
WFH 2014
WORLD
CONGRESS
Melbourne, Australia · May 11-15
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WORLD CONGRESS
THE LARGEST INTERNATIONAL MEETING
FOR THE GLOBAL BLEEDING DISORDERS
COMMUNITY MELBOURNE, AUSTRALIA · MAY 11-15
ORGANIZED BY: WORLD FEDERATION OF HEMOPHILIA
HOSTED BY: HAEMOPHILIA FOUNDATION AUSTRALIA

Progress in Hemophilia Care during the later part of the 20th Century

Prophylaxis

Other Benefits of prophylaxis

- ✓Less need for orthopedic surgeries
- ✓Less need for hospitalizations
- ✓Less time lost from school/work
  - ➔Better school performance
  - ➔Better Quality of Life

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Declared

Prophylaxis = standard of care for persons with severe hemophilia

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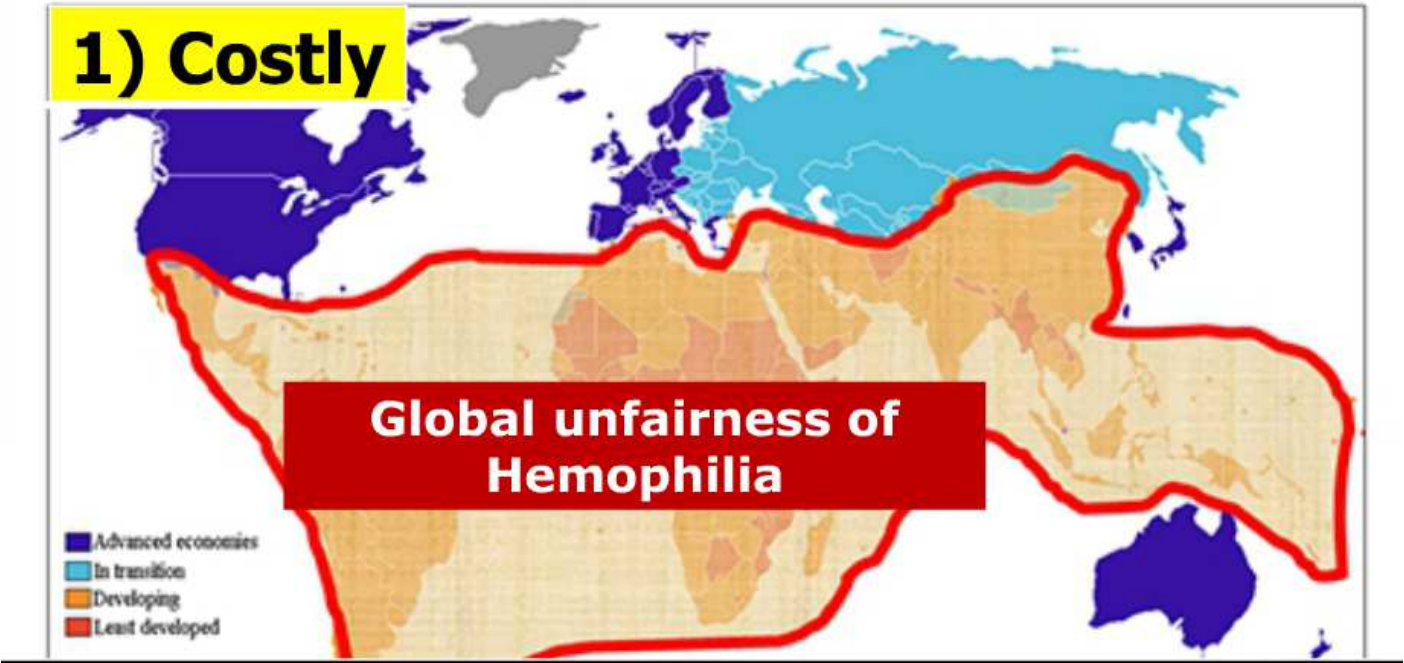
Although Prophylaxis works –there are problems with prophylaxis with current factor concentrates!



Much of the world can't afford factor or prophylaxis

Although Prophylaxis works –there are problems with prophylaxis with current factor concentrates!

