

Evolving perspectives on access to hemophilia treatment

The best is yet to come

Albert Farrugia
WFH Global Forum
Montreal
September 26, 2013

- 1st GF – Self Sufficiency
- 2nd GF - Regulation
- 3rd GF – Cryo
- 4th GF – Regulation
- 5th GF - Biosimilars
- 6th GF – vCJD
- 7th GF – HTAs
- 8th GF - Economic considerations – pricing, sustainability, access, increased supply?(???)

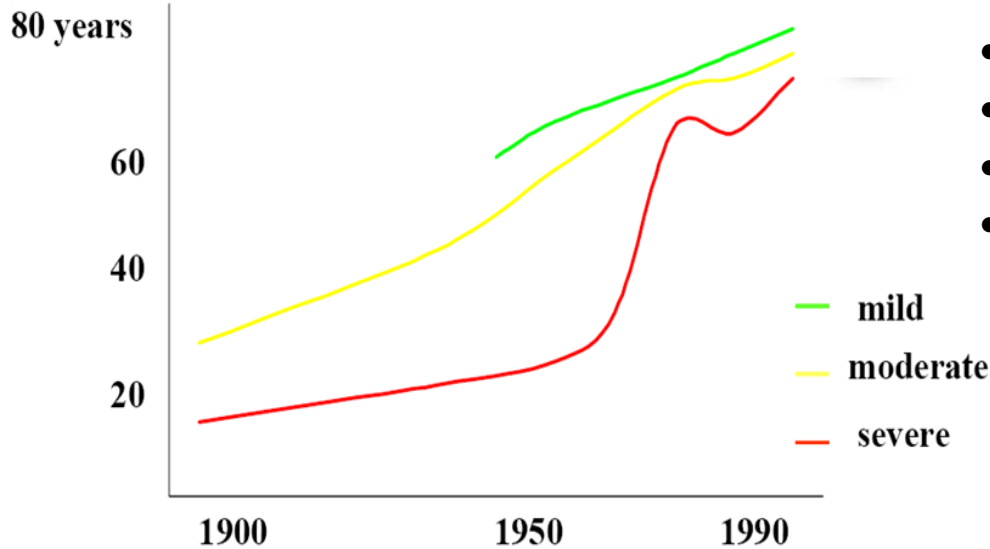


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"Jeremy refuses to study. He says he's going to become an economist and they don't have to know anything."

