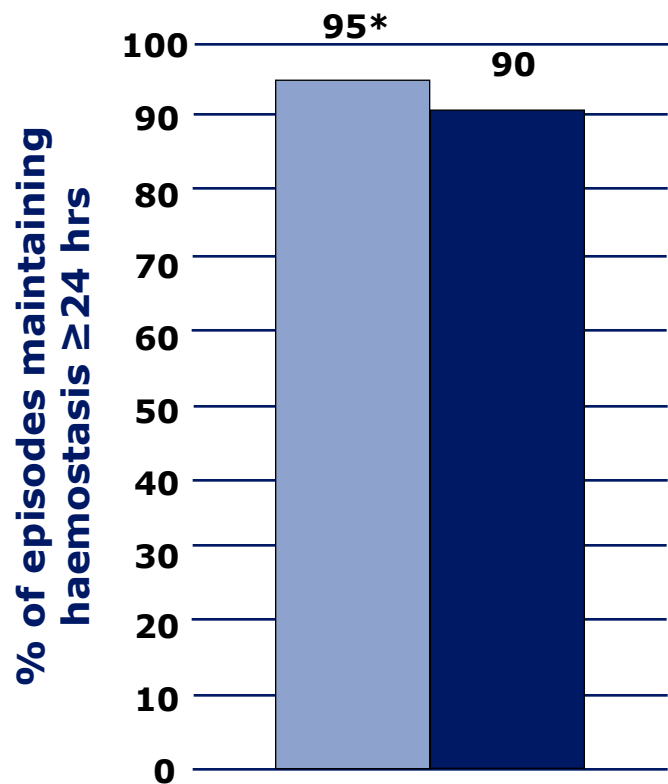
- Factor concentrates
- Prothrombin Complex Concentrates
- Activated Prothrombin Complex Concentrates*
- Recombinant F VIIa*
- Immunosuppression/ Immunomodulation

* Bypassing therapies

Dosing of r VIIa

- Initial registration based on 90ug/kg doses
- Requires 2 hourly reinfusion interval
- Average requirement to control haemarthroses 2-3 doses

Rationale for less frequent dosing



Key et al. study (90 µg/kg, n=614)
*Mean no. of injections = 2.2
Kenet et al. study (300 µg/kg, n=114)

Kenet G. *J Thromb Haemost* 2003; 1:450-455.
Key NS. *Thromb Haemost* 1998; 80:912-918.

Haemostasis with higher NovoSeven[®] doses

“Bolus doses (>200 µg/kg) were significantly more efficacious with an overall bleed cessation rate of 97%, with the lowest reported mean and median number of doses. An initial high bolus dose was associated with significantly higher response rates.”

– R Parameswaran, 2005

Prospective studies show

- Single dose 270 µg/kg treatment with NovoSeven® will improve convenience and increase patients' quality of life
- A single dose of NovoSeven 270 µg/kg and three doses of NovoSeven 90 µg/kg are both effective treatment options to achieve haemostasis
- A single dose of NovoSeven 270 µg/kg and three doses of NovoSeven 90 µg/kg are both safe in treating bleeding

Hacker MR. *Haemophilia*. 2001; 7:392-396.

Kavakli K. *Thromb Haemost* 2006; 95:600-605.

Kenet G. *J Thromb Haemost* 2003; 1:450-455.

Kenet G. *Semin Hematol* 2006; 43(1 Suppl 1):S108-S110.

Key NS. *Thromb Haemost* 1998; 80:912-918.

Manco-Johnson MJ. *Semin Hematol* 2003; 40(3 Suppl 3):3-9.

NovoSeven® Product Monograph.

Parameswaran R. *Haemophilia* 2005; 11:100-106.

Santagostino E. *J Thromb Haemost* 2006; 4:367-373.

Young et al. *Haemophilia* 2007.

In practice

- Reports confirm that doses $>200\mu\text{g}/\text{kg}$ are effective in single dosage in treating joint bleeds
- These dose protocols have not been studied in the long term frequent use of r FVIIa
e.g. in treatment of intra-cranial haemorrhage, surgery etc.

Prophylaxis in patients with haemophilia

- Prophylaxis is a program of administration of clotting factors at regular intervals to prevent bleeding episodes¹
 - Reduces bleeding frequency, helps to preserve joint function and improves quality of life^{1,2}
- Prophylaxis is used to manage haemophilia complications in patients without inhibitors³
 - Recommended by national and international authorities in almost all patients with severe haemophilia⁴

'The goal of all haemophilia care programs until a cure is available.'³

Types of prophylaxis

Management strategy	Definition
Primary prophylaxis (by age)	Long-term continuous* treatment started before 2 years of age, prior to any clinical evidence of joint bleeding
Primary prophylaxis (by first bleed)	Long-term continuous* treatment started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed) irrespective of age
Secondary prophylaxis	Long-term continuous* treatment not fulfilling the criteria for primary prophylaxis
Short-term prophylaxis	Short-term treatment to prevent bleeding
On demand treatment	Treatment given when bleeding occurs

*with the intent of treating 52 weeks/year up to adulthood and receiving treatment for ≥ 46 weeks/year

Prophylaxis for patients without inhibitors

- Effective haemophilia management includes coagulation factor replacement therapy for:¹
 - On-demand treatment of acute bleeding episodes
 - Primary prophylaxis (up to 3 times per week)
 - Secondary prophylaxis to manage severely affected target joints
 - Reductions in bleeding frequency of approximately 65% have been reported over a 1-year period²

Prophylaxis for Patients with Inhibitors

- Patients with persistent, high titres of inhibitors are at greater risk for serious bleeding episodes and debilitating joint disease¹
 - Unmet need for effective preventive treatment (prophylaxis) in these patients
- Standard FVIII and FXI concentrates cannot be used because they are ineffective¹
- Prophylaxis not widely practiced due to a lack of published data, and concerns about insufficient efficacy and thrombotic effects². despite an at least equal need to reduce further bleeds and joint damage

Report from a prospective study

Inclusion

- Patients with haemophilia A/B
- Inhibitor titre >2 BU/mL
 - In preceding 12 months
- Requirement for treatment using a bypassing agent
- Occurrence of >4 bleeds in the previous month
- Adequate venous access for daily infusion (270 vs 90ug/kg/day))