2) Venous access & Adherence

Problem everywhere with current "short acting" concentrates

"Source: Copyright-free, Google Images"

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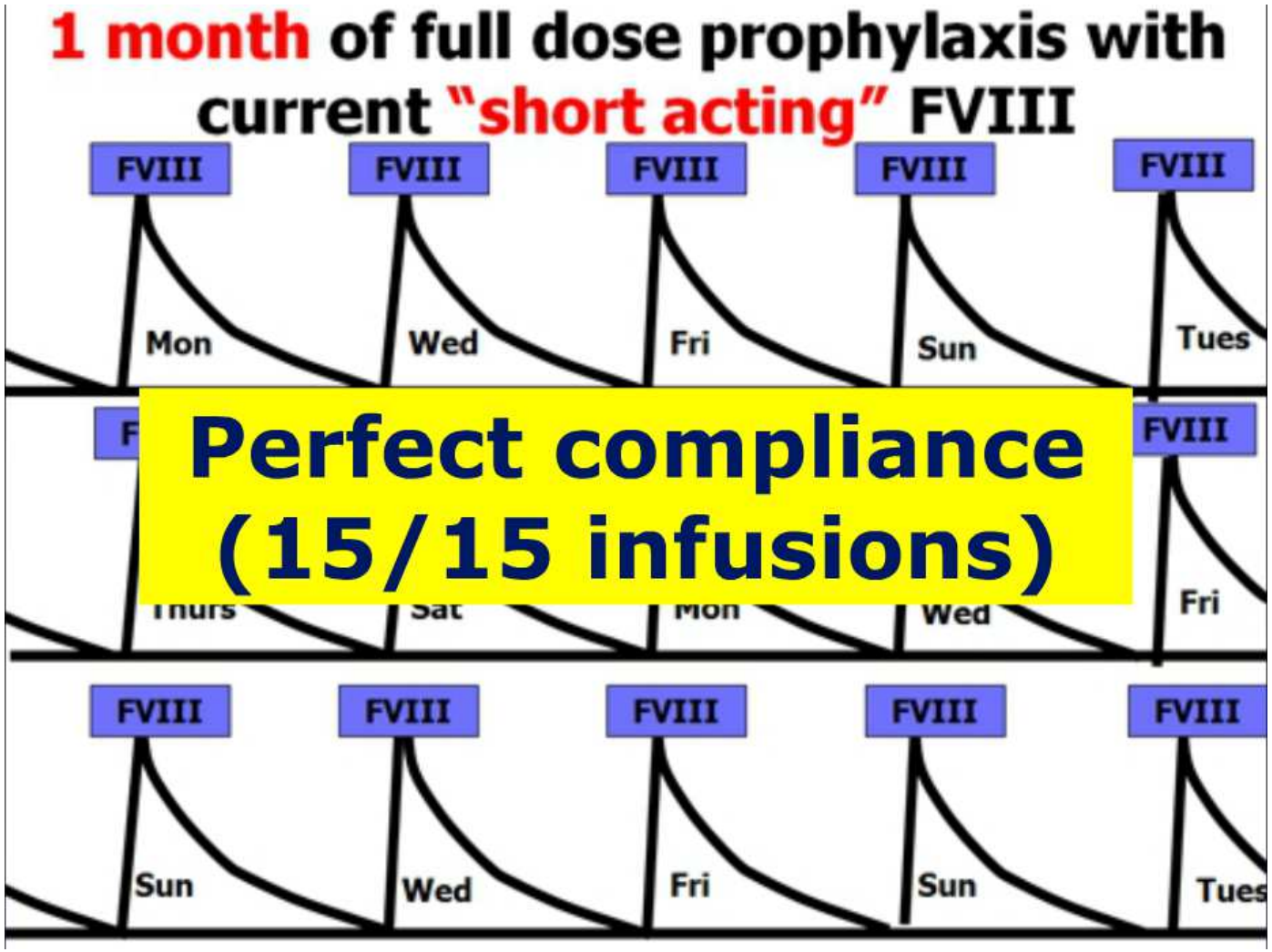
1 month of full dose prophylaxis with current "short acting" FVIII
FVIII
FVIII
FVIII
FVIII
FVIII
Mon
Wed
Fri
Sun
Tues
Perfect compliance (15/15 infusions)
FVIII
Fri
FVIII
FVIII
FVIII
FVIII
FVIII
Sun
Wed
Fri
Sun
Tues

