Caring for People with Inhibitors

Chris Barnes
Henry Ekert Haemophilia Treatment Centre

The Royal Children's Hospital Melbourne

Inhibitors in Haemophilia

- Greater risk of joint bleeding episodes
- Risk of developing arthropathy
- Reduced QOL
- Physical disability
- Mortality

	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 Haemophilia 2007

	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 Haemophilia 2007

	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 Haemophilia 2007

	All patients				
Scale Scores	*n*	Min	Max	Mean	SD
Physical functioning (PF)	50	22.1	56.5	42.6**	13.5
Role physical (RP)	50	20.3	57.2	41.2**	11.6
Bodily pain (BP)	50	16.7	57.4	42.0**	12.7
General health (GH)	47	18.9	62.0	46.5*	11.6
Vitality (VT)	48	27.6	67.9	51.7	10.9
Social functioning (SF)	49	16.2	56.6	43.6**	12.7
Role emotional (RE)	50	11.3	56.1	46.0**	12.5
Mental health (MH)	48	21.9	64.5	49.9	10.4
Physical component summary (PCS)	45	12.9	57.8	39.9**	12.5
Mental component summary (MCS)	45	19.7	65.4	49.9	12.1

Comparison with US population norms [18].

*$P < 0.05$.

**$P < 0.01$.

Brown Haemophilia 2009

	All patients				
Scale Scores	*n*	Min	Max	Mean	SD
Physical functioning (PF)	50	22.1	56.5	42.6**	13.5
Role physical (RP)	50	20.3	57.2	41.2**	11.6
Bodily pain (BP)	50	16.7	57.4	42.0**	12.7
General health (GH)	47	18.9	62.0	46.5*	11.6
Vitality (VT)	48	27.6	67.9	51.7	10.9
Social functioning (SF)	49	16.2	56.6	43.6**	12.7
Role emotional (RE)	50	11.3	56.1	46.0**	12.5
Mental health (MH)	48	21.9	64.5	49.9	10.4
Physical component summary (PCS)	45	12.9	57.8	39.9**	12.5
Mental component summary (MCS)	45	19.7	65.4	49.9	12.1

Comparison with US population norms [18].

*$P < 0.05$.

**$P < 0.01$.

Brown Haemophilia 2009

Inhibitors in Haemophilia

- Mortality
  - 2 fold increase in haemorrhagic related death 1977 – 1992
  - Normalisation of mortality rate 1993 – 1999 with more widespread availability of effective bypassing agents

Darby Haemophilia 2004

Management of patients with inhibitors

- 1. Management of bleeding episodes
- 2. Eradication of inhibitors
- 3. Prevention of joint bleeds (prophylaxis)

Management of bleeding episodes

- Use of factor VIII / factor IX ineffective
- Treatment of high titre inhibitors require bypassing treatment
  - Activated prothrombin complex concentrates
  - Recombinant factor VIIa
  - Porcine FVIII (not available)

aPCCs FEIBA

- Available since 1970s
- Plasma derived product
- Exact mechanism of action not known
  - Activate platelets
  - Contains levels of FIXa
  - Induce tissue factor
  - Contains “protected FVIII”

Lundblad Thromb Haemostat 1998

Vermylen BJH 1978

Teitel Thromb Haemostat 1988

The Royal Children's Hospital Melbourne

Effectiveness FEIBA

- Open label studies
  - 87% response rates in 120 bleeding episodes
  - 78% response rate in 150 bleeding episodes

Krantowitz Clin Ther 1987

Sjamsoedin NEJM 1981

The Royal Children's Hospital Melbourne

FEIBA Dose

- Dose based on “Factor VIII bypassing activity”
- Typically need to give no more regularly than 6 – 12 hourly (50 - 100 units per/kg)