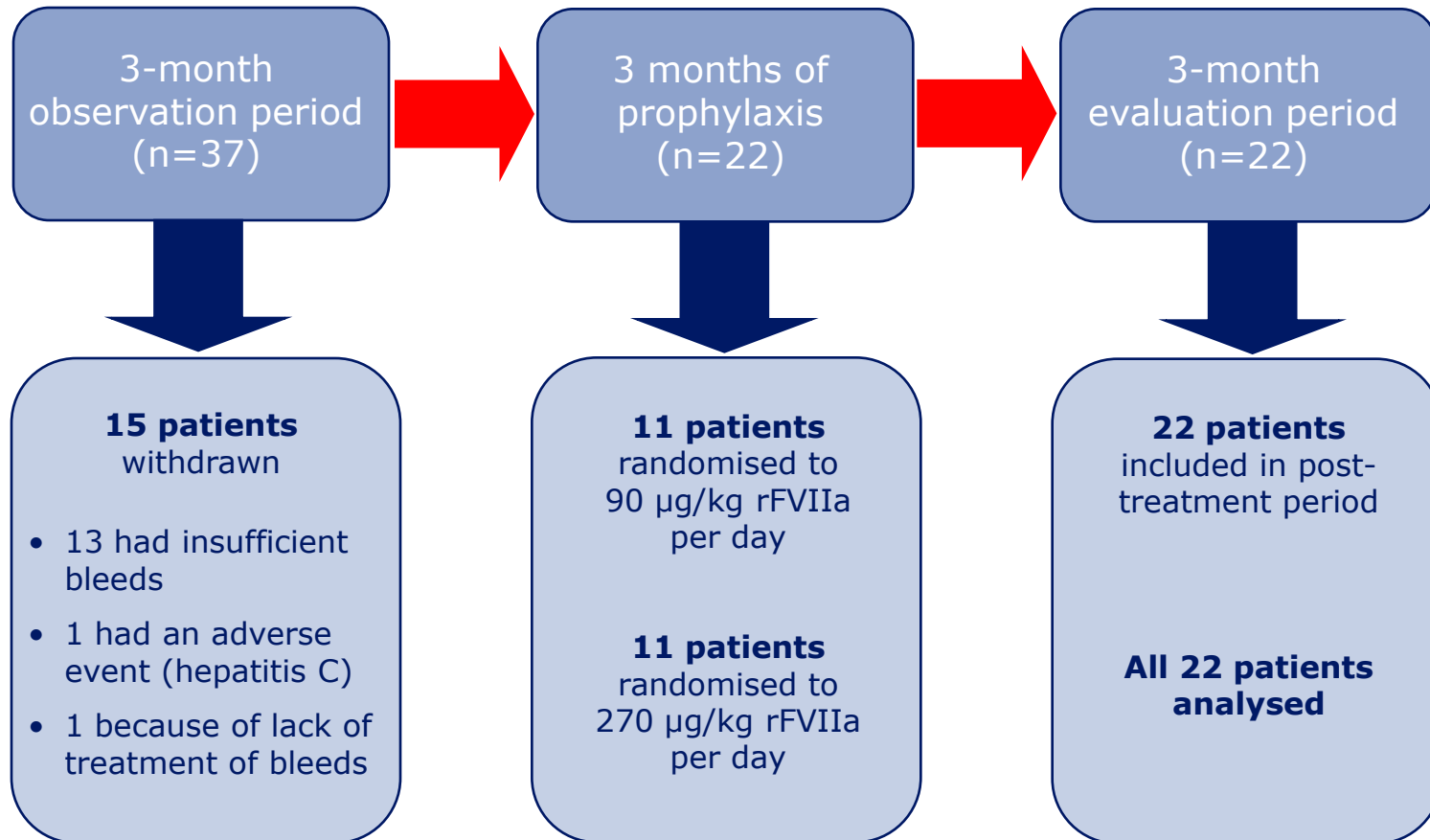
Exclusion

- Prophylaxis with any haemostatic drug during the previous 3 months
- ITT attempted within the month prior to enrolment
- Known pseudo-tumours
- Platelet count $<50,000$ cells/ μ L
- Advanced atherosclerotic disease
- Congenital/acquired bleeding disorders other than haemophilia A/B

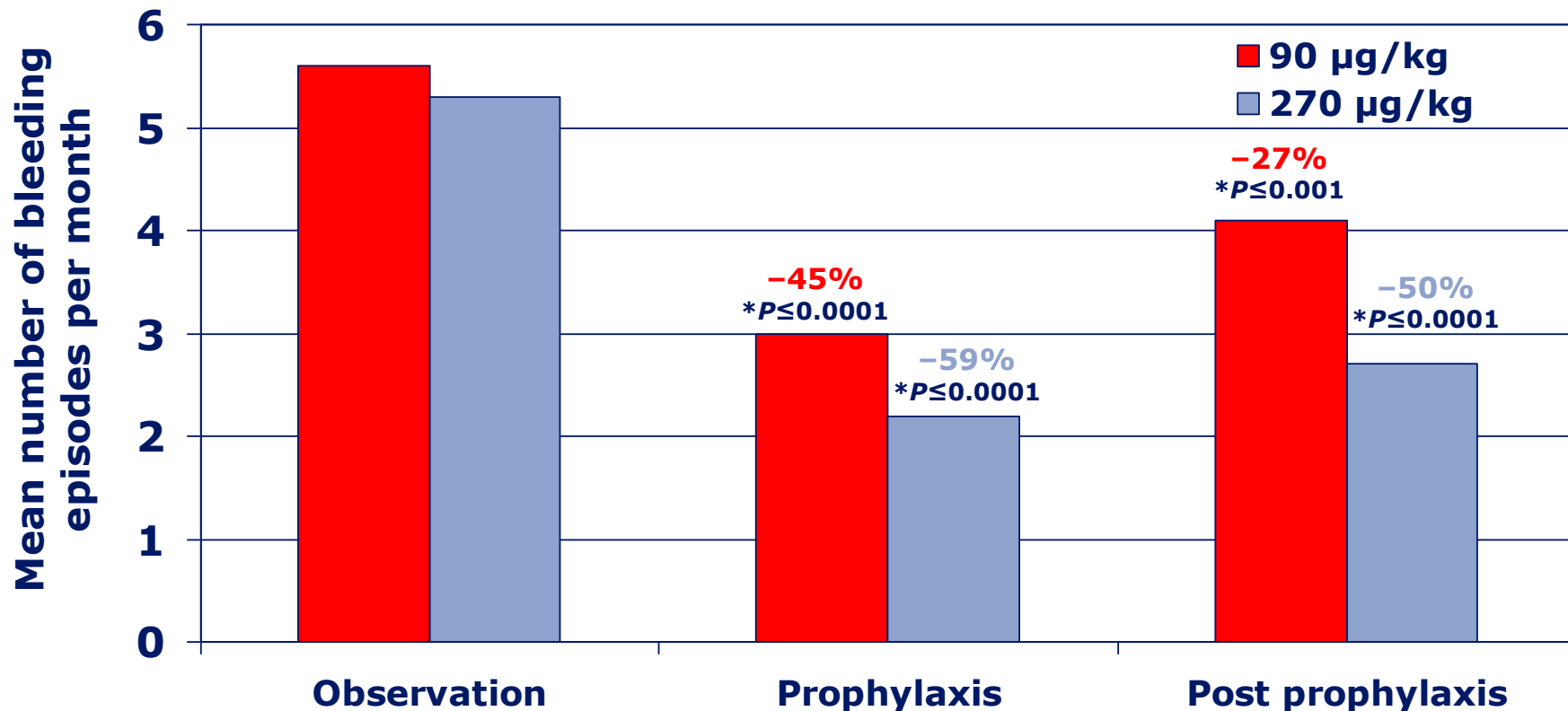
Protocol

Primary endpoint

The total number of bleeds during prophylaxis compared with the observation period