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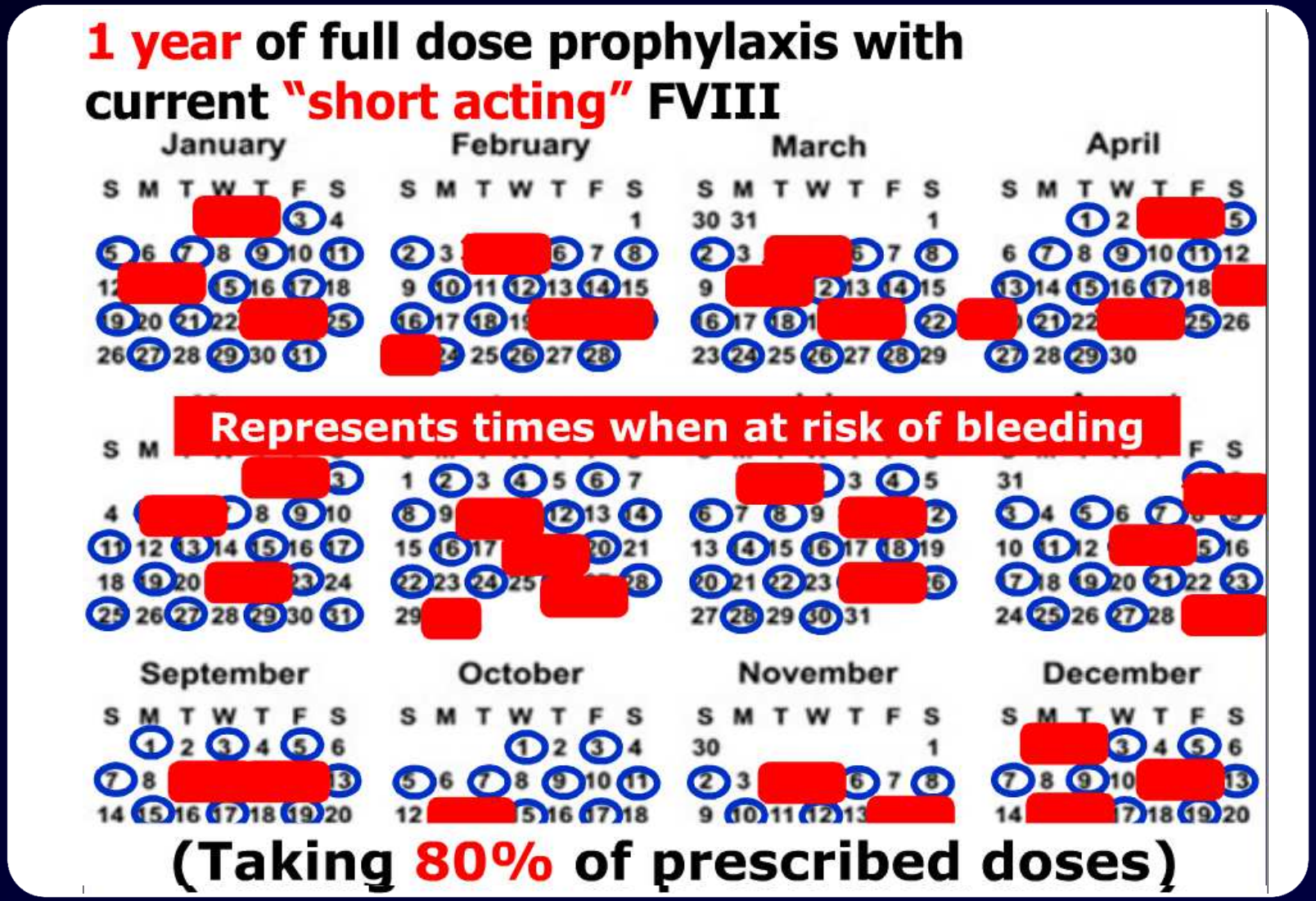

1 year of full dose prophylaxis with current "short acting" FVIII
January
February
March
April
Represents times when at risk of bleeding
September
October
November
December
(Taking 80% of prescribed doses)