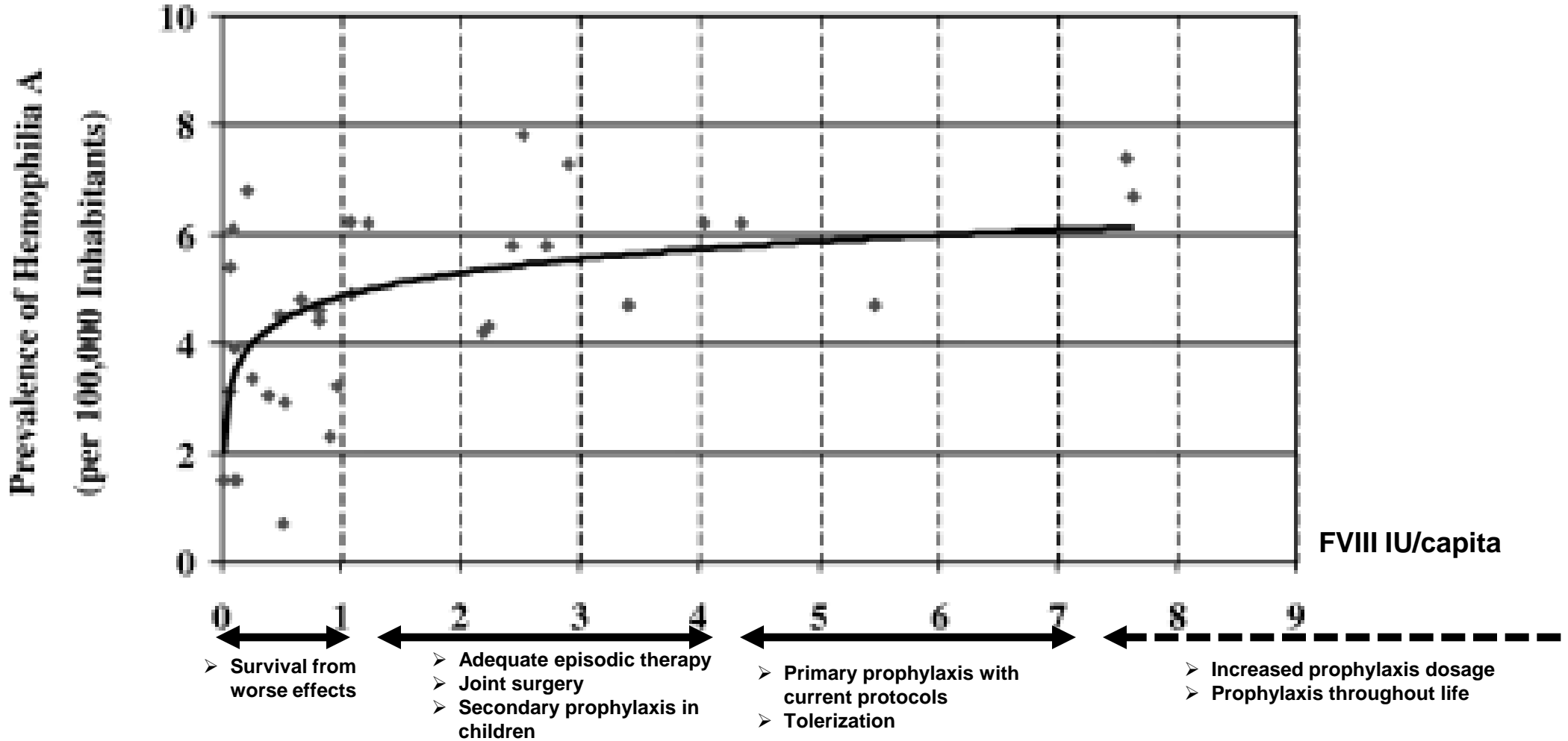
Life expectancy in Hemophilia



- Hemophilia
- Cystic fibrosis
- Thalassemia major
- Muscular dystrophy



- 75 years
- 37 years
- 30 years
- 10-20 years



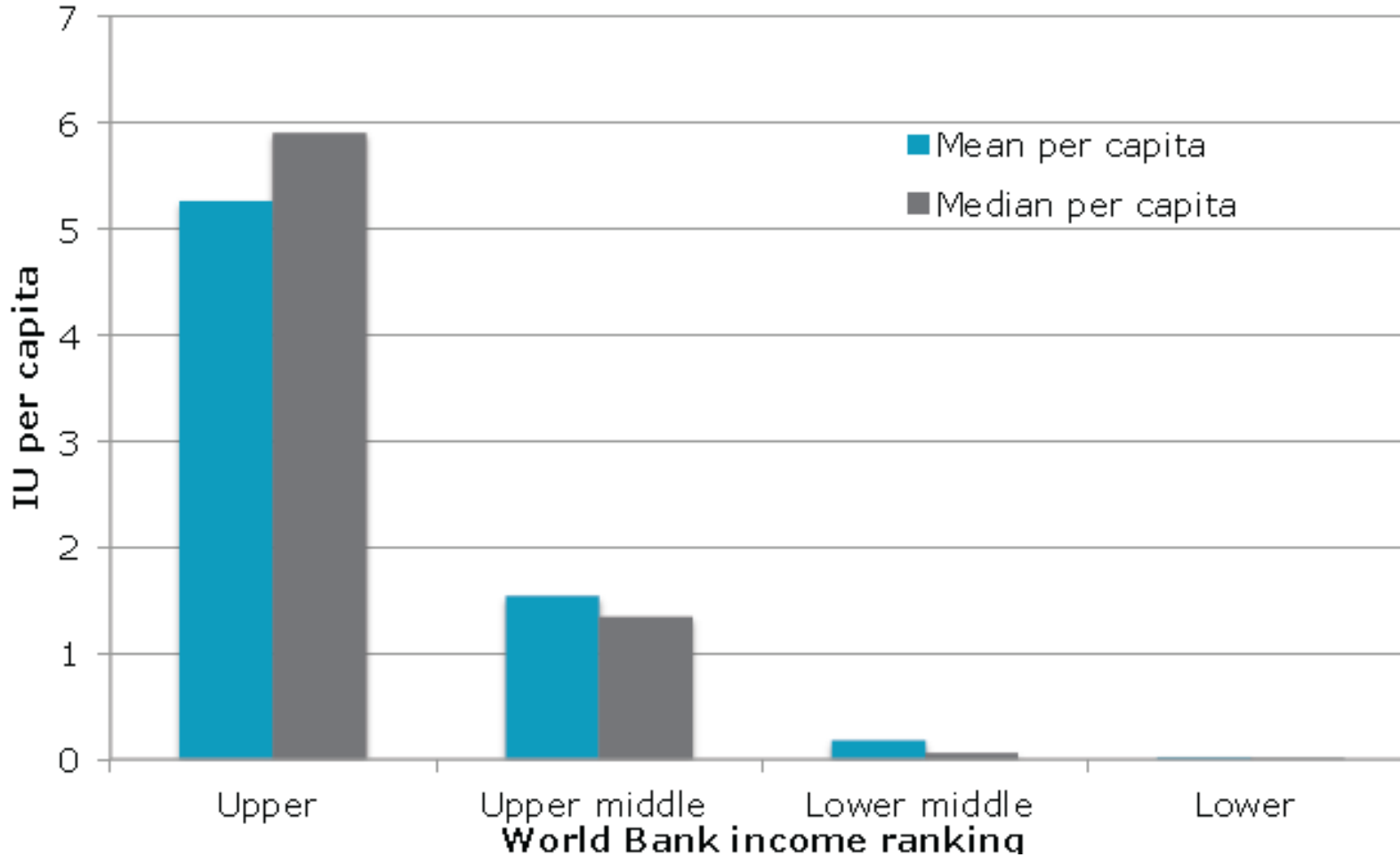
- *“an acceptable frequency of bleeds”*
- *“adequate preservation of joint function”*
- *“prophylaxis should be commenced after the second joint bleed”*