With three months daily prophylaxis



*P values are for change in number of bleeds per month vs observation period

n=11 patients in each group

Comments on study

- During the prophylaxis and post-prophylaxis periods rFVIIa reduced
 - **The number of days spent in hospital**
 - **The number of days patients were absent from work or school**
- In addition, patients reported fewer pain and mobility problems during the treatment and post-treatment periods
- The post prophylaxis reduction has not been studied beyond 3 months and presumably is due to settling target joints similar to secondary prophylaxis in patients without inhibitors

Conclusions from study

- The prospective multidose study of rVIIa results showed that in frequently bleeding haemophilia patients with inhibitors secondary prophylaxis with rFVIIa over a 3-month period:
 - **Halved the frequency of bleeding episodes, particularly spontaneous joint bleeds, compared with on-demand treatment**
 - **Achieved significant reductions in the frequency of spontaneous and target joint bleeds that are sustained after prophylaxis for ≥ 3 months**
 - **Improved patient quality of life and reduces the frequency of hospital visits and absences from work or school**
 - **Was not associated with any unexpected safety concerns**

How should we proceed?

- Registration of Novoseven for secondary prophylaxis has followed this report
- Careful selection of patients (consistent with the study) required
- Further studies are needed to establish the optimum dose and duration of treatment (which may require individual tailoring)
- Clinical and Cost effectiveness reviews are required to establish and continuously review policies and protocols in all aspects of hemophilia treatment including those for inhibitors
- So how do we use this data in practice?

There are challenges in delivering haemophilia care

- Depends on the model for Haemophilia Care within a country or region
- Education and Training of professionals
- Availability of Product

In choosing inhibitor Treatment

- How does this fit in to the model of Haemophilia Care?
- Development of Guidelines (CPG)
- Management of serious bleeds
- Management of Joint Bleeds (single dosage)
- Home Therapy considerations (prophylaxis)

Summary

- Development of inhibitors of FVIII and FIX is now the major problem in patients being treated for haemophilia
- Studies of the equivalence of single dosage rVIIa compared with three two hourly injections and efficacy and safety of short-term secondary prophylaxis with rVIIa lead to practice changes in using this
- Inhibitor treatment should be recommended through CPG to achieve best patient outcomes and cost effectiveness

QUESTIONS AND COMMENTS

PLEASE

Multiple-dose vs. single dose for haemophilia A or B patients with inhibitors

- Multiple-dose treatment
 - » Patients typically require two to three bolus injections for haemostasis (2.2 doses/bleed required on average)
 - » Currently recommended initial dose, 90 µg/kg
- Single dose treatment using NovoSeven[®] 270 µg/kg
 - More convenient than multiple injections
 - » Improved quality of life
 - » Better compliance
 - » Proven to be effective and safe

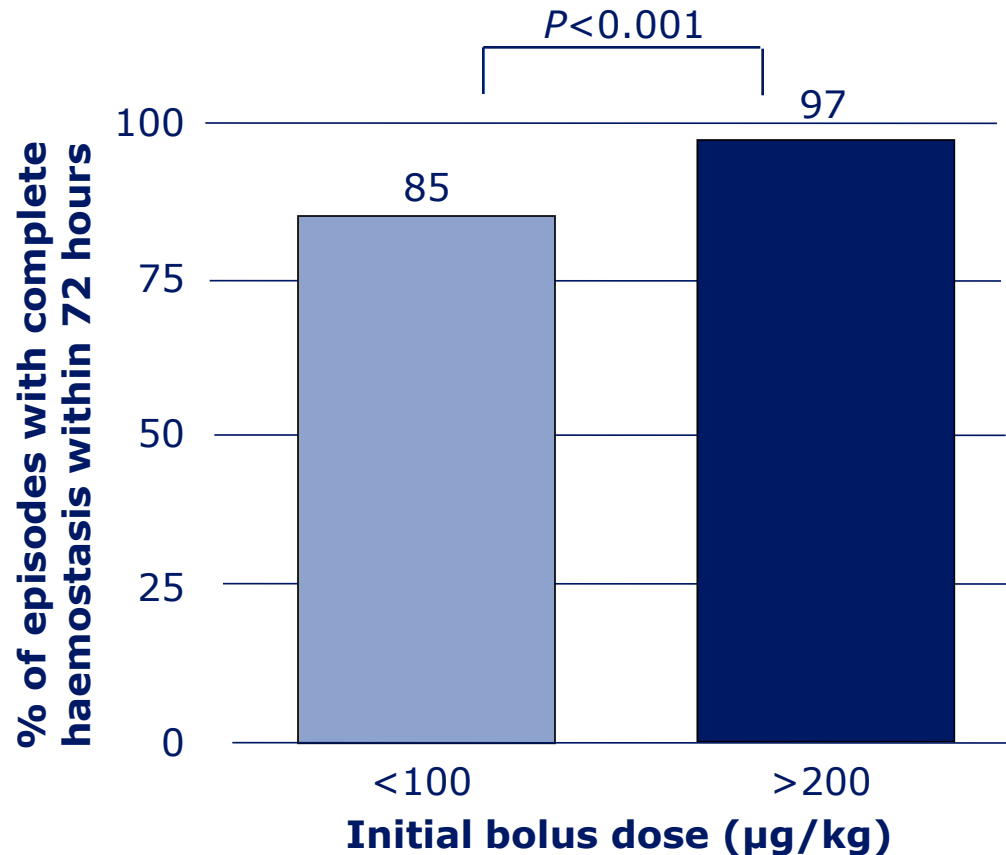
NovoSeven Product Monograph.

Kavakli K. *Thromb Haemost* 2006; 95:600-605.

Santagostino E. *J Thromb Haemost* 2006; 4:367-373.

Further support for higher doses: Parameswaran 2005

Retrospective analysis of 555 bleeding episodes with initial doses of <100 to 346 µg/kg NovoSeven®



Parameswaran R. *Haemophilia* 2005; 11:100-106.

Testing the hypothesis: Is 270 µg/kg also efficacious in a clinical trial setting?