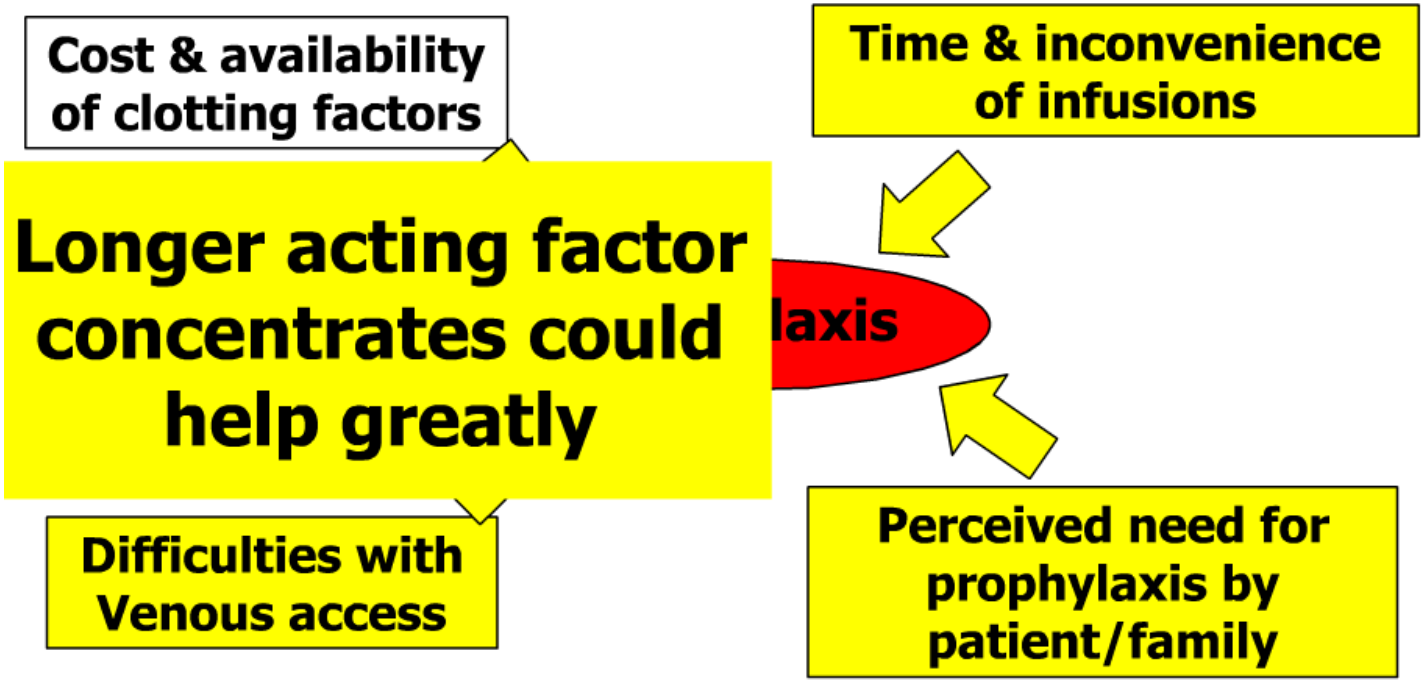
How adherent are patients with prophylaxis?

Being adherent
Defined: taking =80% of prescribed doses

Studies	Region	Rate of Adherence
1. Manco-Johnson MM et al. Am J Hematol 1994 2. Hacker MR et a 3. Thornburg CD Haemophilia. 2	1 USA	60%
4. De Moerloose 2008	Europe	80%

Not great!

Barriers to patients' adherence to prophylaxis



Petrini P. Hemophilia 2007
De Moerloose P et al, Haemophilia 2008

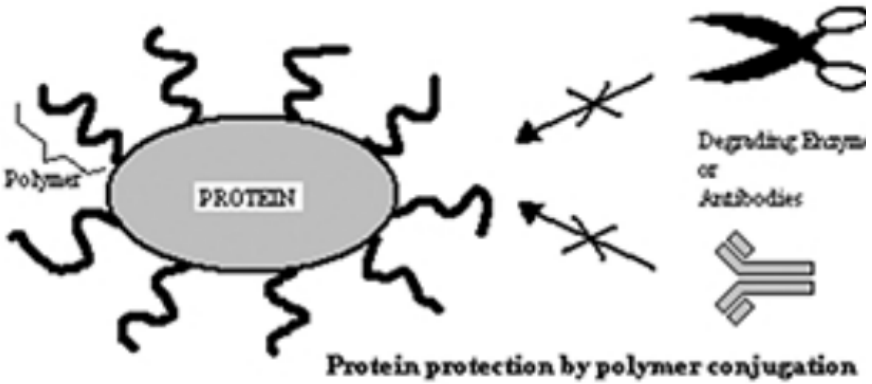
Main technologies used to extend half-life of factor

Pegylation

Pegylation of proteins (20 yrs)

1. ↓ renal clearance
2. Protects against enzyme digestion
3. Blocks interaction with clearance receptors (LRP)

Hydrophilic cloud around a protein



Protein protection by polymer conjugation

e.g. Cimzia, Neupogen & Peg-asparaginase (Oncaspar)

Pasut G & Veronese FM . Adv Poly Sci 2006

Main technologies used to extend half-life of factor

	Fusion	
	Albumin	Fc (of IgG)
Fc fusion drugs Etanercept & romiplostin	$T_{1/2}$ ≈3 wks	$T_{1/2}$ ≈3 wks
Albumin fusion drugs albiglutide & neugranin	Neonatal Fc receptors on endothelial cells Internalize IgG & albumin ↓ protect them from lysosomal degradation ↓ recycle them back into blood	

