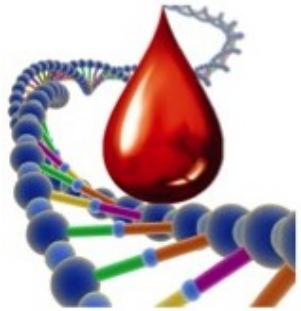
”Treatment of Patients with Extended Half-Life FVIII and FIX Products"

David Lillicrap
Department of Pathology and Molecular Medicine
Queen’s University, Kingston, Canada

ECAT Leiden, November 2018

Queen's University



Clinical and Molecular Hemostasis Research Group

Queen's University

KGH Kingston General Hospital

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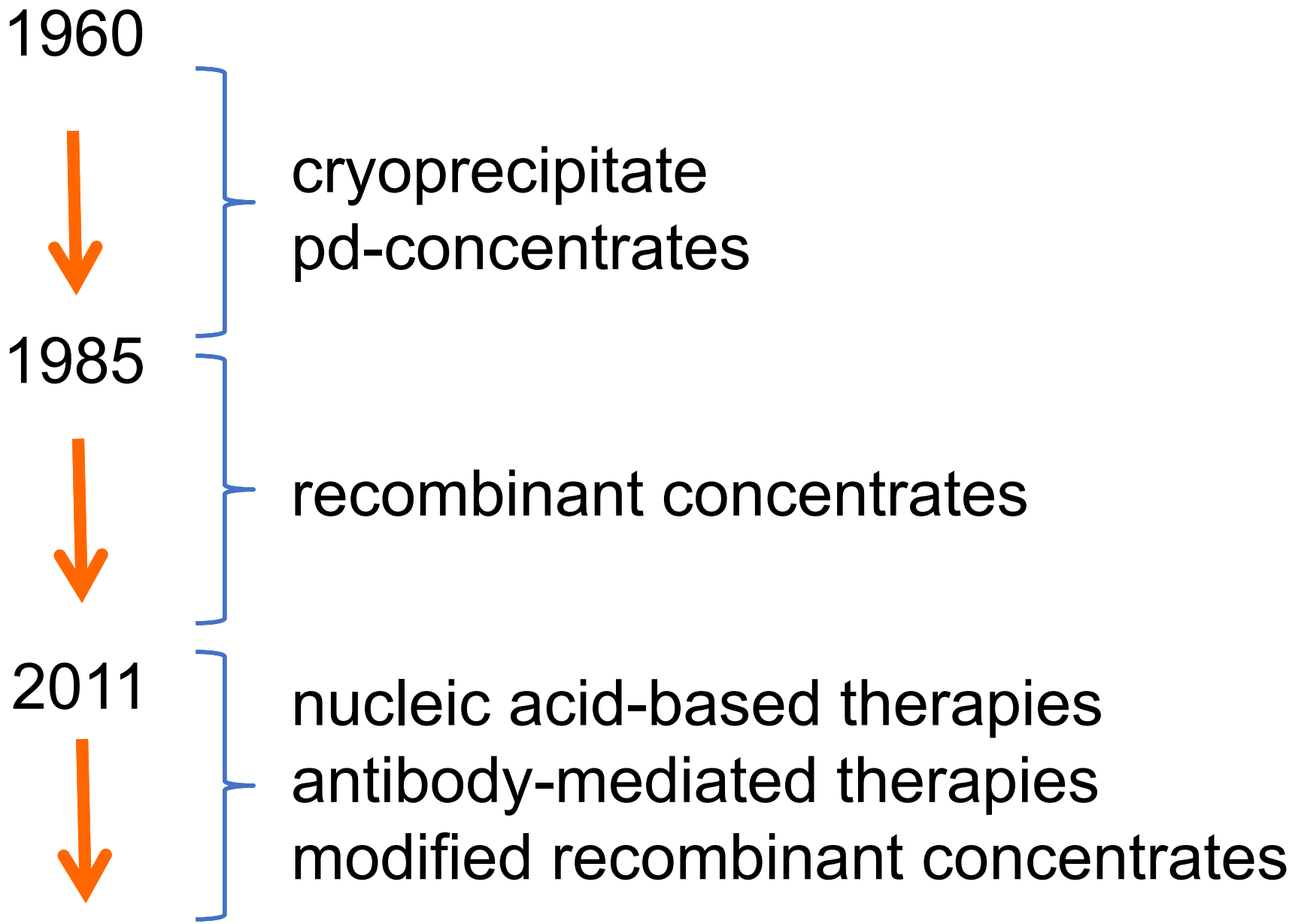
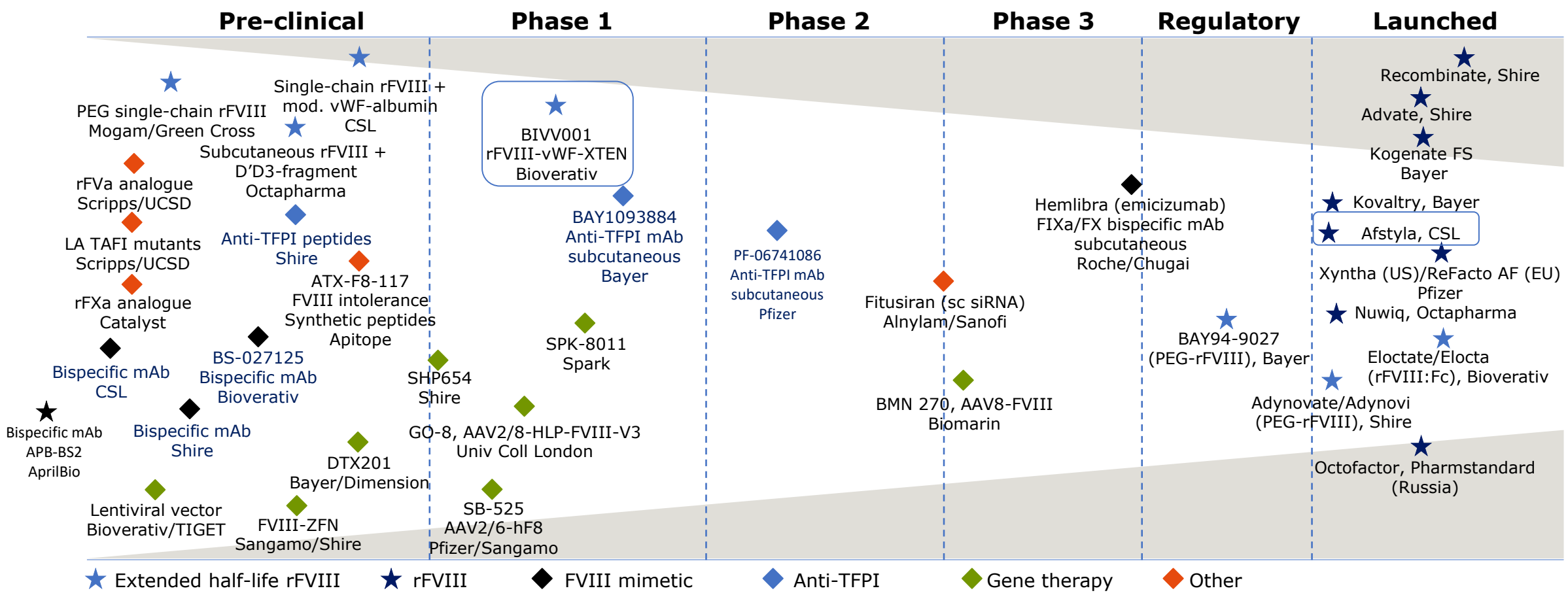
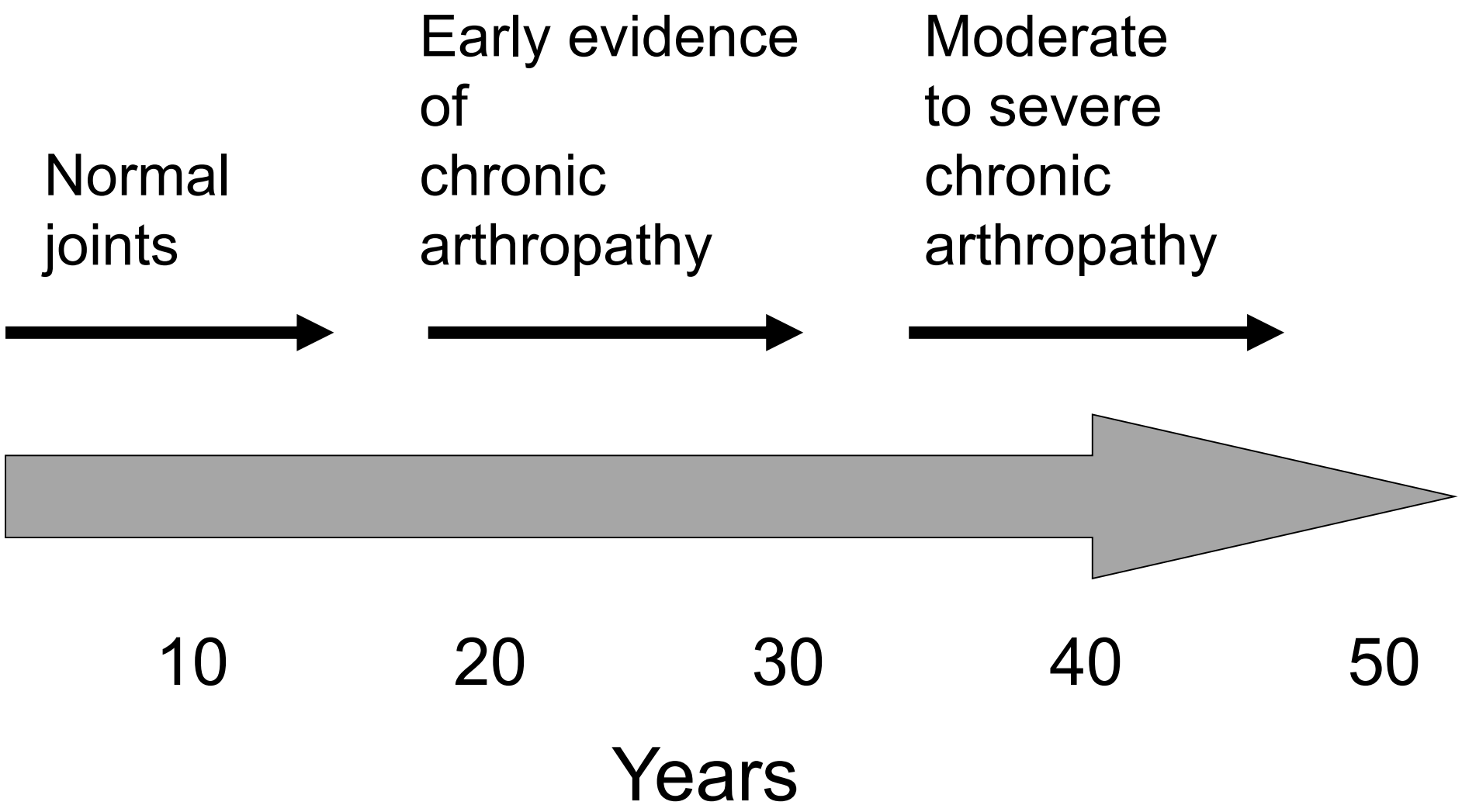