The Royal Children's Hospital Melbourne

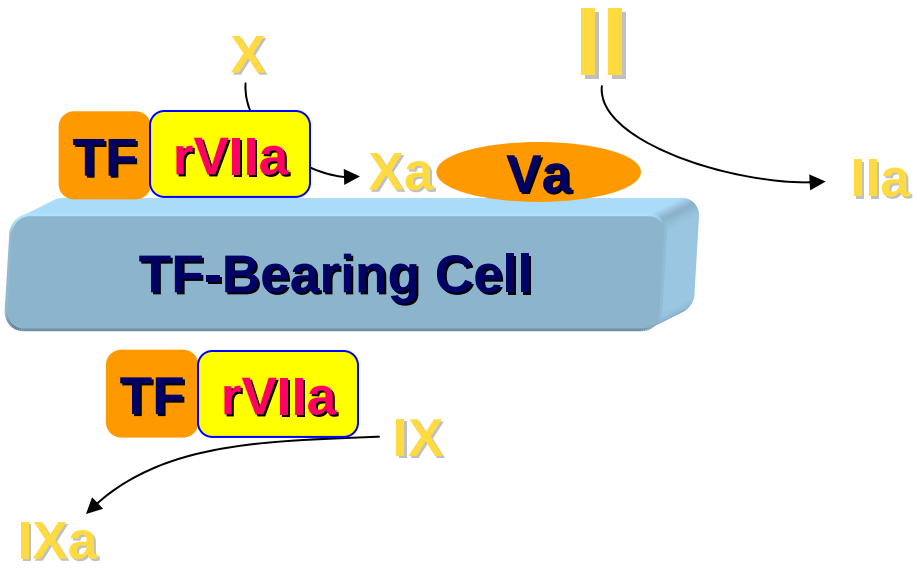
FEIBA safety

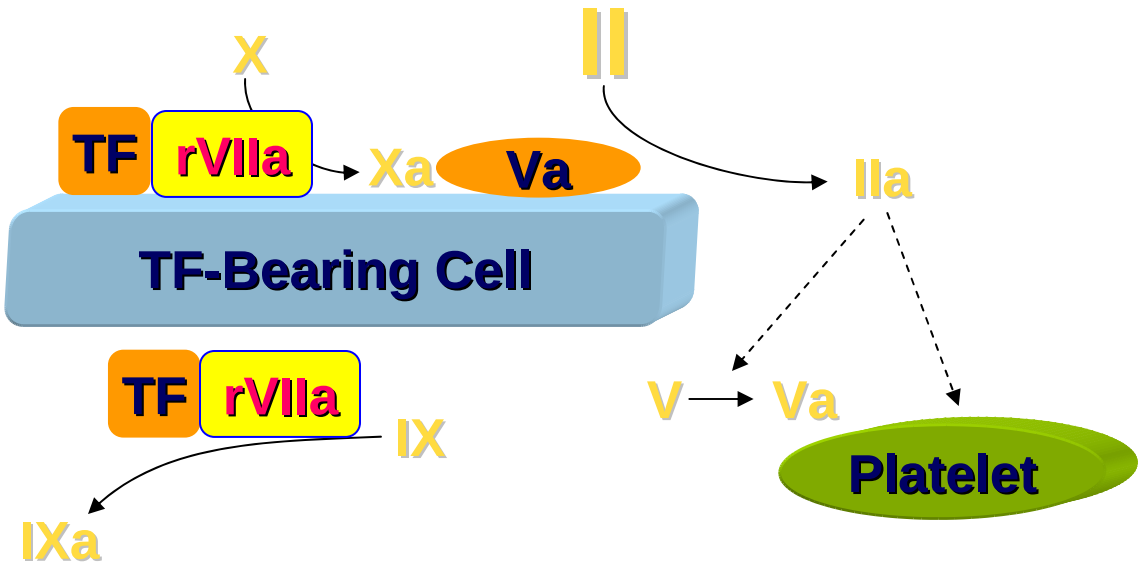
- Plasma product so potential for transmission of viral infection but this risk is negligible
- Thrombogenicity a problem shortly after discovery but true incidence not known

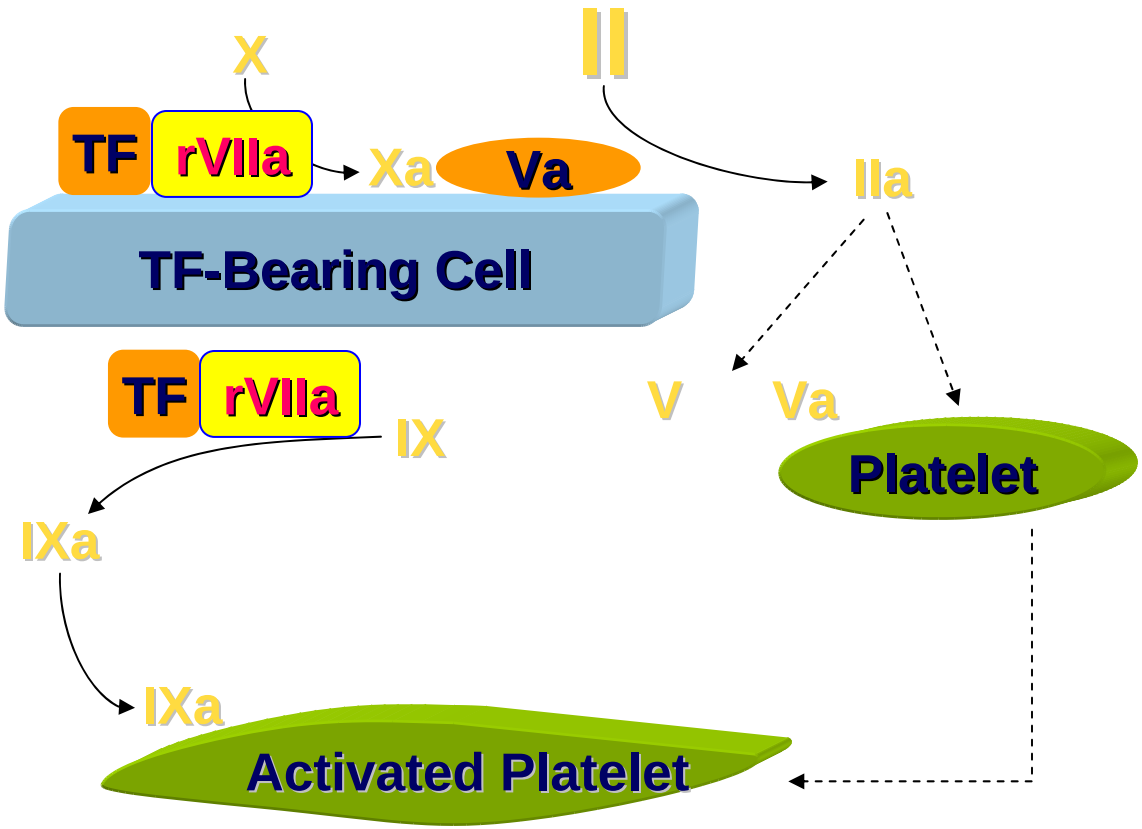
rFVIIa (NovoVII)