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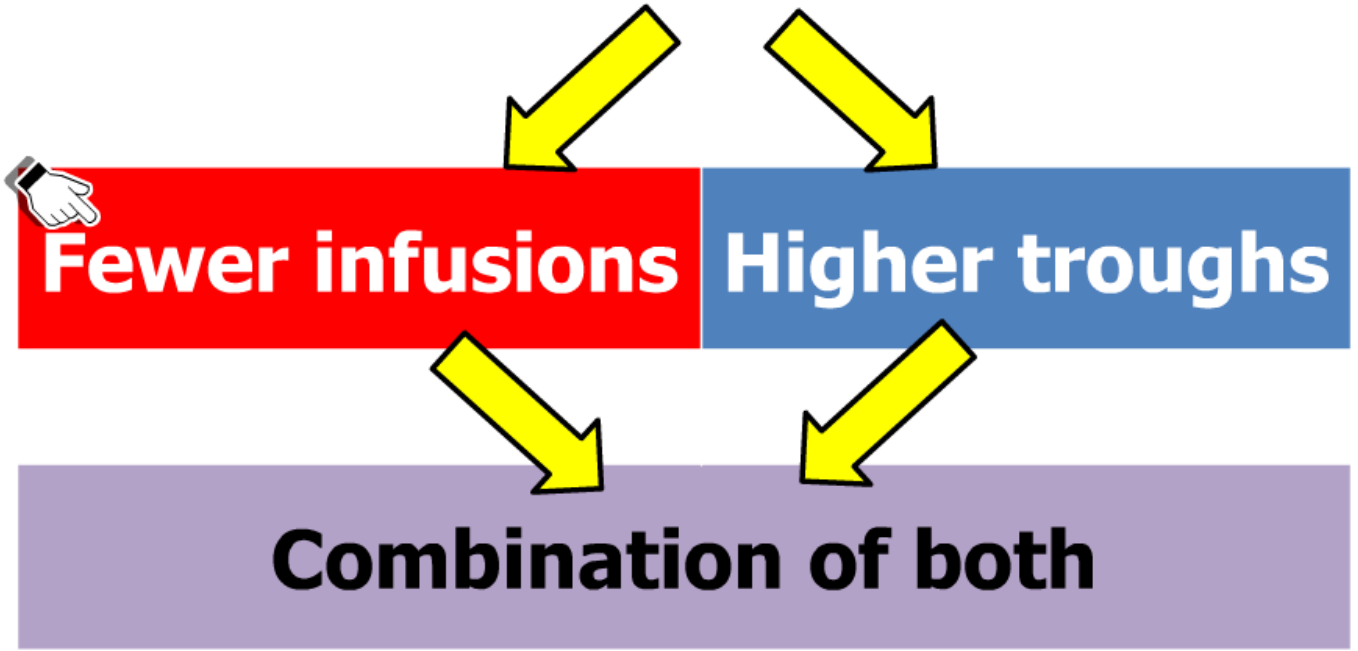
Product /Manufacturer	Technology	Cell line	$T_{1/2}$ (hr)	$T_{1/2}$ vs. FIX	≈ time to 1% after 50 U/kg
rFIXFc (Biogen Idec)	Fc-Fusion protein	HE	57-83	3X	10 days (2 wks with 100 U/kg)
N (N N			96-110	>5X	2-3 weeks
rIX-FP (CSL-Behring)	Albumin Fusion protein	CH	89-96	>5X	2-3 weeks

Very Significant prolongation of $T_{1/2}$

How will these longer acting concentrates impact on prophylaxis?



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If goal is fewer infusions

LA-FIX	Give factor once every 10 days - 3 wks (and still) Maintain trough FIX >1%	Current: 104 infusions/yr Future: 18-36 infusions/yr
LA FVIIII	Give factor 2/wk (and still) Maintain trough FVIII >1%	Current: 182 infusions/yr Future: 104 infusions/yr

Powell JS et al. *NEJM*, 2013.
Mahlangu JP et al. Blood, 2014.