Need to test findings in a prospective clinical trial

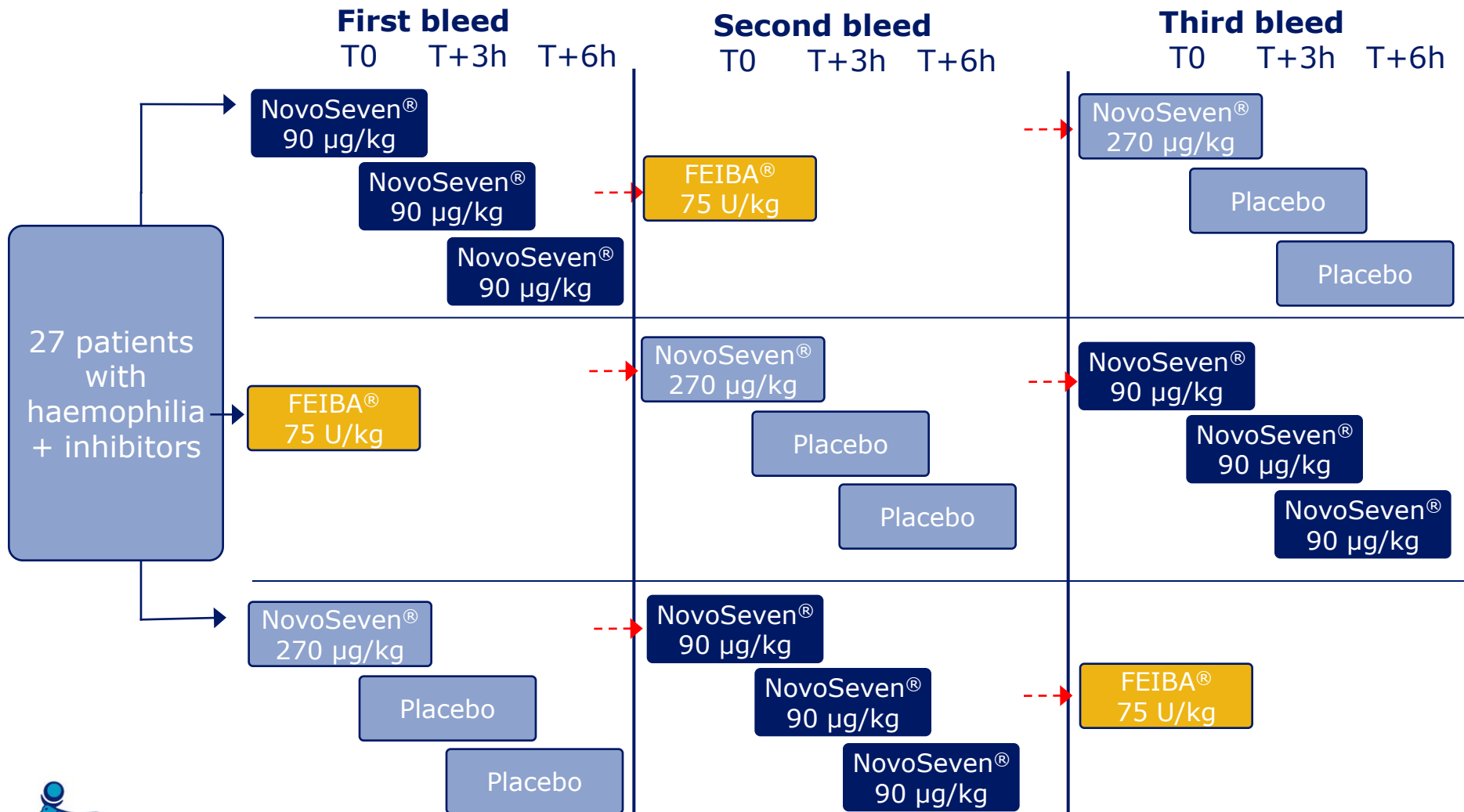
- **Kavakli et al. (2006)**

- 19 patients/38 episodes (efficacy analysis)
- One dose of 270 µg/kg (plus two placebo doses) versus three doses of 90 µg/kg
- Double blind, crossover design
- Measured efficacy using the Global Treatment Response score

- **Young et al. (2007, submitted)**

- 24 patients/68 episodes
- One dose of 270 µg/kg (plus two placebo doses), versus three doses of 90 µg/kg, versus FEIBA 75 U/kg
- Double blind, crossover design, FEIBA dose not blinded
- Measured efficacy using the Global Treatment Response score