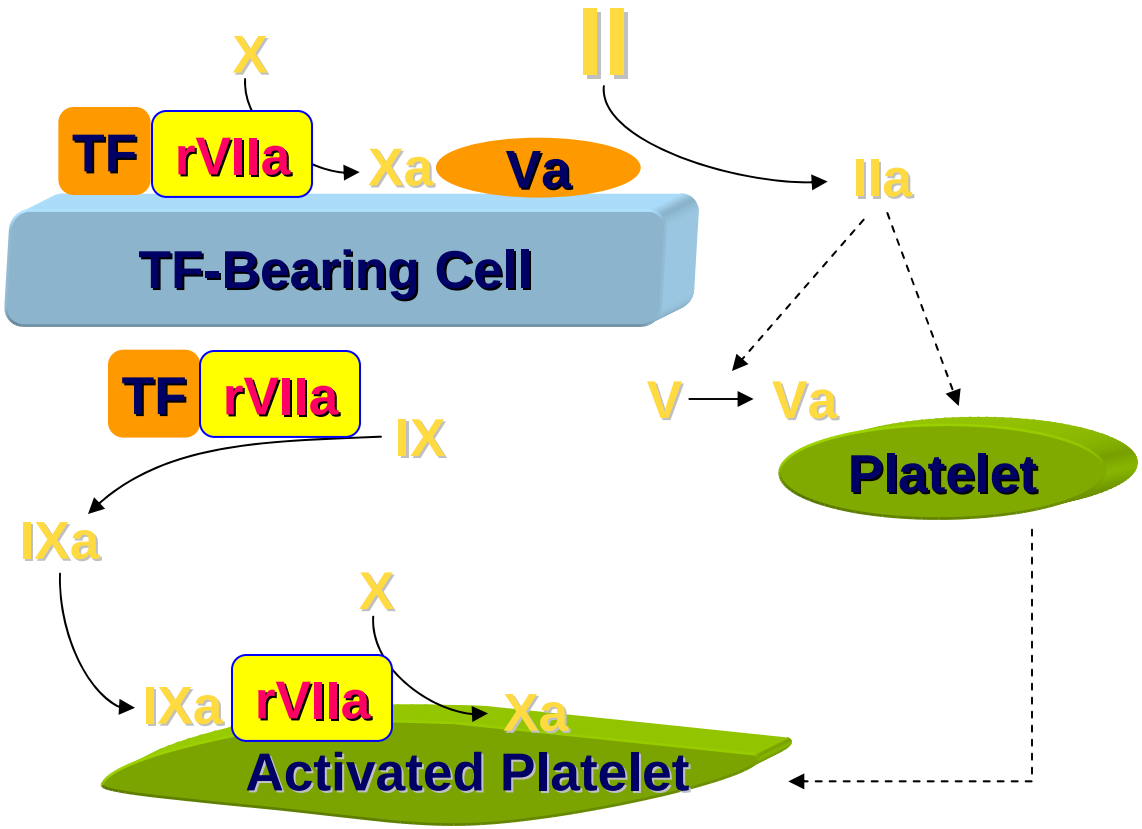
- Available from the mid 1990s
- Recombinant product