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If goal is Higher troughs

LA-FIX	Give LA-FIX 2X/wk	Maintain trough FIX > 30-40%
LA-FVIIII	Give LA-FVIII Every other day	Maintain trough FVIII >10%

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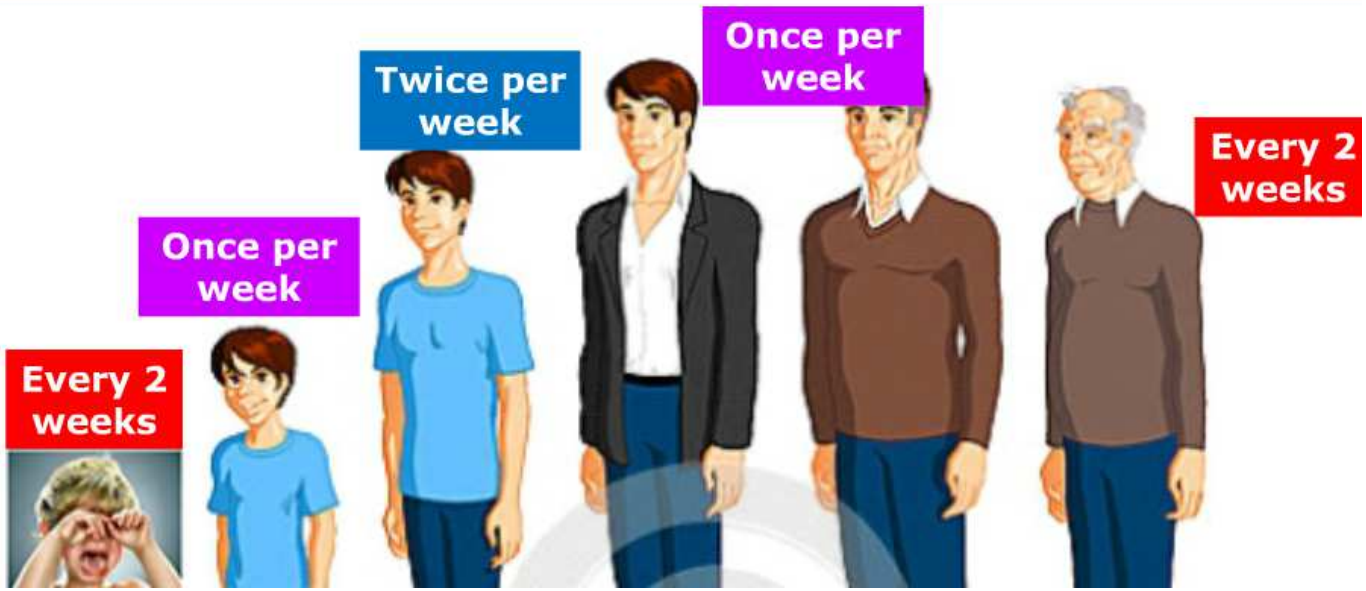
Allows for more individualization of therapy

One size does not fit all nor does it fit one's entire life



Immunogenicity

- Will they result in...

More (>25%)	Same	Less (<25%)

- Community will not tolerate more

  - So far so good in studies on PTPs
  - We await studies on PUPS

Ivens IA et al. Haemophilia, 2013.
Mei B et al. Blood, 2010.
Kaufman RJ & Powell JS. Blood, 2013.

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Who should decide if a patient switches to a longer acting factor (once available)?

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What will be the cost of prophylaxis with longer acting concentrates?

Will it be more costly than prophylaxis with current concentrates?

Will these products all cost the same or will some be more costly?