1960
1985
2011
cryoprecipitate
pd-concentrates
recombinant concentrates
nucleic acid-based therapies
antibody-mediated therapies
modified recombinant concentrates

Overview of products available and in development for hemophilia A

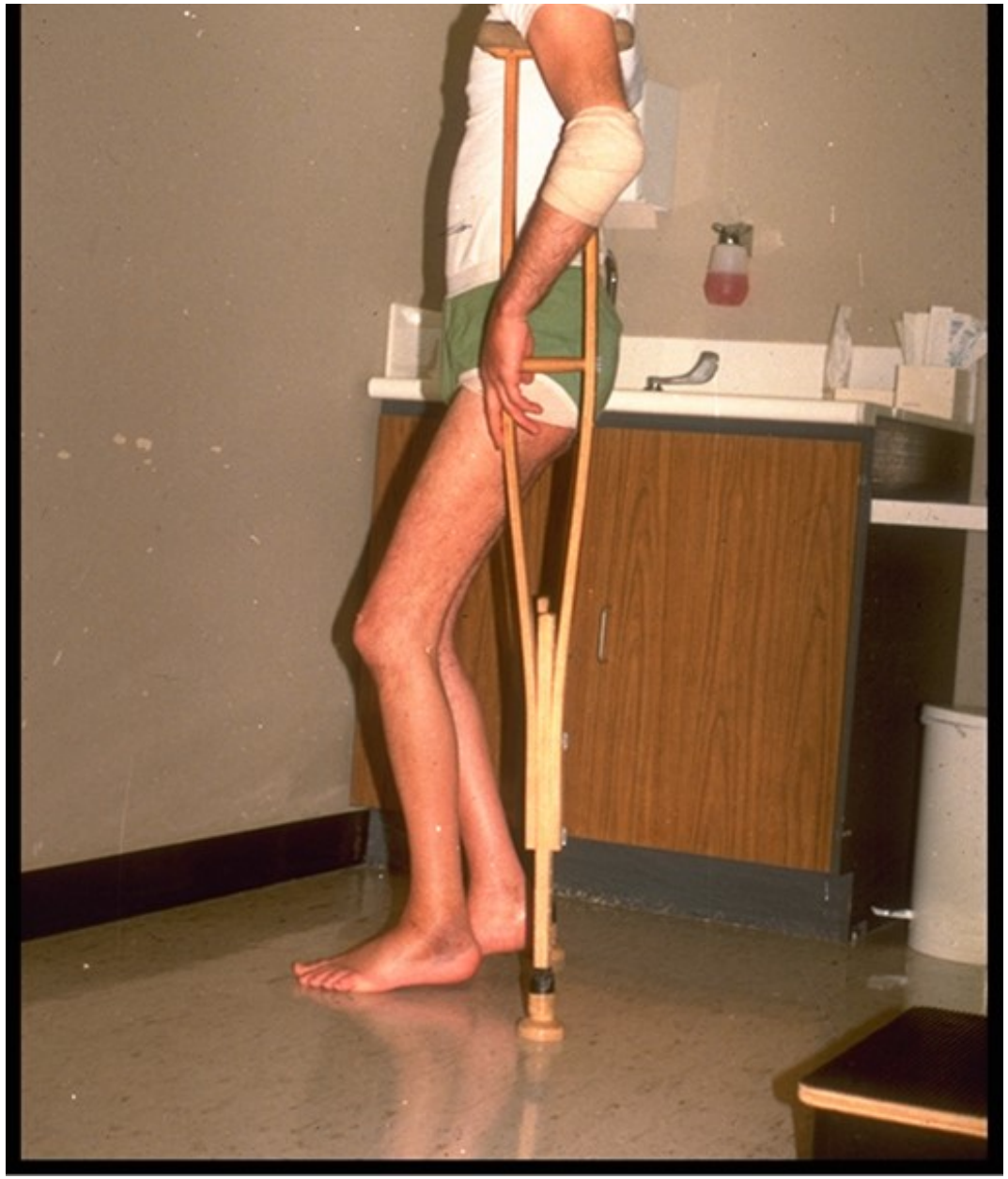


Limitations to Current Hemophilia Treatment

- Inconvenient
  - repeated intravenous infusions
- Immunogenic
  - 30% inhibitor incidence in hemophilia A
- Costly
- Only available to ~30% of all hemophiliacs globally