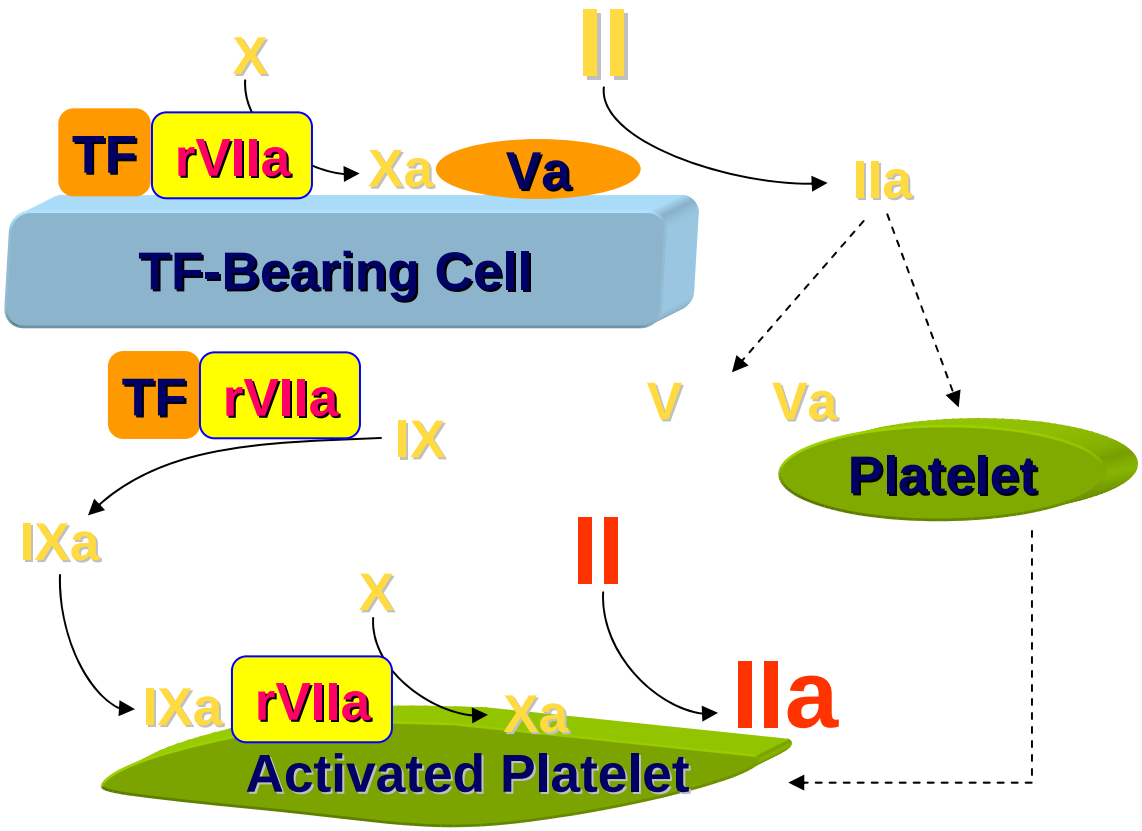
The Royal Children's Hospital Melbourne


X
II
TF
rVIIa
Xa
Va
IIa
TF-Bearing Cell
TF
rVIIa
IX
IXa


X
II
TF
rVIIa
Xa
Va
IIa
TF-Bearing Cell
TF
rVIIa
IX
IXa
V
Va
Platelet


X
II
TF
rVIIa
Xa
Va
IIa
TF-Bearing Cell
TF
rVIIa
IX
V
Va
Platelet
IXa
IXa
Activated Platelet


X
II
TF
rVIIa
Xa
Va
IIa
TF-Bearing Cell
TF
rVIIa
IX
V
Va
Platelet
IXa
X
IXa
rVIIa
Xa
Activated Platelet


X
II
TF
rVIIa
Xa
Va
IIa
TF-Bearing Cell
TF
rVIIa
IX
V
Va
Platelet
IXa
II
X
IXa
rVIIa
Xa
IIa
Activated Platelet

Effectiveness NovoVII

- International open label studies
  - 85% effective in 149 serious bleeds
  - 82% for 92 episodes in surgical prophylaxis
- US based open label of home infusions
  - 92% effective in 614 bleeding episodes

Bech Blood 1994

Key Blood Coag Fibrinol 1998

rFVIIa Dosing

- Standard dosing 90 mcg / kg 2 hourly for three doses
- Recent randomised, cross over, double blind study examining effect of single dose (270mcg) versus standard dosing

Table 3: Global treatment response (effective/ineffective) and "preference".

	90 × 3/270 μg/kg rFVIIa regimen n=11	270/90 × 3 μg/kg rFVIIa regimen n=10	Total n=21
90 μg/kg × 3			
n	11	9	20
Effective	7 (64%)	7 (78%)	14 (70%)
Ineffective	4 (36%)	2 (22%)	6 (30%)
270 μg/kg			
n	10	10	20
Effective	6 (60%)	7 (70%)	13 (65%)
Ineffective	4 (40%)	3 (30%)	7 (35%)
Preference			
n	10	9	19[a]
90 μg/kg × 3	2 (20%)	2 (22%)	4 (21%)
No preference	6 (60%)	5 (56%)	11 (58%)
270 μg/kg	2 (20%)	2 (22%)	4 (21%)
			p=0.637[b]

[a]Two patients experienced only one haemarthrosis during the trial; [b]p-value for the exact version of McNemar's test of preference.

Kavalki Blood Coag Fibrinolysis 2006

Table 3: Global treatment response (effective/ineffective) and "preference".

	90 × 3/270 µg/kg rFVIIa regimen n=11	270/90 × 3 µg/kg rFVIIa regimen n=10	Total n=21
90 µg/kg × 3			
n	11	9	20
Effective	7 (64%)	7 (78%)	14 (70%)
Ineffective	4 (36%)	2 (22%)	6 (30%)
270 µg/kg			
n	10	10	20
Effective	6 (60%)	7 (70%)	13 (65%)
Ineffective	4 (40%)	3 (30%)	7 (35%)
Preference			
n	10	9	19[a]
90 µg/kg × 3	2 (20%)	2 (22%)	4 (21%)
No preference	6 (60%)	5 (56%)	11 (58%)
270 µg/kg	2 (20%)	2 (22%)	4 (21%)
			p=0.637[b]

[a]Two patients experienced only one haemarthrosis during the trial; [b]p-value for the exact version of McNemar's test of preference.

Kavalki Blood Coag Fibrinolysis 2006

Comparison studies

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

[1]Department for Hematology and Coagulation Disorders, Malmö University Hospital, Malmö, Sweden; [2]Department of Biostatistics, Rho, Chapel Hill, NC; [3]Department of Pediatrics, Weill Medical College, Cornell University, New York, NY; [4]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, University of Milan, Italy

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

Efficacy of recombinant activated factor VII vs. activated prothrombin complex concentrate for patients suffering from haemophilia complicated with inhibitors: a Bayesian meta-regression