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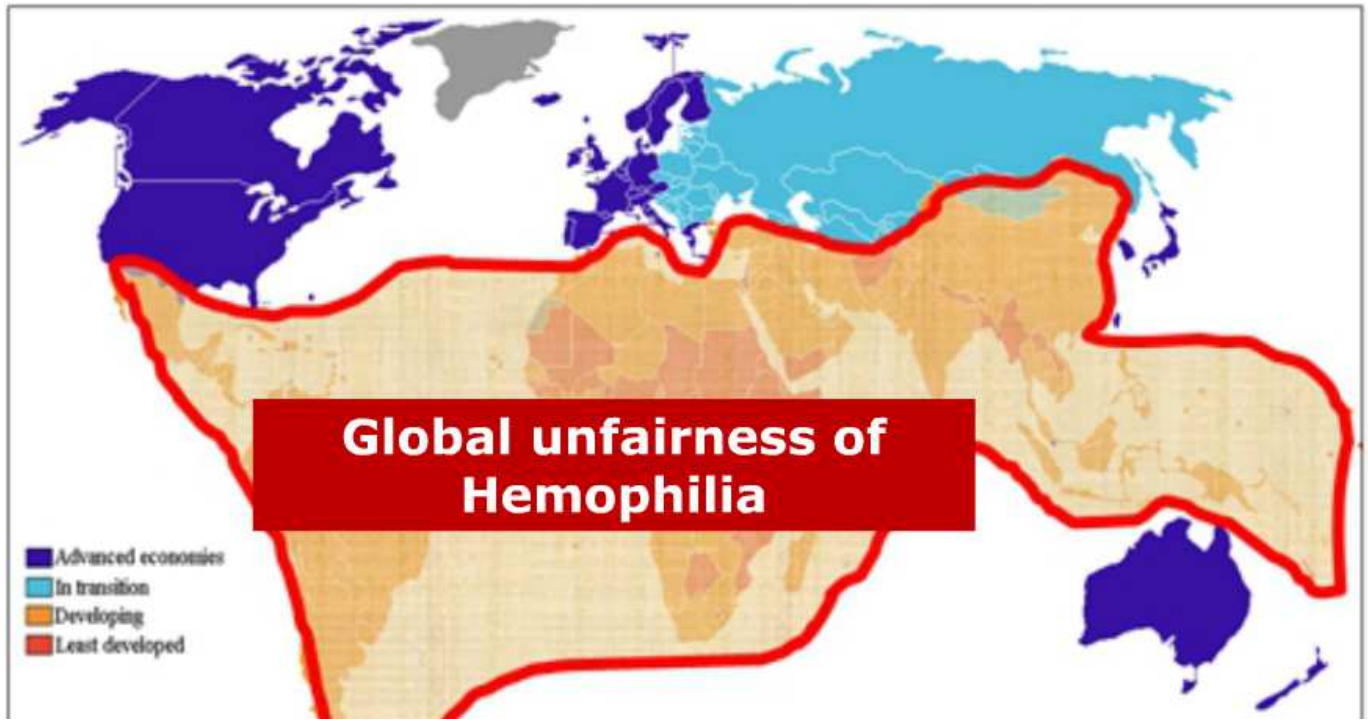
World-wide impact of newer longer acting factor concentrates

- **Will prophylaxis with longer acting concentrates be even less attainable for most of the world**



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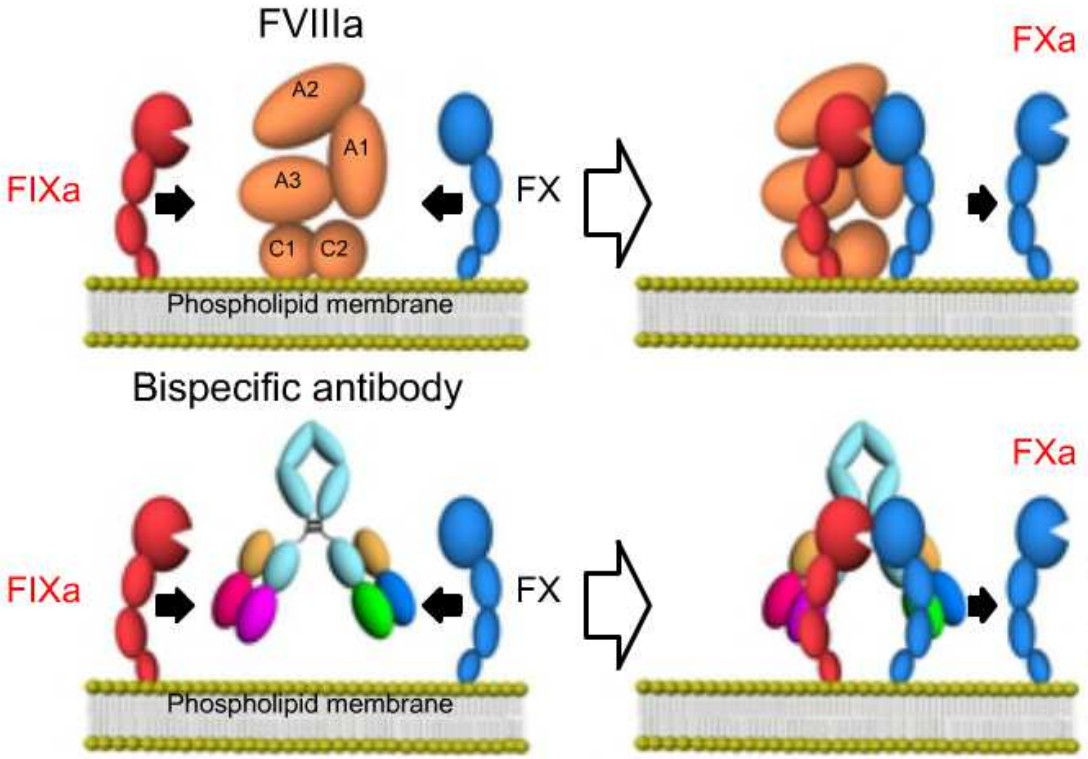
Concept of FVIIIa-mimetic bispecific antibody