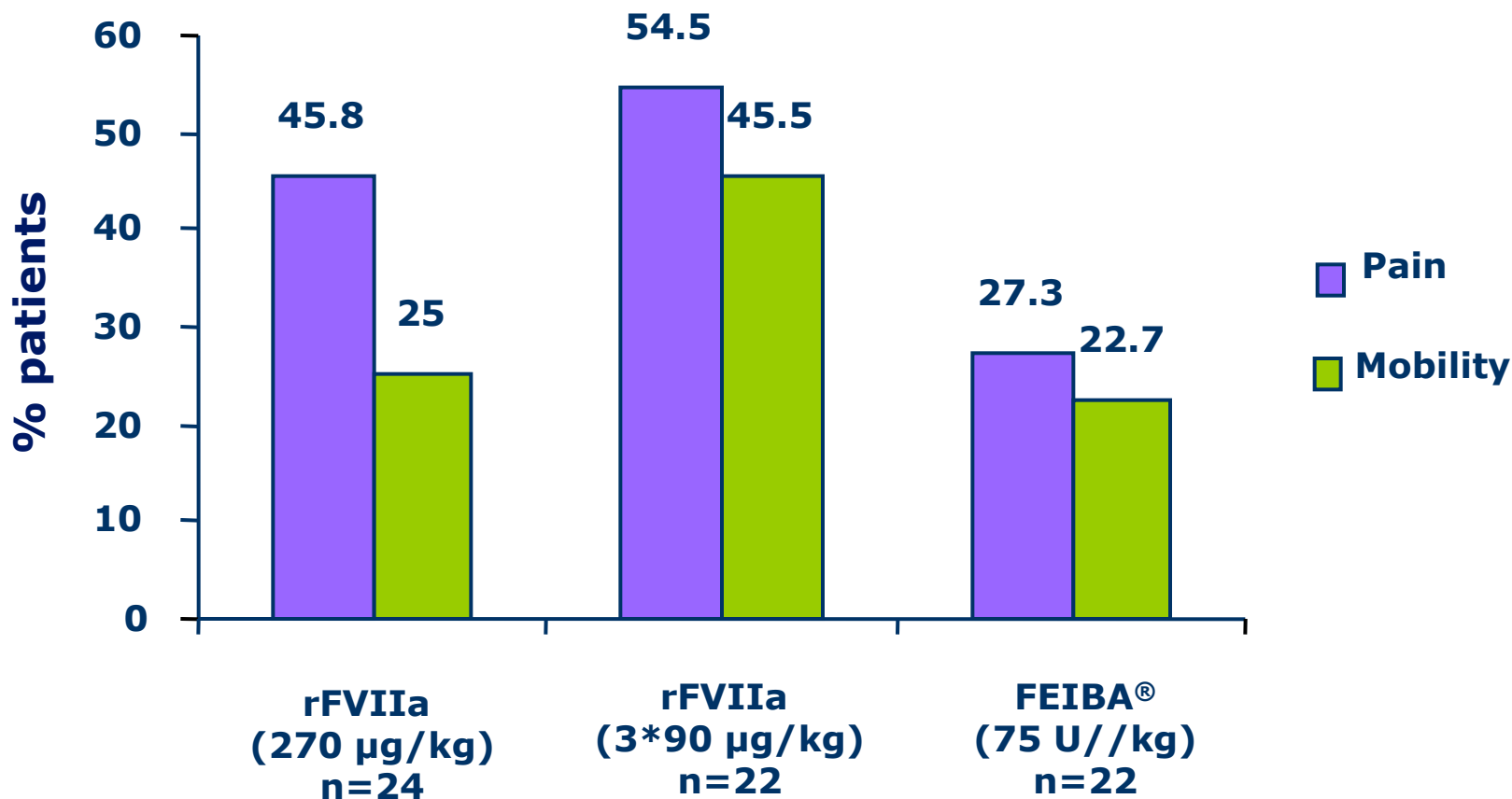
Young *et al.* Study design



The rFVIIa doses were blinded and placebo controlled

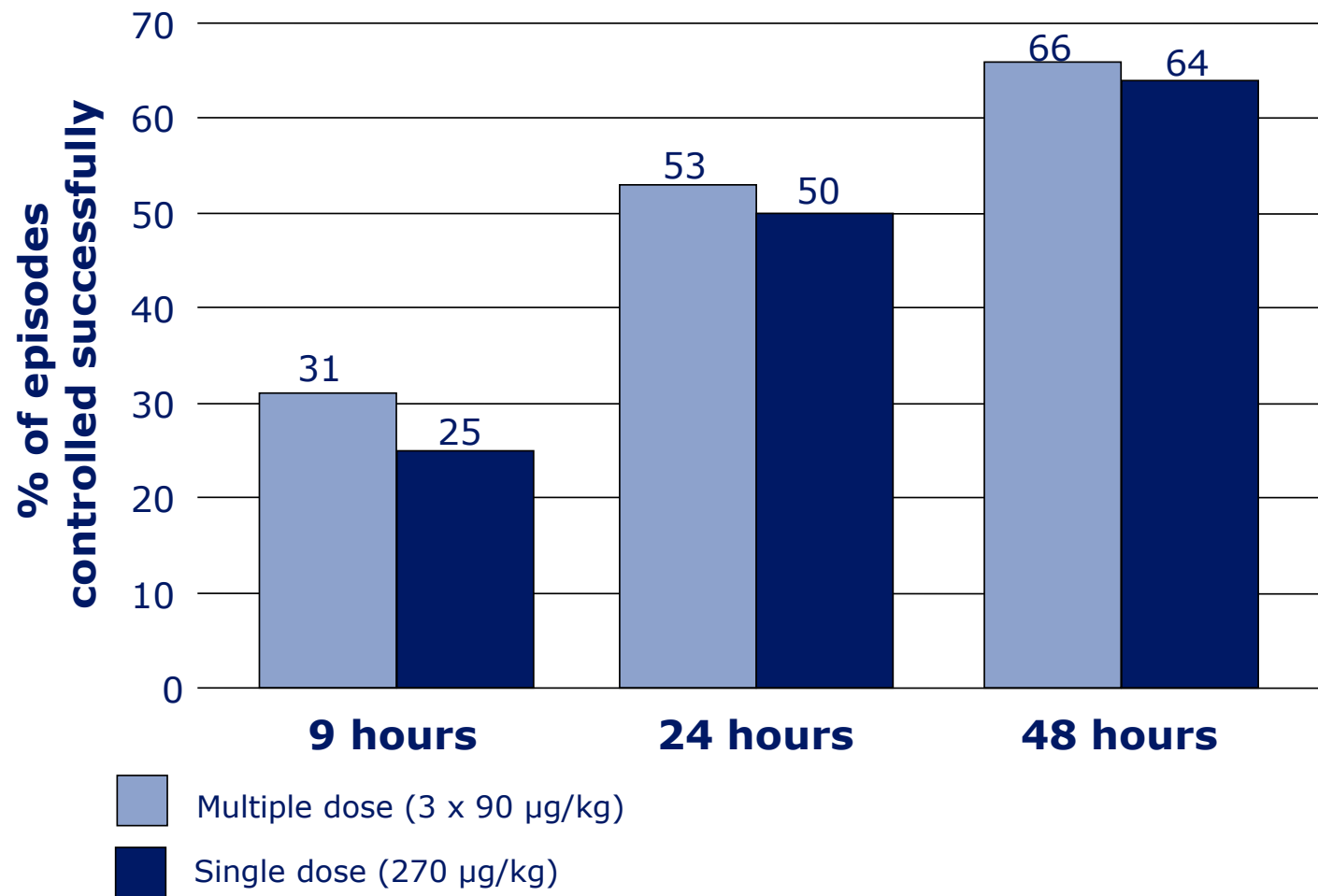
Results—Global Assessment: Pain and mobility responses

No statistical significance between groups



Young et al. Haemophilia 2007

Single dose and repeated doses: equal time to haemostasis



Santagostino E. *J Thromb Haemost* 2006; 4:367-373.

Efficacy and safety of single dose NovoSeven[®]: Summary

- Higher bolus doses of NovoSeven provide effective haemostasis with fewer injections
- Bolus doses >200 $\mu\text{g}/\text{kg}$ were significantly more effective than any of the lower NovoSeven dose ranges
- Most patients achieve haemostasis with a single bolus injection of NovoSeven 270 $\mu\text{g}/\text{kg}$
- No adverse thrombotic or other events observed

Early evidence supporting prophylaxis in patients with inhibitors

- The effectiveness of rVIIa as prophylaxis in patients with inhibitors has been reported since 1998
 - rFVIIa has been used effectively for prophylaxis in the surgical setting¹
- Small case studies have also demonstrated the beneficial effects of rFVIIa prophylaxis using various dosing regimens with reduced bleed frequency and improved QOL²⁻⁴
- Results from a prospective, randomised trial of a bypassing agent as secondary prophylaxis for patients with inhibitors was first reported in 2006 showing efficacy and safety of this approach⁵

1. Shapiro *et al.* *Thromb Haemost* 1998;80:773-8

2. Young *et al.* *Haemophilia* 2005;11:203-7

3. Data on file. Novo Nordisk 2006

4. Saxon *et al.* *Thromb Haemost* 2001;86:1126-7

5. Konkle *et al.* *Blood* 2006;108(11):Abstract 766

rFVIIa – a prospective, randomised clinical trial of secondary prophylaxis in patients with haemophilia and inhibitors

NN1505 study by Konkle et al.