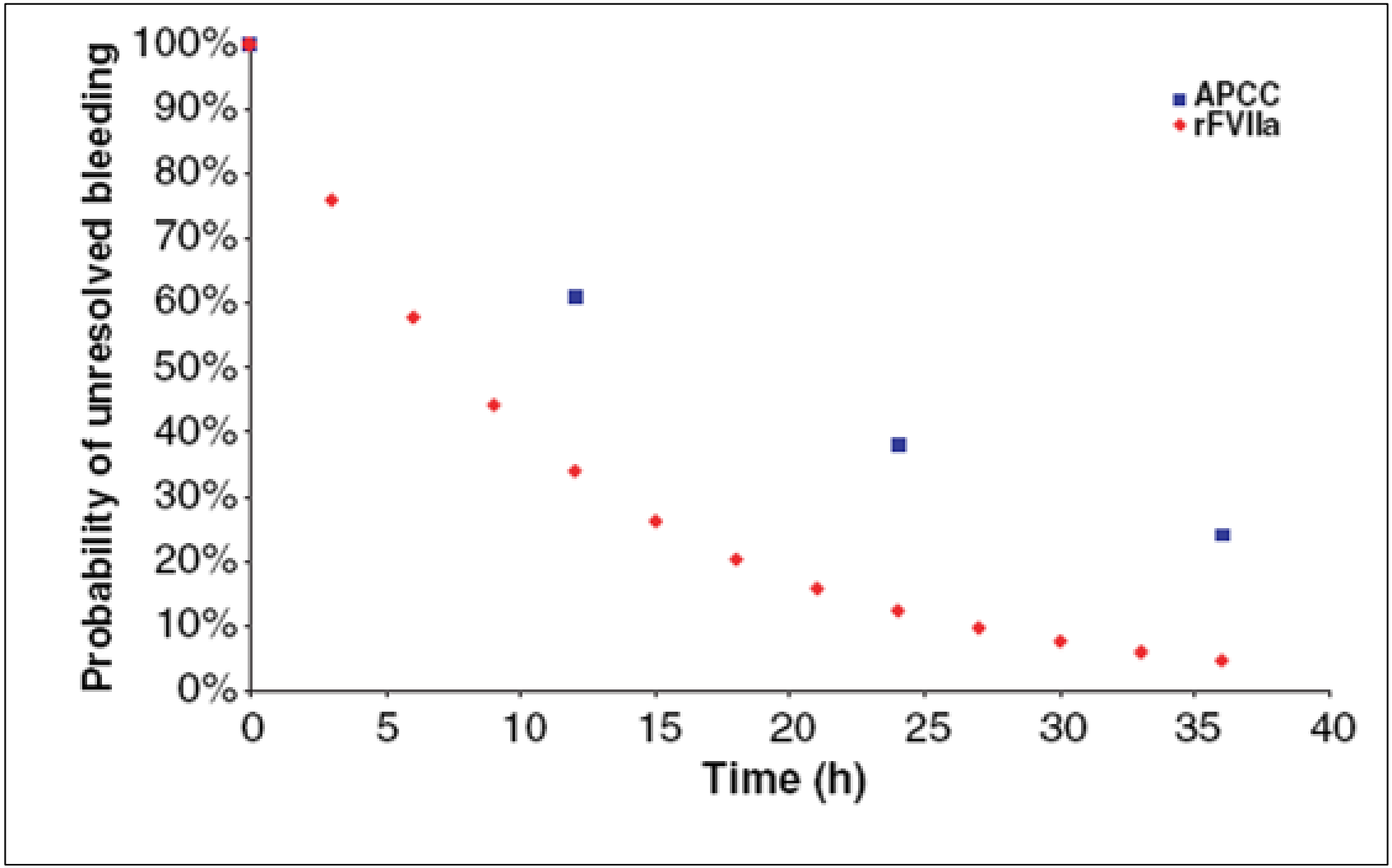
M. J. TREUR,* F. MCCRACKEN,† B. HEEG,* A. V. JOSHI,‡ M. F. BOTTEMAN,§ F. DE CHARRO* and B. VAN HOUT†

Meta-analysis

- Ability to pool results to compare the reported efficacy of NovoVII and FEIBA in treating joint bleeds in patients with inhibitors
- Using Bayesian meta-regression model
- 17 studies pooled involving over 2000 joint bleeds

Treur Haemophilia 2009

R3


Probability of unresolved bleeding
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
5
10
15
20
25
30
35
40
Time (h)
APCC
rFVIIa