Etc etc

I want to make three points

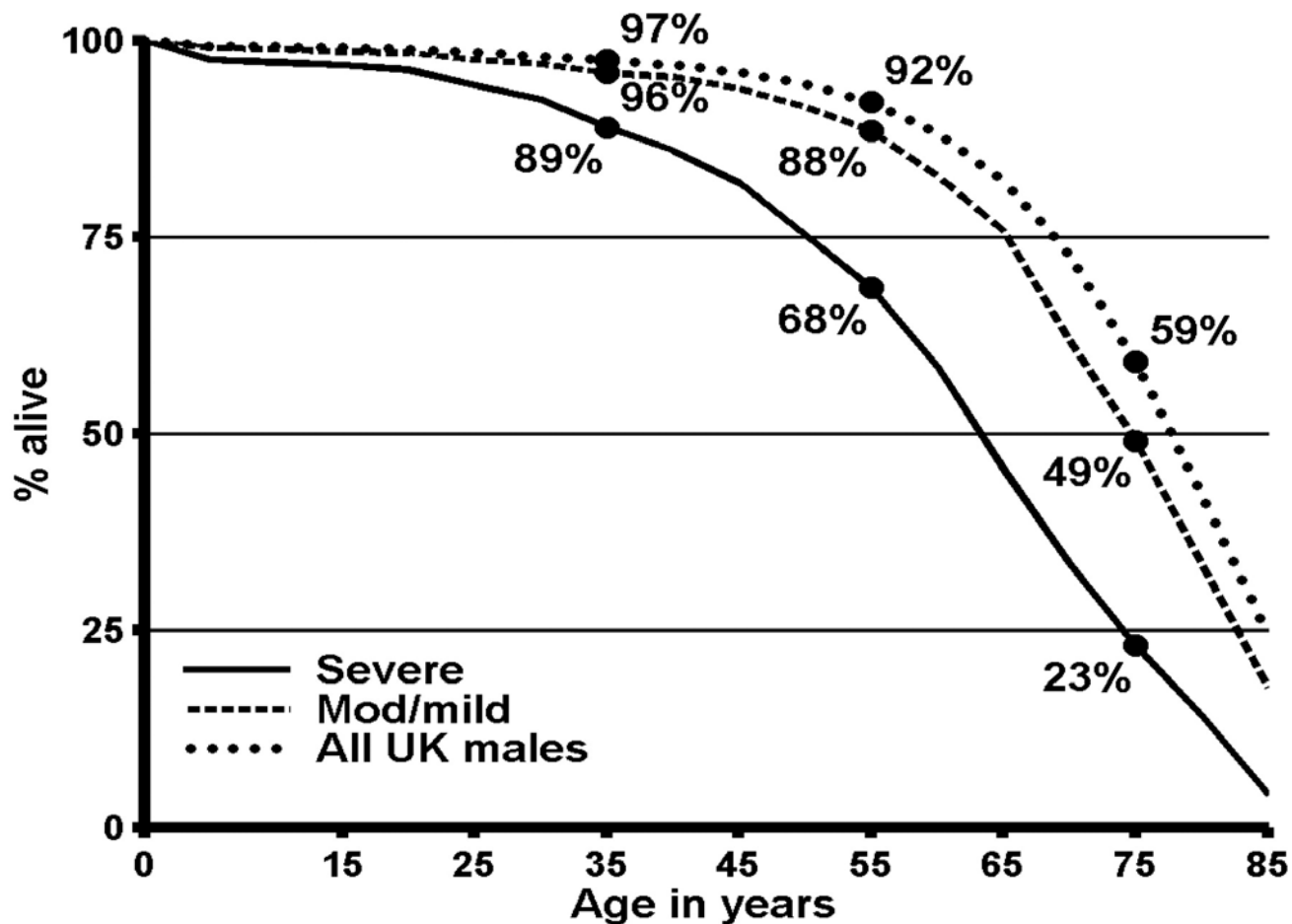
- We need ***more*** treatment product
- There ***is*** more treatment product
- We ***can*** have more treatment product

WE NEED ***MORE*** TREATMENT PRODUCT



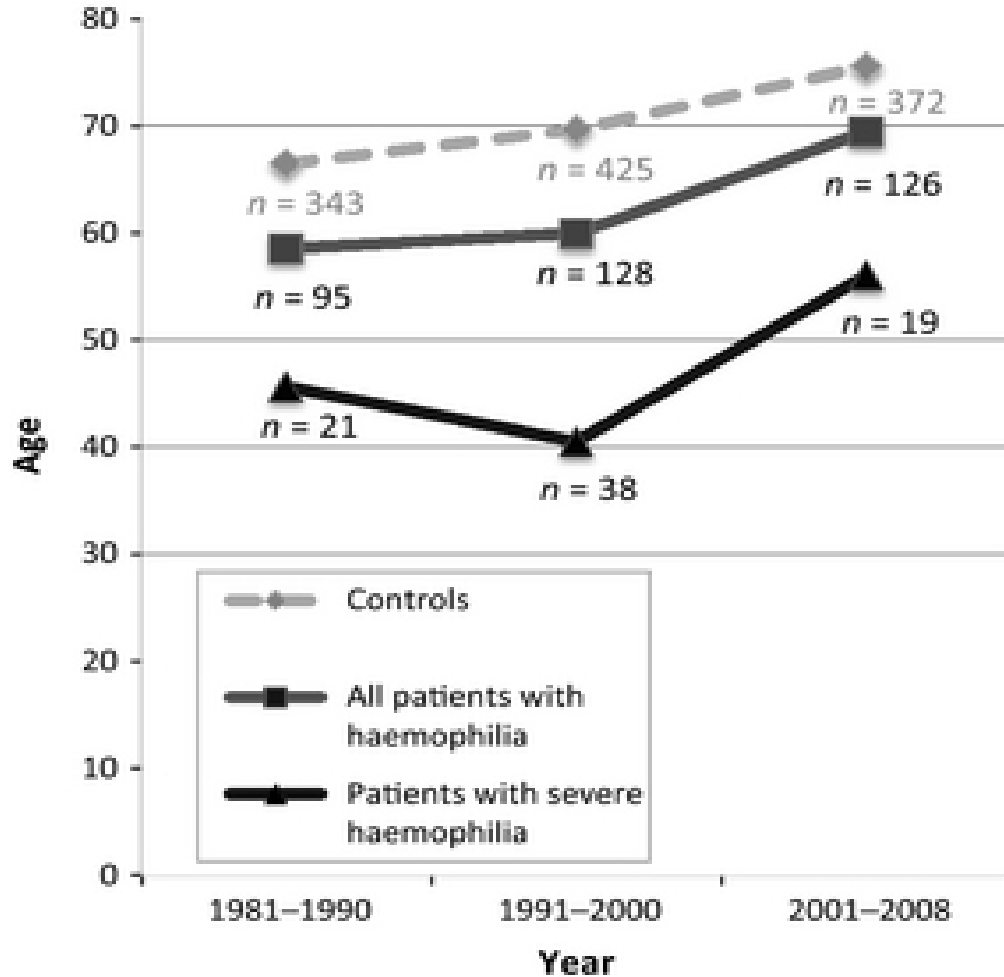
70% of the world's hemophilia population receives no or inadequate treatment (?)