Primary endpoint

- Number of bleeds per month during the treatment period compared with the observation period
 - **Re-bleed**
 - Any bleed at the same site within 6 hours of treatment
 - **New bleed**
 - Any bleed at the same site 6 hours after treatment or at a new site
 - **Target joint**
 - A bleed that occurred in a joint ≥ 3 times in previous 6 months

Secondary endpoints

- Number of bleeds per month in the post-prophylaxis period compared with the observation and prophylaxis periods
- Changes in bleed site over the entire trial period
- Causes of bleeds over the entire trial period
- Timing of bleeding episodes
- Quality of life
 - EQ-5D utility scores
 - Hospitalisation burden
 - Impact of illness on school/work
- Safety

Statistical considerations

- Sample size required: 20 patients
- Assumptions
 - **4 bleeds per month in the observation period**
 - **40% reduction in bleeds in the prophylaxis vs observation periods with each patient acting as own control**
- Expected withdrawal rate of <30% during prophylaxis
- 10 patients were required in each arm to detect a treatment difference at 80% with a 5% significance level

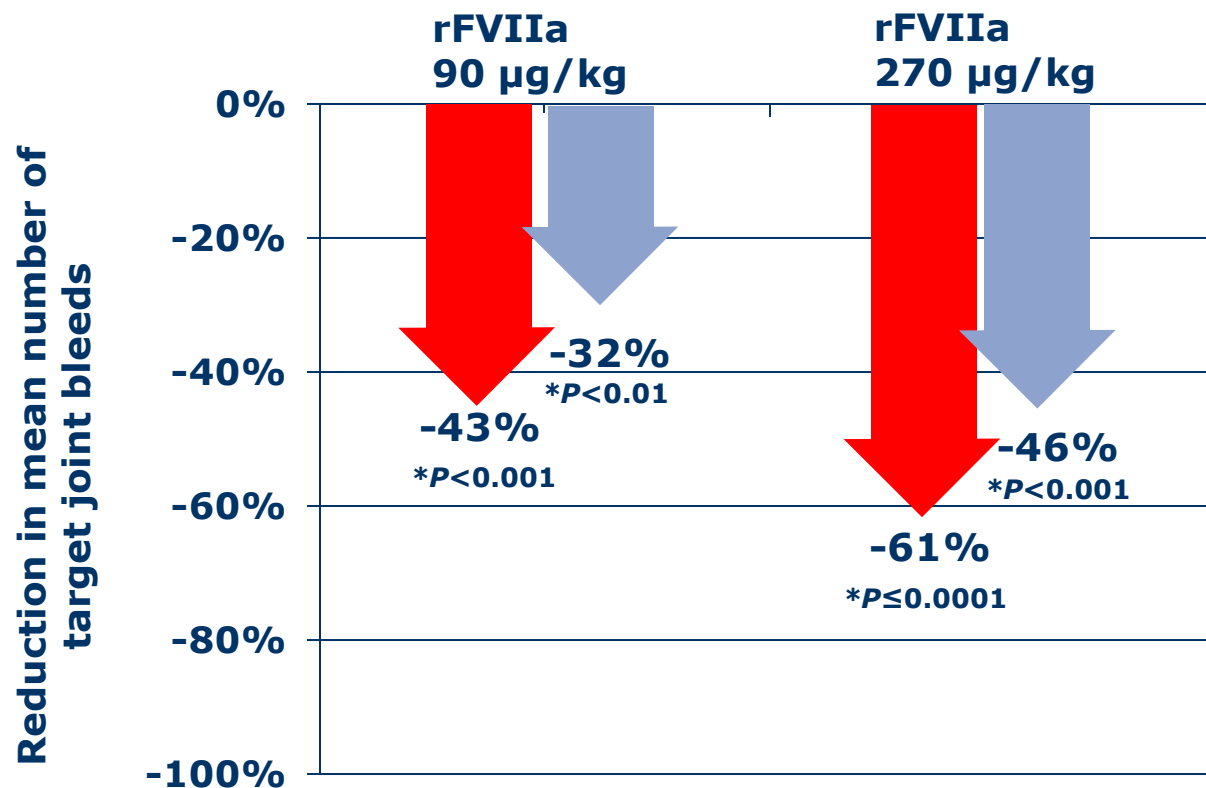
Baseline characteristics

Characteristic	rFVIIa 90 µg/kg (n=11)	rFVIIa 270 µg/kg (n=11)
Median age (years)	13.0 (5.1–50.5)	17.8 (10.6–56.1)
Median body weight (kg)	51.4 (17.4–75.0)	66.0 (26.0–79.2)
Haemophilia A	10 (91%)	11 (100%)
Target joint involvement	10 (91%)	11 (100%)
Mean orthopaedic joint score* (all joints)	1.74 (1.06)	2.95 (2.69)
Mean orthopaedic joint score (target joints)	3.01 (1.16)	4.00 (3.94)

Median values are presented with the range; mean values are presented \pm standard deviation

*Orthopaedic joint score is assessed based on physical examination of ankle, knee and elbow joints, and pain scores at trial entry and at the end of each 3-month trial period

Reductions in the frequency of target joint bleeds are sustained for ≥ 3 months with rFVIIa