Slide 27

R3 Make comment on efficacy here
RCH, 3/10/2009

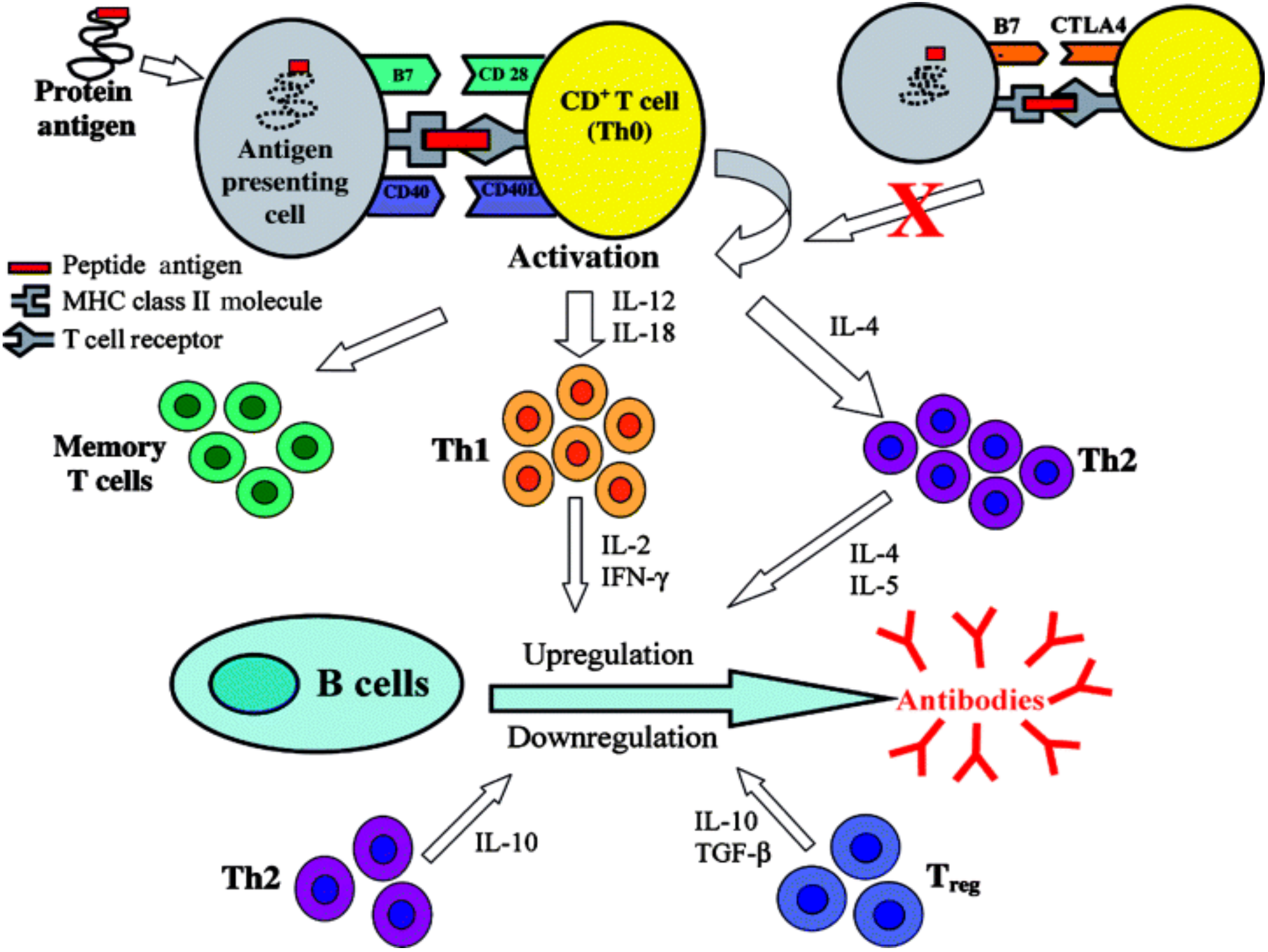
Meta-analysis

- Typical treatment of NovoVII @ 90mcg / kg every 3 hours if needed will result in cumulative joint bleed resolution of **66% 88% and 95%** after 12, 24 and 36 hours respectively

- Typical treatment of FEIBA @ 75IU / kg repeated every 12 hours if needed will result in cumulative joint bleeding resolution of **39%, 62% and 76%** after 12, 24 and 36 hours respectively

Immunetolerance

- Remains the cornerstone of effective treatment for patients with inhibitors
- Rationale for ITT involves understanding pathogenesis of development of inhibitors


Protein antigen
Antigen presenting cell
B7
CD 28
CD40
CD40L
CD+ T cell (Th0)
B7
CTLA4
X
Activation
Peptide antigen
MHC class II molecule
T cell receptor
IL-12
IL-18
IL-4
Memory T cells
Th1
Th2
IL-2
IFN-γ
IL-4
IL-5
B cells
Upregulation
Downregulation
Antibodies
Th2
IL-10
IL-10
TGF-β
Treg

Immunetolerance

- Create “tolerance to the immune system” by high dose antigen exposure (producing anergy) +/- immune modulation
  - A number of different protocols employing different dosing schedules, different “antigen” (i.e recombinant versus plasma derived) and different immune modulation (including extracoroporeal removal of inhibitor, steroids, etc.)
  - Invasive & expensive
    - Predominantly a pediatric phenomenon
  - The role of using plasma derived versus recombinant factor VIII for ITT remains unresolved

Immunetolerance

Protocol	Therapeutic regimen
Bonn	Daily factor exposure at high doses (100 U/kg/day)
Kasper	FVIII - 50 U/kg OD & oral prednisone
Dutch	FVIII - 25 U/kg BID X 1-2 wks than 25 U/kg 3 X/wk
Gruppo	FVIII - 100 U/kg/wk ± IVIG, cyclophosphamide, prednisone
Malmo	Extracorporeal immune absorption to <10 BU using protein gel columns (high avidity for IgG) FVIII - 50-200 U/kg q8-12h + IVIG +cyclophosphamide

Immunetolerance

- ITT Registries
  - North American Immune Tolerance Registry (NAITR)
  - International Immune Tolerance Registry (IITR)
  - German Immune Tolerance Registry (GITR)
  - Spanish Registry (SR)