Development of long-term musculoskeletal disability in hemophilia



Chronic Hemophilic Arthropathy

Hemophilia Therapy in 2018

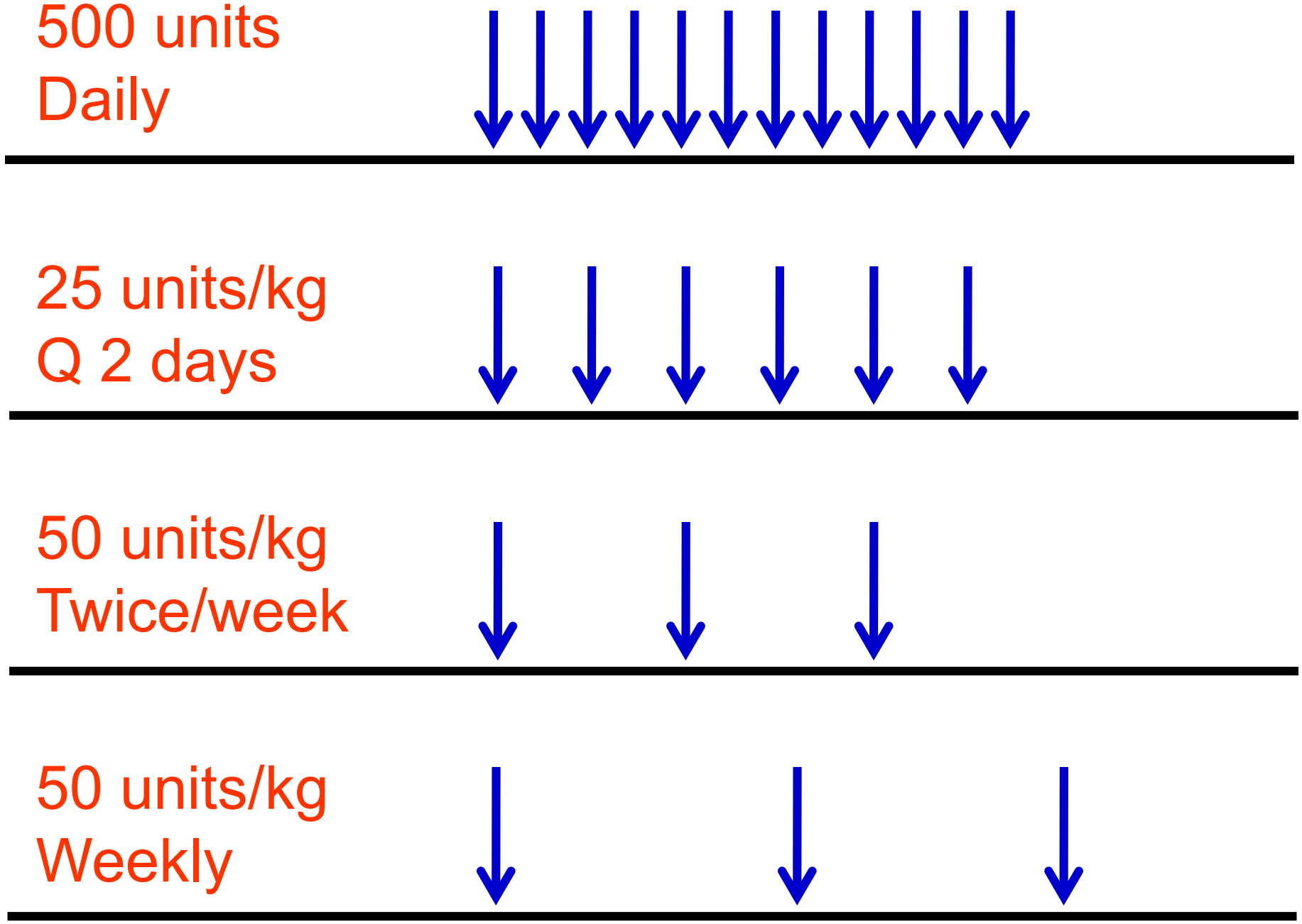
For Severe Hemophiliacs <1% FVIII/FIX

On-demand therapy

~2-6 infusions/month - Chronic hemophilic arthropathy

Prophylactic therapy

1-3 infusions/week - Long-term musculoskeletal benefit


500 units
Daily
25 units/kg
Q 2 days
50 units/kg
Twice/week
50 units/kg
Weekly

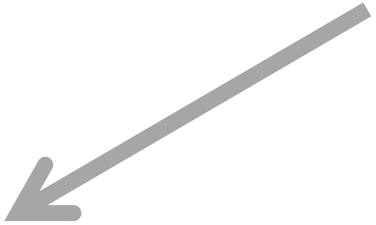
Coagulation Factor Half-lives

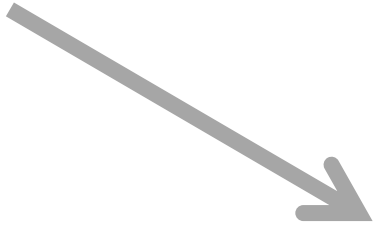
Factor VIII ~12 hrs (x3/week)

Factor IX ~24 hrs (x2/week)