After the viral safety problems, men with hemophilia are approaching a normal life expectancy



Darby S C et al. Blood 2007;110:815-825

But bleeding is still a killer! Haemophilia patients in Sweden



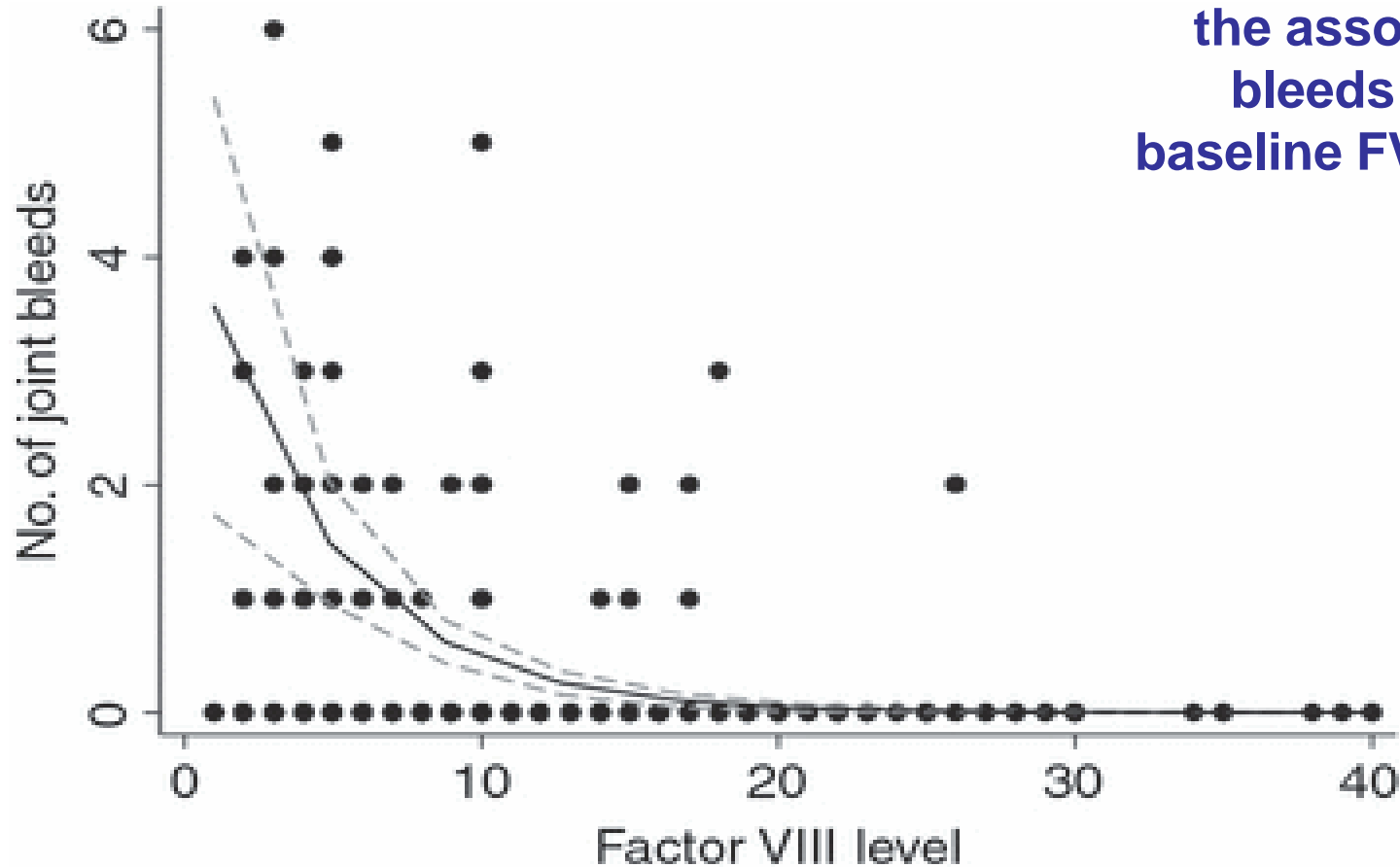
Causes of death in haemophilia in Sweden – HIV and HCV excluded

	Haemophilia %	Control %
Total deaths	100	100
Malignancies	23	23
Hemorrhagic	13	0
Ischaemic heart disease	17	29
Cardiovascular disease	7	8