Immunetolerance registries

	Number of patients	Success rate (95% CI)	Reported failure rate
GITR	126	78.6% (71.4 – 85.7)	16%
IITR	263	48.7% (42.6 – 52.7)	25%
NAITR	130	69.2% (61.3 – 77.2)	
SR	38	68.4% (53.6 – 83.2)	

Predictors of Successful ITI

- Low pre-ITT inhibitor titre
  - (<10BU compared favourably with >10BU in IITR and NAITR)
- Low peak inhibitor titre
  - (Less significant variable)
- Dose FVIII controversial

Mariani Vox Sang 1997

Di Michelle Thromb Haem 2000

Immunetolerance and Immunemodulation

- Useful in patients with high risk inhibitors
- Modulating the immune system may have impact on improving success in patients

- Mabthera (monoclonal antiCD20 antibody) has demonstrated some effect in high risk inhibitor patients
  - Reporting bias
  - Potential side effects

- Important for patients with haemophilia B and inhibitors(?)

R6

International Immune Tolerance Study

- Opened for recruitment late in 2002.
- Compares the efficacy, morbidity and cost effectiveness of low (50 units per kilogram three times per week) versus high-dose (200 units per kilogram daily) immune tolerance in good-risk patients.
- These patients have severe haemophilia A, an inhibitor for 12 months or less and a historical peak inhibitor titre of > 5BU but < 200 units.
- 133 patients recruited

Slide 37

R6 Look at the recent update on ITT for RCH

RCH, 3/10/2009

Tolerisation Advisory Committee (TAC)

- Sub-committee of AHCDO
- To provide clinical advice on cases of immune tolerisation for clinicians managing patients with haemophilia and inhibitors in Australia
- To monitor the ongoing progress of cases of patients with haemophilia and inhibitors within Australia
- To liaise with the supplying agencies (NBA) regarding upcoming cases immune tolerisation cases
- Encourage cases of immune tolerance to be included in clinical trials
- Telephone conferences will be held between members of the TAC every month and arranged by the Chair of the TAC with assistance from the Project Officer AHCDO.

Prophylaxis in patients with inhibitors

- A number of studies have highlighted the success of prophylaxis in preventing joint disease in patients with haemophilia **(without inhibitors)**

- Prophylaxis protects against intracranial hemorrhage, improves academic performance and improves QOL

MancoJonhson NEJM 2007

Aledort J Intern Med 1994

Shapiro Pediatrics 2001

Antunes Haemophilia 2003

The **Royal Children's Hospital** Melbourne

Prophylaxis in patients with inhibitors

- Emerging studies have demonstrated effect of prophylaxis in patients with inhibitors

Leissinger Haemophilia 2007

Konkle J Thromb Haemostat 2007

The Royal Children's Hospital Melbourne

Prophylaxis in inhibitors - FEIBA

- Retrospective chart audit of 5 patients
- Patients receiving treatment for > 6 months
- Patients received 50 – 75 units three times per week (one patient received 100 units daily)
- Assessment of number of bleeding episodes

Leissinger Haemophilia 2007

Table 3. Reduction of bleeding frequency with prophylactic aPCC (FEIBA®).

	Bleeding episodes (per 6 months)						Reduction in bleeding episodes (per 6 months) with prophylactic aPCC (FEIBA®)			
	Before prophylactic aPCC (FEIBA®)			During prophylactic aPCC (FEIBA®)						
Patient	Joint	Muscle and other	Total	Joint	Muscle and other	Total	Joint	Muscle and other	Total	Total (%)
1	–	–	10	2	0	2	–	–	8	80
2	0	36	36	0–6	6	6–12	0	30	24–30	67–83
3	24	0	24	3	0	3	21	0	21	87
4	4	10	14	<1	0	<1	4	10	14	98
5	0–6	18	18–24	0–4	8	8–12	0–6	10	6–16	33–67
Mean	7–8*	16*	20–22	1–3	3	4–6	6–8*	12*	15–18	73–83

Note: Because this was a retrospective study, only data regarding total bleeds were available for patient 1, and exact data regarding the numbers of joint bleeds and total bleeds before and after prophylaxis were not available for patients 2 and 5.

aPCC, activated prothrombin complex concentrate; FEIBA, Factor Eight Inhibitor Bypassing Activity, Anti-Inhibitor Coagulant Complex.

*Mean value based on data for patients 2 through 5.

Leissinger Haemophilia 2007

Table 3. Reduction of bleeding frequency with prophylactic aPCC (FEIBA®).

	Bleeding episodes (per 6 months)						Reduction in bleeding episodes (per 6 months) with prophylactic aPCC (FEIBA®)			
	Before prophylactic aPCC (FEIBA®)			During prophylactic aPCC (FEIBA®)						
Patient	Joint	Muscle and other	Total	Joint	Muscle and other	Total	Joint	Muscle and other	Total	Total (%)
1	–	–	10	2	0	2	–	–	8	80
2	0	36	36	0–6	6	6–12	0	30	24–30	67–83
3	24	0	24	3	0	3	21	0	21	87
4	4	10	14	<1	0	<1	4	10	14	98
5	0–6	18	18–24	0–4	8	8–12	0–6	10	6–16	33–67
Mean	7–8*	16*	20–22	1–3	3	4–6	6–8*	12*	15–18	73–83

Note: Because this was a retrospective study, only data regarding total bleeds were available for patient 1, and exact data regarding the numbers of joint bleeds and total bleeds before and after prophylaxis were not available for patients 2 and 5.

aPCC, activated prothrombin complex concentrate; FEIBA, Factor Eight Inhibitor Bypassing Activity, Anti-Inhibitor Coagulant Complex.