Therapeutic Goal - Weekly Prophylactic Infusions

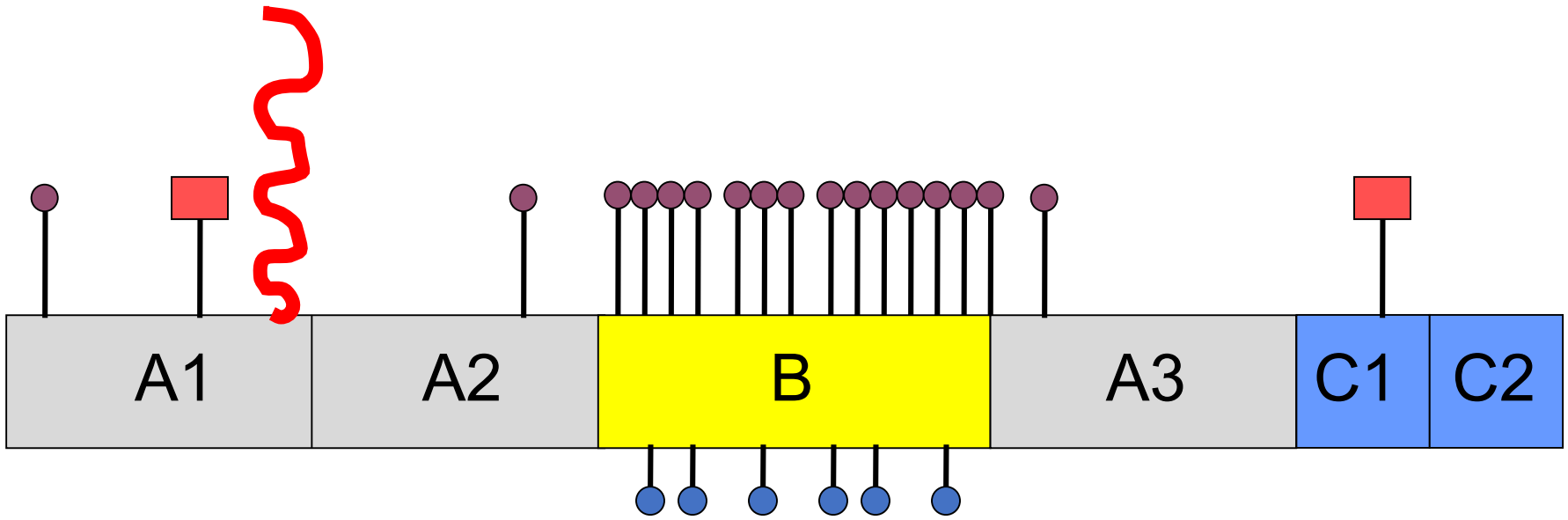
Prolonged Protein Half-life





Hydrophilic Polymer Conjugation
(eg PEGylation)

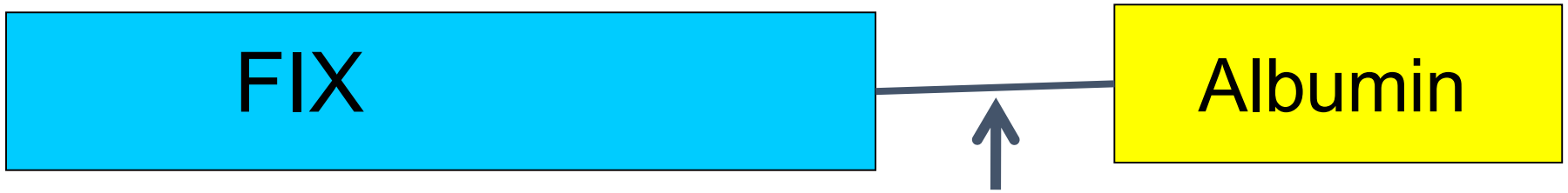
Variant Protein Generation
(eg fusion factors)



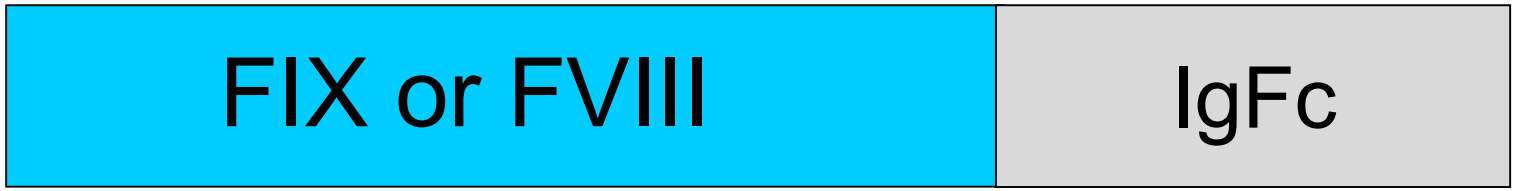
Site-Specific or Random Chemical Modification