The future for Hemophilia

Higher dosages

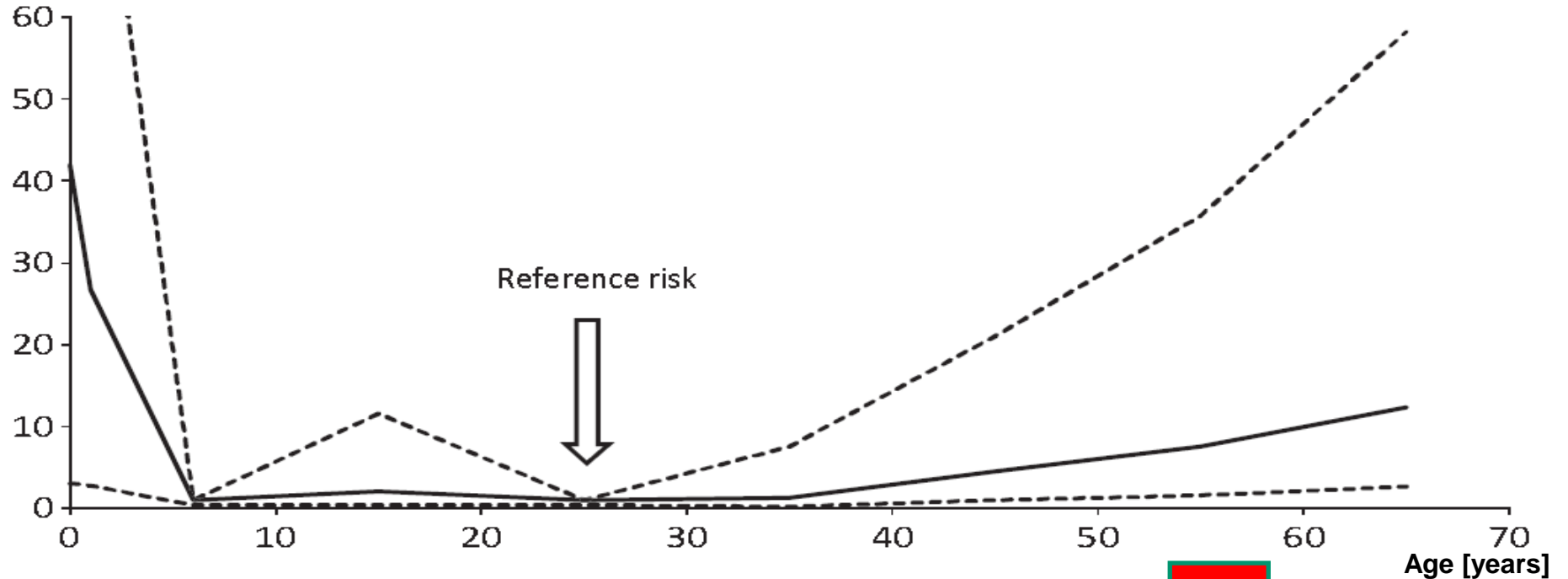
Analysis of low frequency bleeding data:
the association of joint bleeds according to baseline FVIII activity levels



Risk of ICH in Italian haemophiliacs

Relationship to age

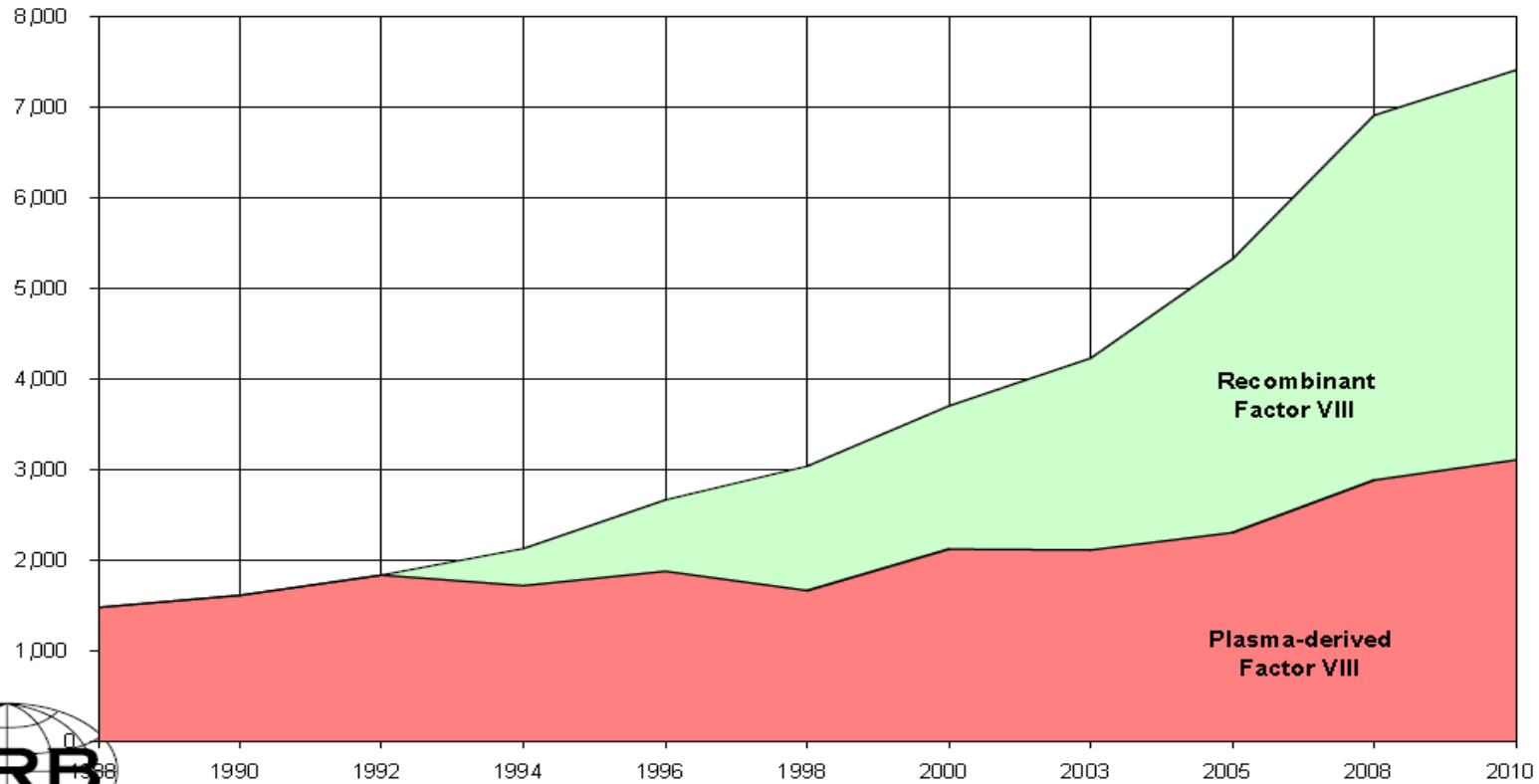
% Relative risk
to reference



Risk first decreases, then **INCREASES** with age

THERE *IS* MORE TREATMENT PRODUCT

Demand for FVIII 1980-2010



NB – in 2010, ca 3000 IU pd FVIII consumed



Plasma-derived FVIII

- In 2010, ca 3B IUs of pd FVIII consumed
- In 2010, ca 3000 tonnes plasma fractionated
- Estimate only ca 50% of the plasma was used to extract FVIII
 - Situation not very different from 35 years ago
 - Not necessarily reflective of “cryo wastage”