Kitazawa, - Shima, Yoshioka, Hattori
Nature Medicine 2012;18(10):1570

Sampei, et al.
PLoS One 2013;8(2):e57479

Muto, - Shima, Hattori
J Thromb Haemost 2014;12:206

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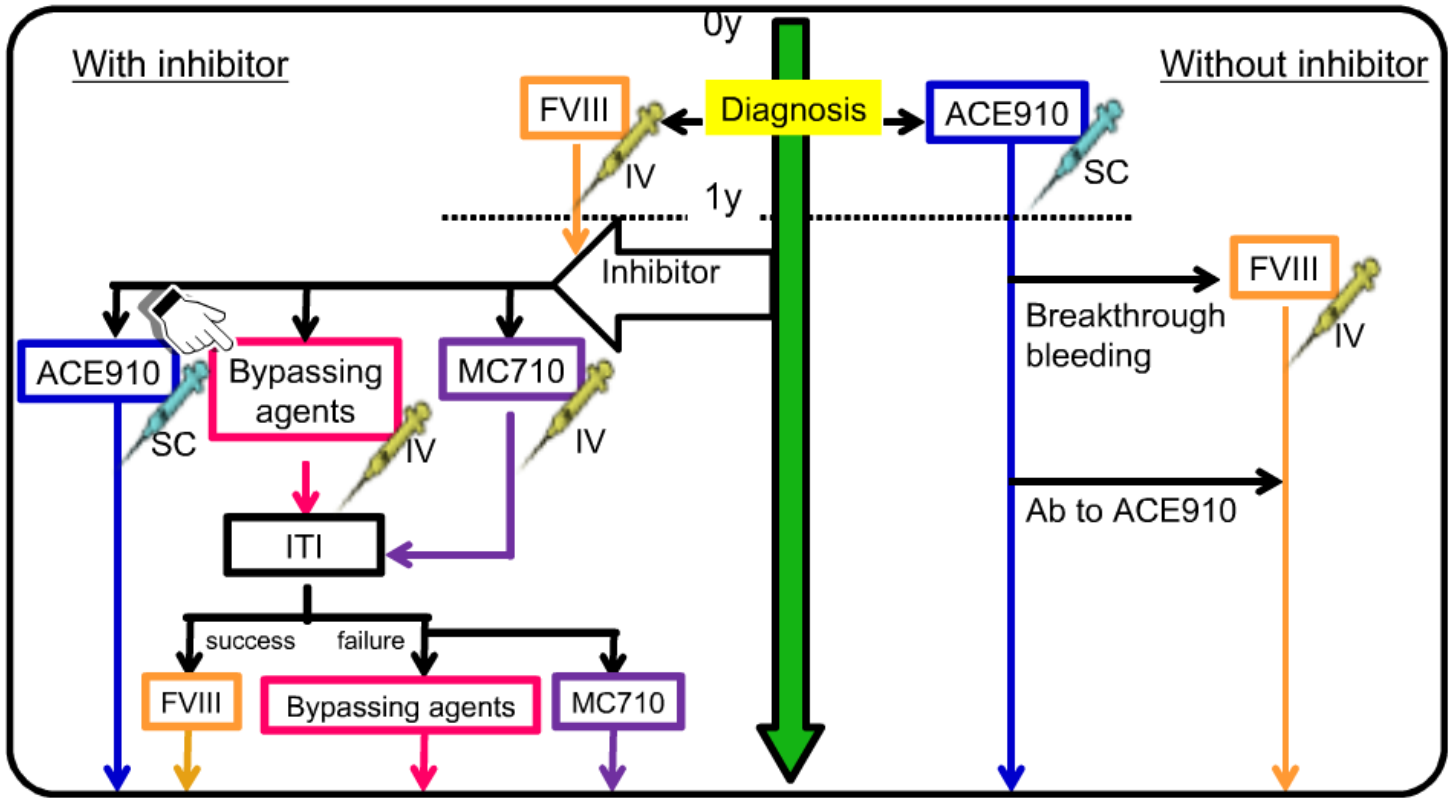
Future therapy for HA patient



ACE910 can be used as the 1st line treatment from early childhood.

Quelle: WHF 2014 (http://wfh.multilearning.com/)