PEG additions interfere with clotting factor clearance mechanisms

But can also interfere with assembly into the intrinsic tenase complex



FXIa cleavage sequence



Factor IX/FVIII Fusion cDNAs - Proteins

Albumin and IgFc as Fusion Partners

- Present in plasma at high concentrations

  IgG 12 g/L Albumin 42 g/L

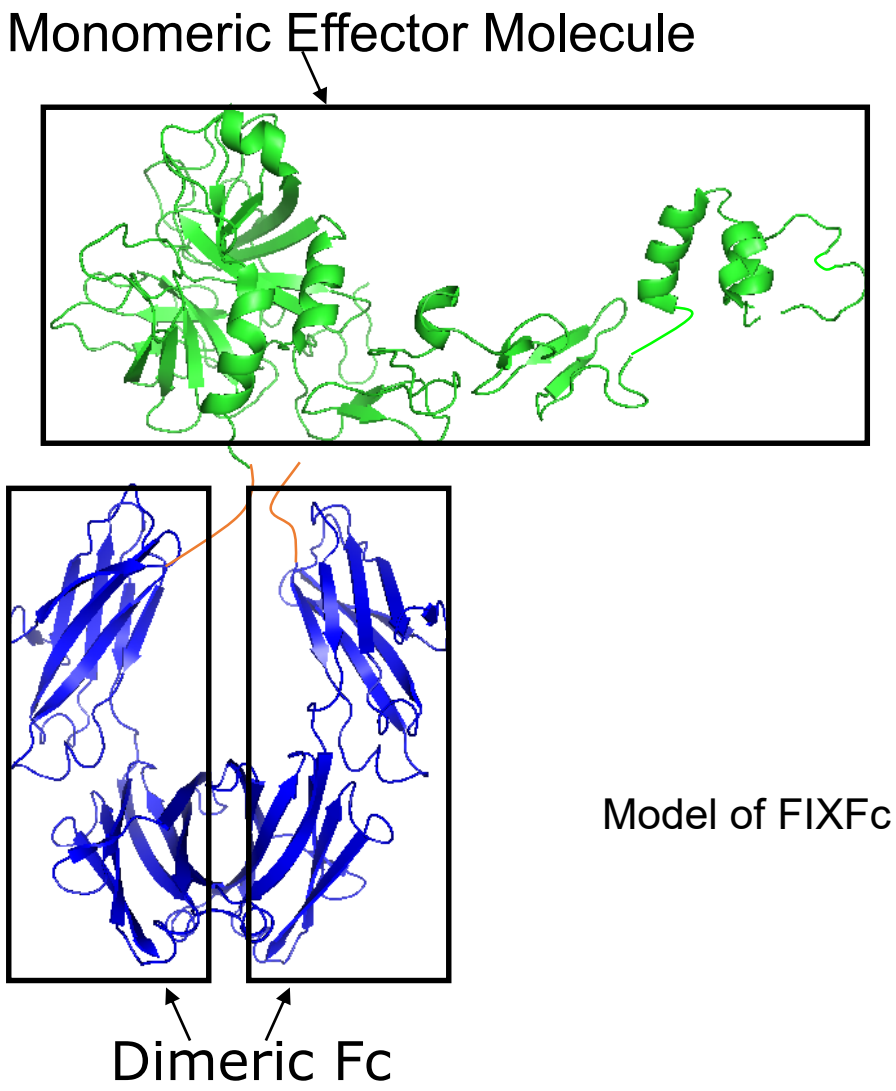
- Half-life ~25 days

- Same mechanism of rescue (FcRn receptor)