Recombinant FVIII

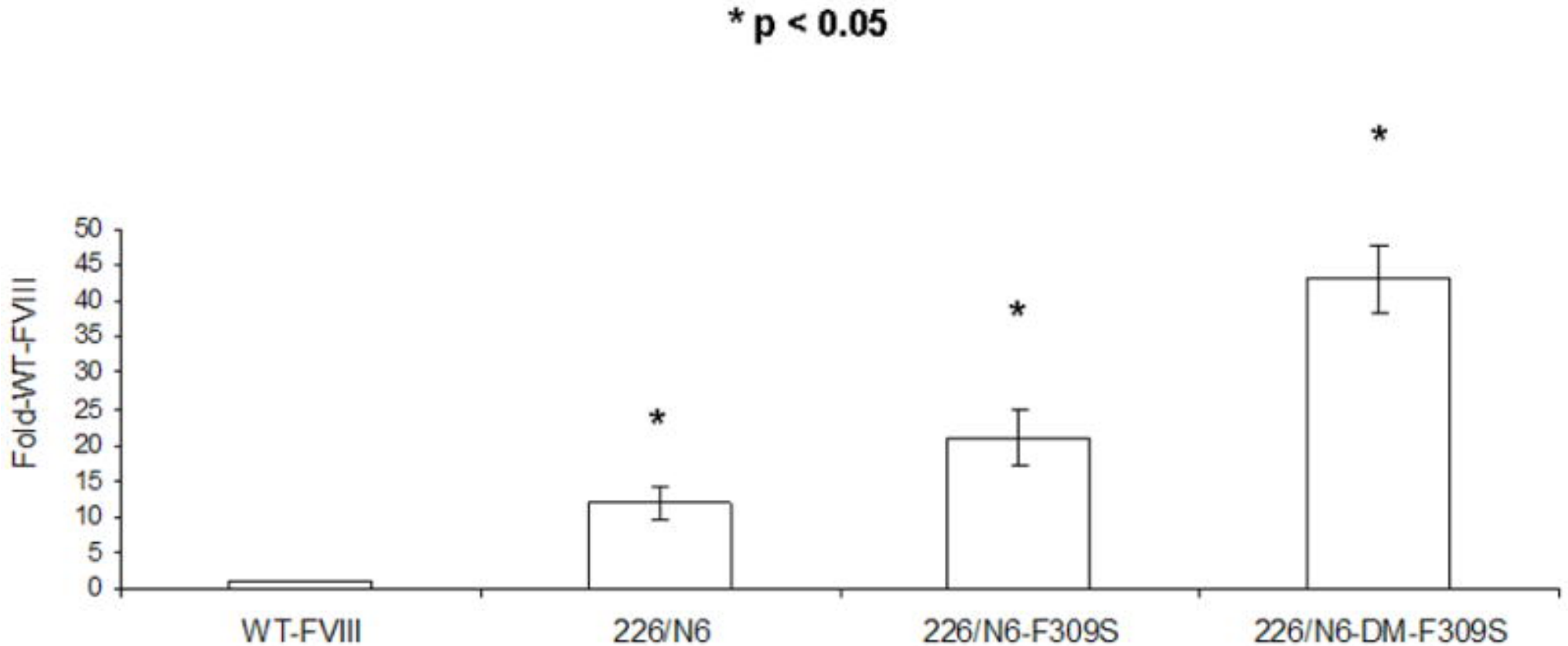
- Supply theoretically infinite (keep feeding the cells)
- What is the current yield from rVIII manufacture?
 - No public information
 - Supply has continued to increase steadily
 - Number of players constant over past 10 years (about to change?)
 - Safe to assume manufacturing efficiency has increased
- ALSO - many published improvements

Lentiviral Vector Platform for Production of Bioengineered Recombinant Coagulation Factor VIII

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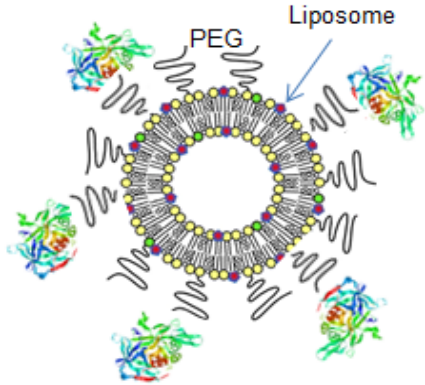
¹Aflac Cancer Center and Blood Disorders Service, Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia, USA; ²Expression Therapeutics, LLC., Tucker, Georgia, USA; ³Lentigen Corporation, Gaithersburg, Maryland, USA

Herein, we describe the development of a bioengineered fVIII product using a novel lentiviral-driven recombinant protein manufacturing platform. The combined implementation of these technologies yielded production cell lines that biosynthesize in excess of 2.5 mg/l of recombinant fVIII at the rate of 9 pg/cell/day, which is the highest level of recombinant fVIII production reported to date,