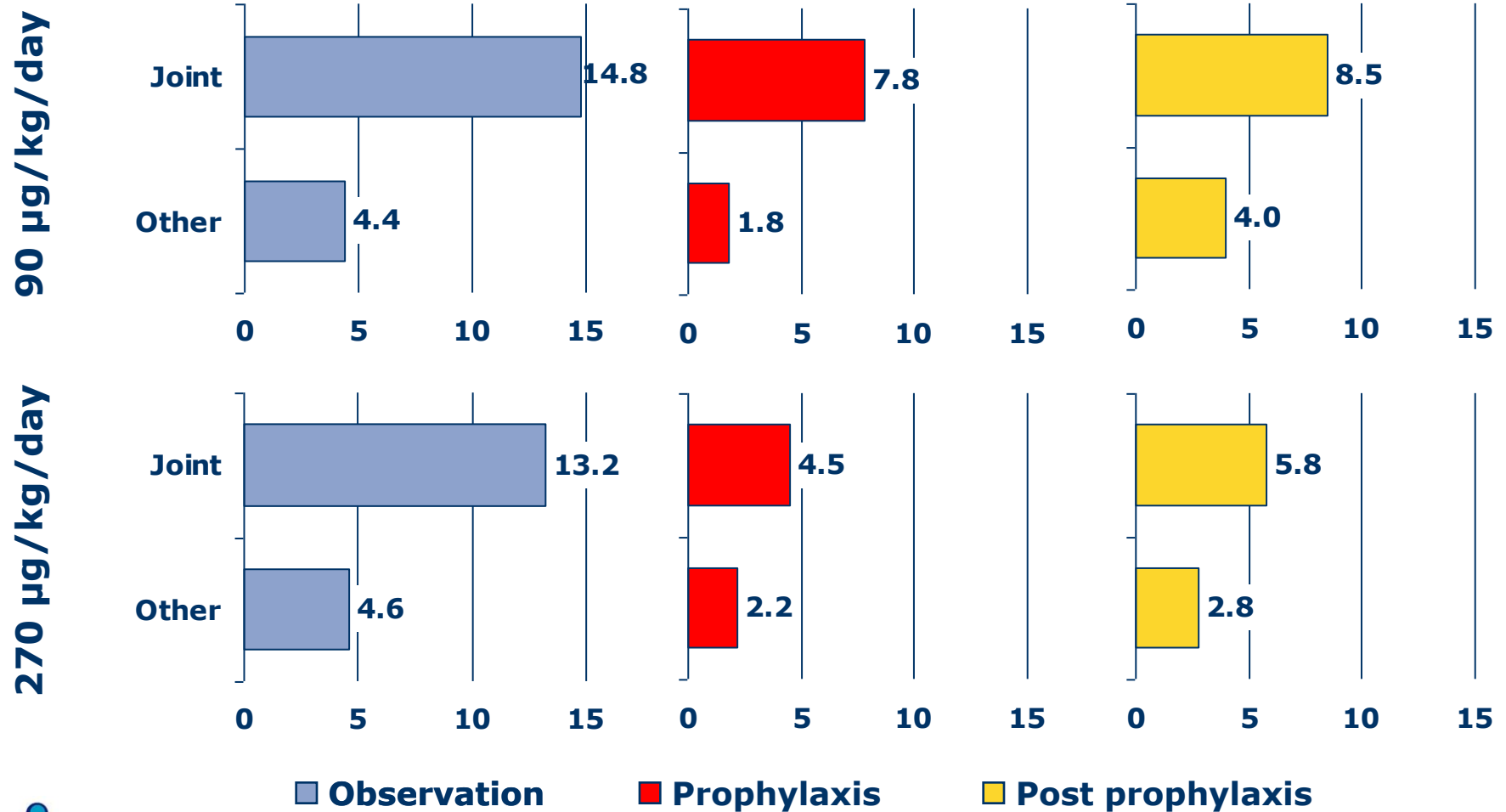
Prophylaxis
Post prophylaxis



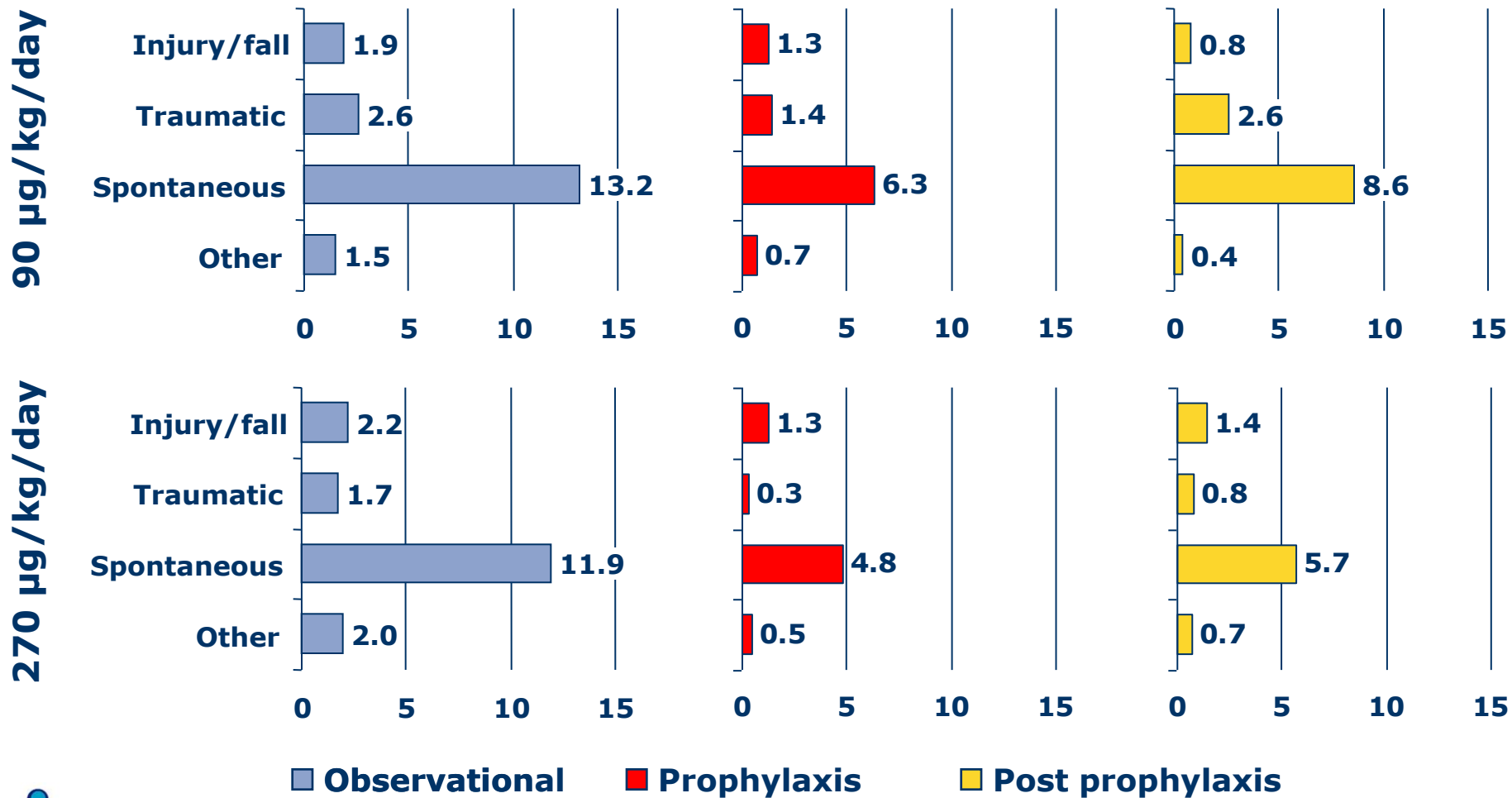
*P values represent the reduction in the number of bleeds from the observation period to the prophylaxis and post-prophylaxis periods, as indicated