*Mean value based on data for patients 2 through 5.

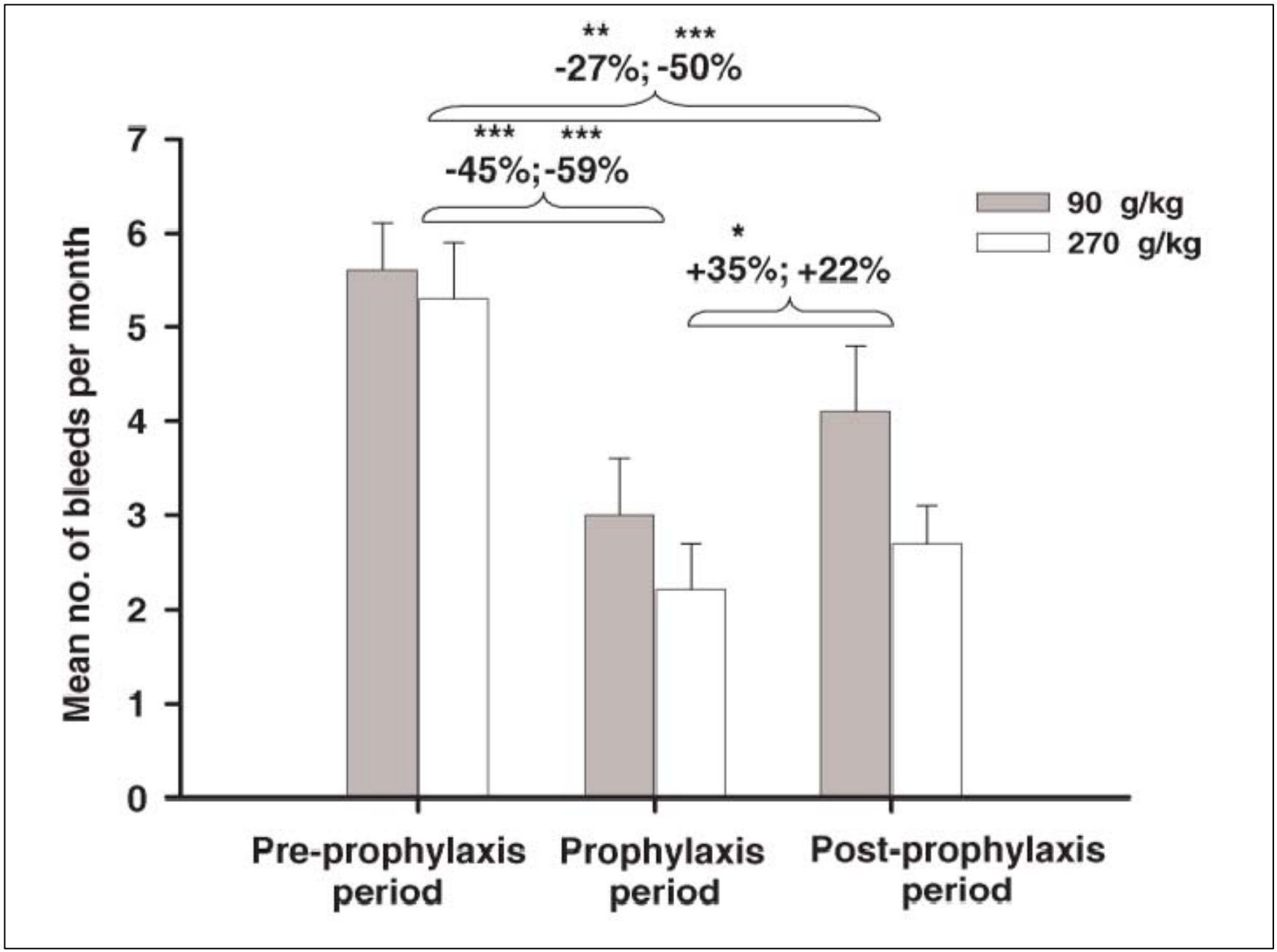
Leissinger Haemophilia 2007

Prophylaxis in inhibitors – Novo VII

- Randomised, prospective trial NovoVII prophylaxis in patients with inhibitors
- Two treatment arms; 90mcg / kg daily versus 270 mcg / daily for three months
- Assessment of bleeding frequency and assessment of hospital admissions / days from work or school

Konkle J Thrombo Haemostat 2007

The Royal Children's Hospital Melbourne


**
***
-27%; -50%
***
***
-45%;-59%
*
+35%; +22%
90 g/kg
270 g/kg
Mean no. of bleeds per month
0
1
2
3
4
5
6
7
Pre-prophylaxis period
Prophylaxis period
Post-prophylaxis period

Summary

- Presence of inhibitor associated with significant morbidity
- Treatment is effective and emerging data is available to assist in the most effective management of bleeding episodes in these patients
- Immunetolerance is the preferred therapy and centralisation of data collection will assist in obtaining optimal management in these patients
- Prophylaxis for patients with inhibitors appears to reduce frequency of bleeding and lead to improved quality of life


15TH
Australian & New Zealand
HAEMOPHILIA CONFERENCE
Life Challenges
Brisbane, 8-10 October 2009 www.haemophilia.org.au