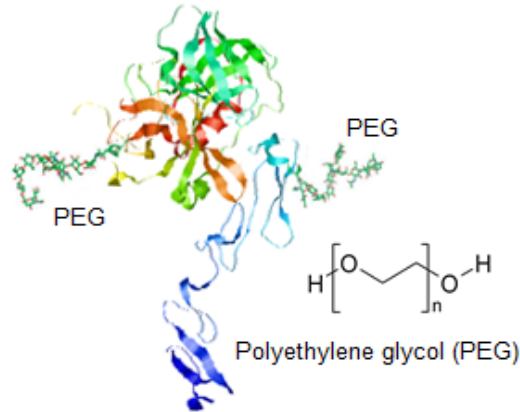
Half-life extension

PEGylated Liposomes



PEGylation

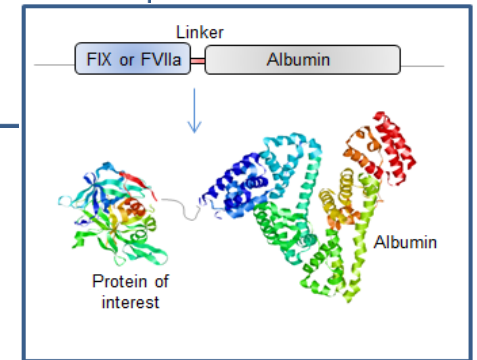
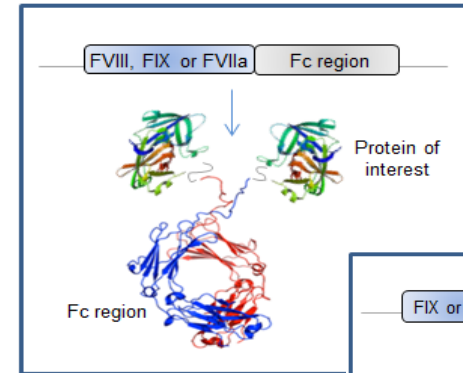
- Random
- Site specific



Fusion protein

- Fc fragment
- Albumin

Modification of amino acid sequence



Peyvandi F.

Factor IX 3 to 5-fold

- rFIX-Fc fusion
- rFIX glycoPEGylated
- rFIX-albumin fusion

Factor VIII 1.5 to 1,8 -fold

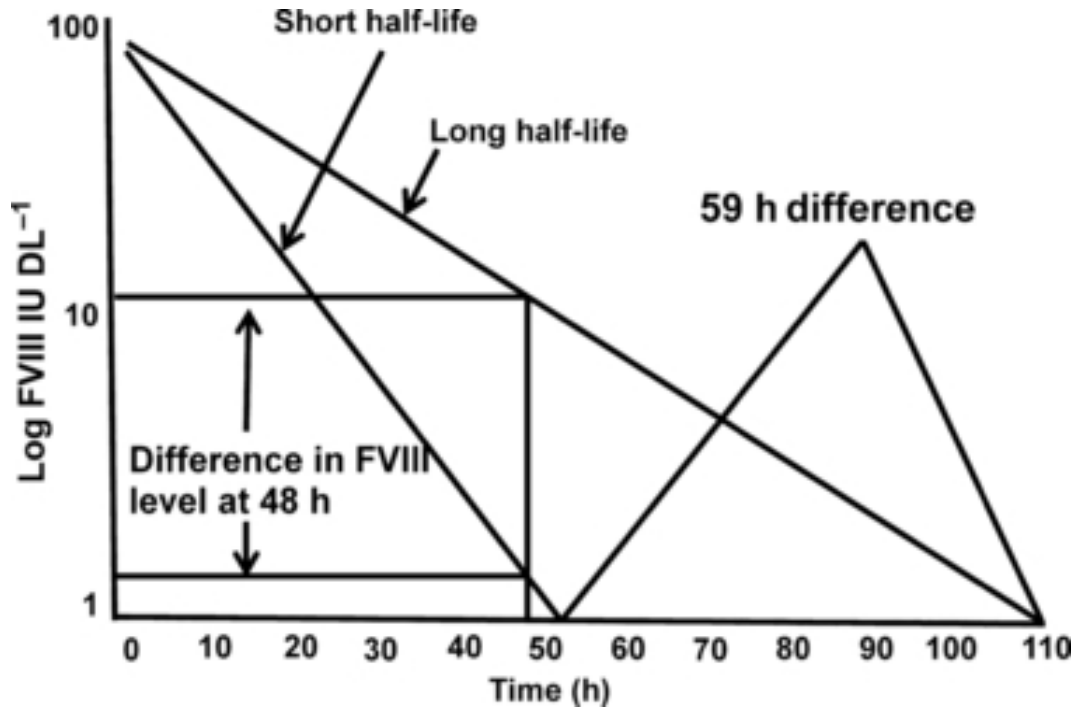
- rFVIII-Fc fusion
- rFVIII-glycoPEGylated

rFVIIa 3 to 5-fold

- rFVIIa glycoPEGylated
- rFVIIa variant with 4 amino acid changes



Peyvandi F.



“Knowledge of individual patient FVIII half-life with these products would appear to be even more important than with conventional products when designing prophylactic regimens. This needs to be taken into account when clinical trials with these products are devised and it is unlikely that once weekly infusions will be suitable for all patients.”

WE **CAN** HAVE MORE TREATMENT PRODUCT

- Coalition of PPTA, treaters and patients
- Used latest best evidence for effectiveness of prophylaxis
- Used patient survey for benefit
- Used modern concept for discounting

Payer Perspective	Cost Effectiveness
UK	Prophylaxis is DOMINANT over On Demand
USA	Cost/QALY is \$68K (Cost-effective)
Sweden (daily prophylaxis)	Prophylaxis is DOMINANT over On Demand

Outcomes of the cost-utility model

Payer Perspective	Cost	QALYs	Incremental Cost	Incremental QALYs	Cost/QALY	ICER
US						
OD	\$4,140,275	19.42	\$412,999	6.06	\$213,759	\$68,109
Pro	\$4,563,274	25.48			\$179,097	
UK						
OD	£1,784,095	27.16	- £280,866	9.69	£65,688	Dominant
Pro	£1,503,229	36.85			£40,798	
Sweden						
OD	SEK 22,101,124	17.87	SEK 5,331,051	10.99	SEK 1,236,772	SEK 484,888
Pro	SEK 27,432,176	28.87			SEK 950,197	
Sweden (Daily Pro dosing)						
OD	SEK 22,101,124	17.87	- SEK 10,541,993	10.99	SEK 1,236,772	Dominant
Pro	SEK 11,559,131	28.87			SEK 400,386	