n=11 patients in each group

Mean number of bleeds and their location by trial period

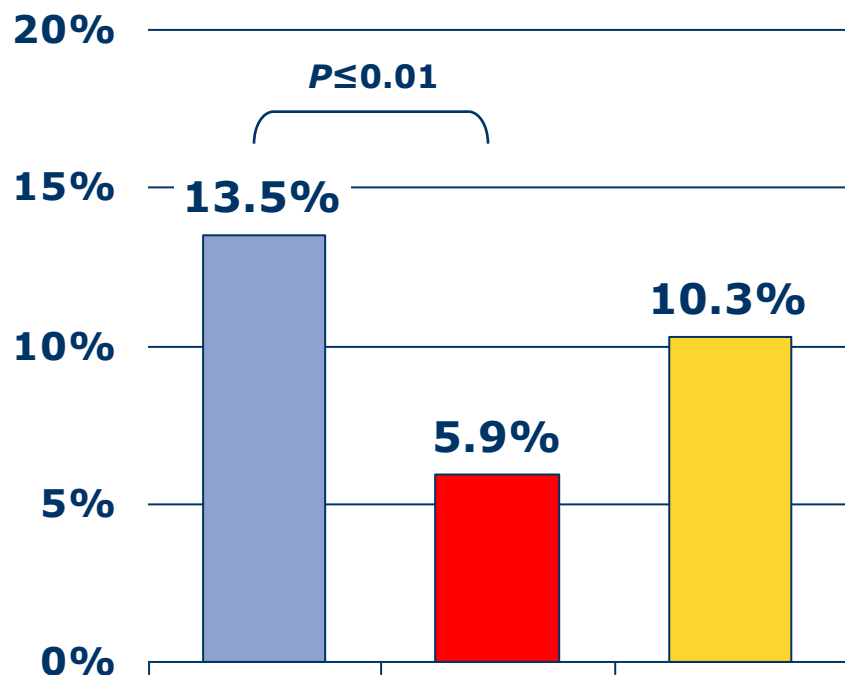


Causes of bleeds

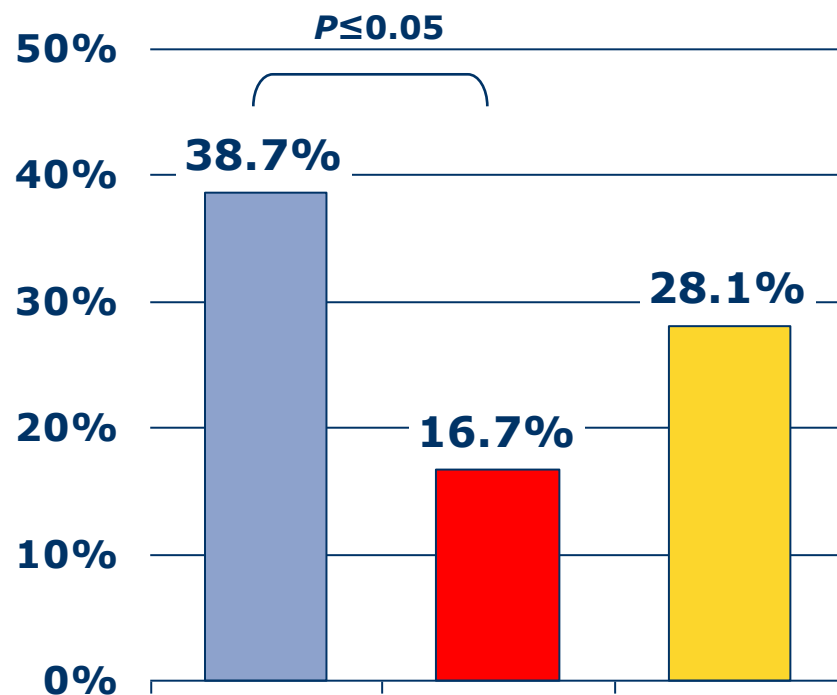


rFVIIa reduced the frequency of hospital visits and absences from work and school

Proportion of days (%) spent in hospital



Proportion of days (%) absent from school/work



■ Observation

■ Treatment

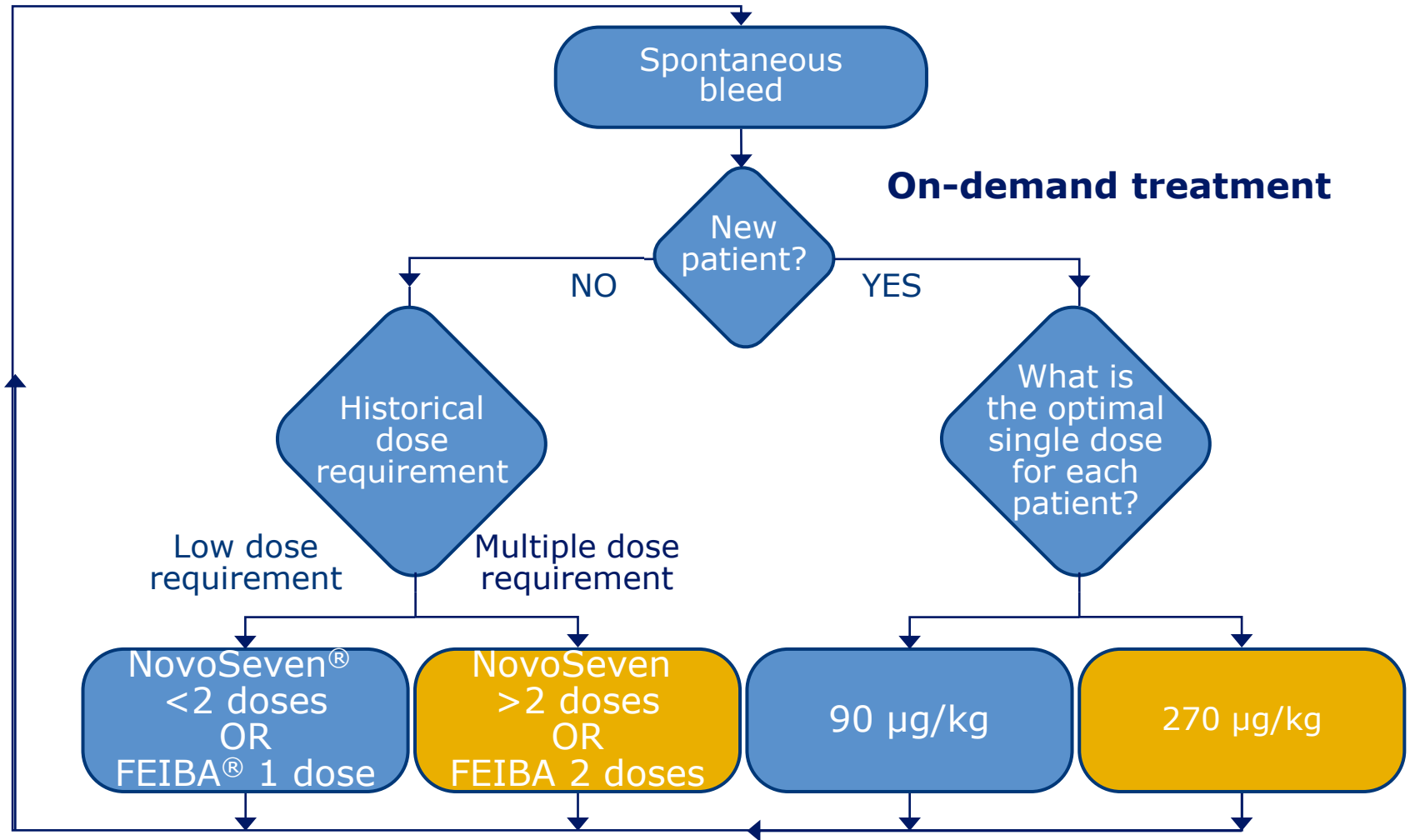
■ Post prophylaxis

rFVIIa was not associated with safety concerns or thromboembolic events (when used as a single agent)

Events	Observation	Prophylaxis	Post-prophylaxis
rFVIIa 90 µg/kg			
All	19	35	13
Possibly/probably related	0	5	0
Serious adverse events	0	0	0
rFVIIa 270 µg/kg			
All	24	16	6
Possibly/probably related	0	0	0
Serious adverse events	0	4*	1*

* The four SAEs (serious adverse events) during the prophylaxis period were a gastrointestinal haemorrhage, interstitial lung disease, fracture of the ulna, and a viral infection. The SAE after prophylaxis was an infected haematoma. None of the reported SAEs were likely to be related to administration of rFVIIa according to the investigator

The single dose segmentation model



 Primary target for single 270 µg/kg dose NovoSeven®