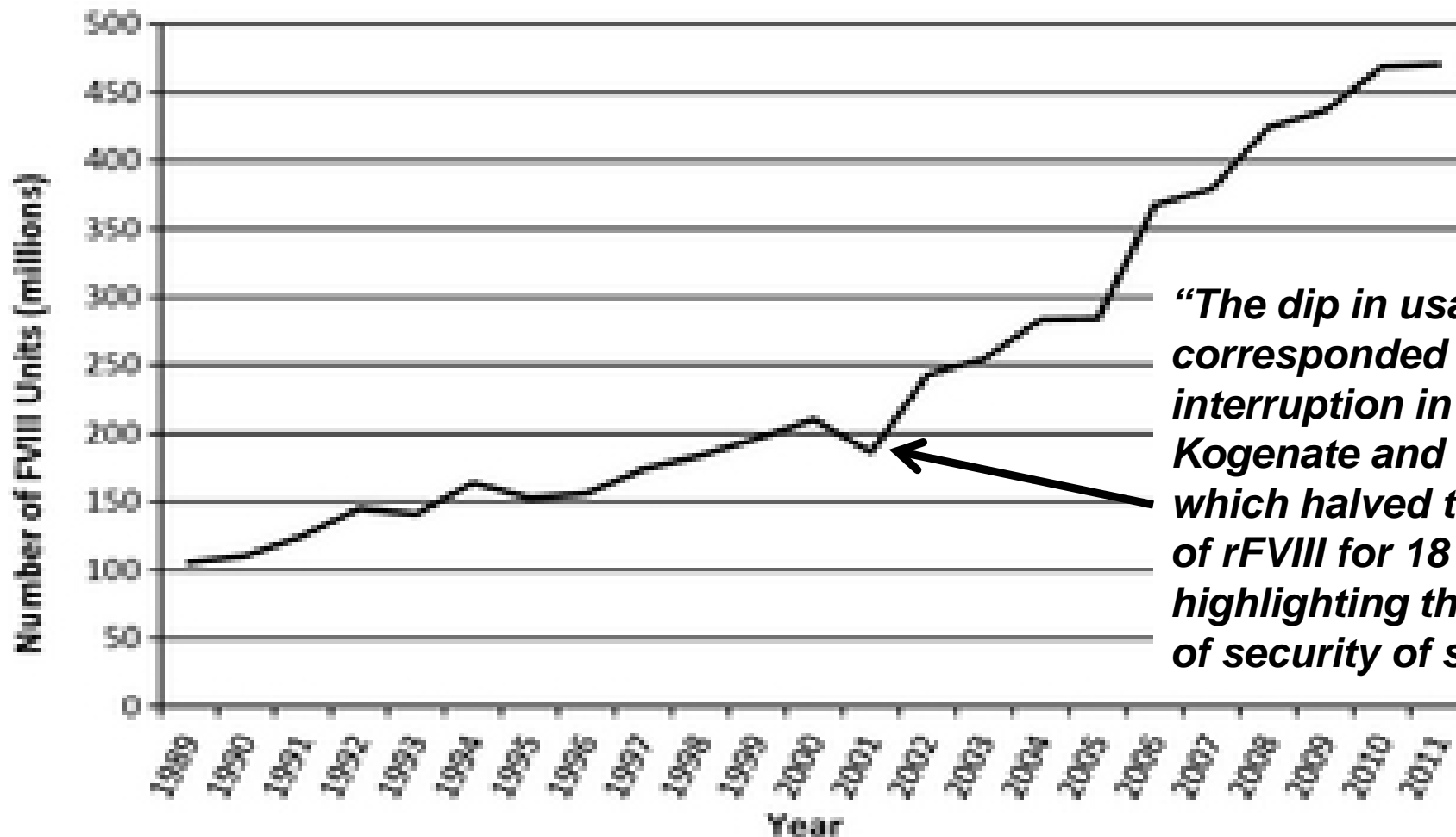


ORIGINAL ARTICLE

Treatment for life for severe haemophilia A– A cost-utility model for prophylaxis vs. on-demand treatment

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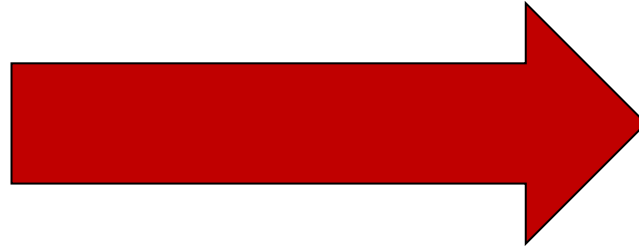


“The dip in usage in 2001 corresponded to the interruption in supply of Kogenate and Helixate, which halved the UK supply of rFVIII for 18 months, highlighting the importance of security of supply.”

We need to grow the cake



Current FVIII usage



- Assessment of elasticity
- Budget impact analysis
-

- *“an acceptable frequency of bleeds”*
 - **ZERO**
- *“adequate preservation of joint function”*
 - **NORMAL**
- *“prophylaxis should be commenced after the second joint bleed”*
 - **AT DIAGNOSIS**

Etc etc

- We've gone a long way – we have a long way to go
- As clinical research continues, we see that more product is needed
- The supply of all forms of FVIII has increased over the past years
- Treatment of FVIII to optimal levels is cost-effective
- While prices remain high, there has been a steady decrease
- If consumption rises to approach the real demand for FVIII, prices may be expected to drop further



*“..the way is long, but the end
is near
Already the fiesta has begun,
The face of God will
appear.....”*

Dylan 1975