  - present in endothelial endosomes

Factor IX EHL Products

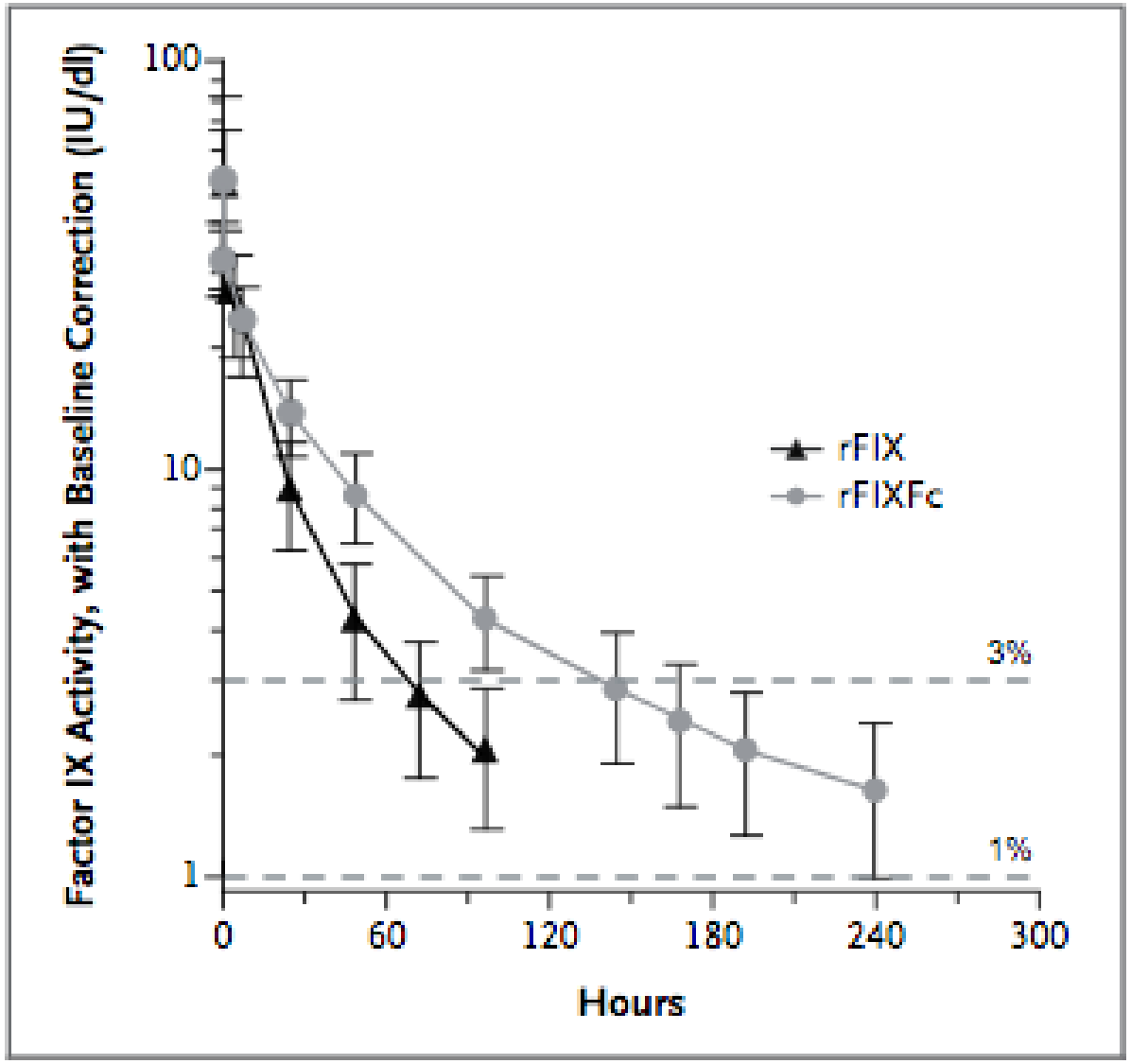
FIXFc, a monomeric Fc fusion



Model of FIXFc

- Monomeric Fc fusions have a single effector molecule attached to Fc
  - FIXFc monomer exhibits improved properties compared with the FIXFc dimer
  - Monomer configuration has demonstrated a range of improvements for a variety of proteins

Comparative FIX Half-lives: rFIX and rFXIFc

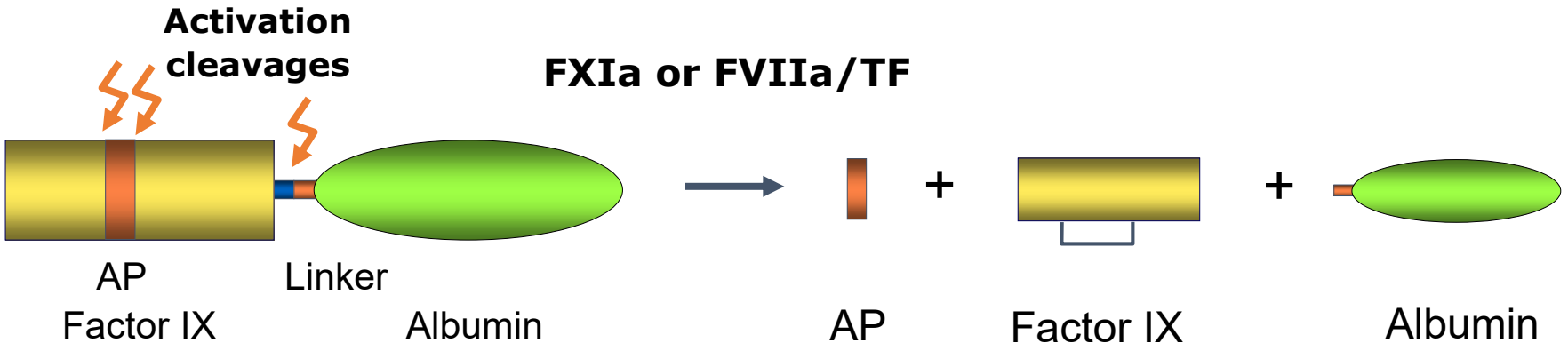


Single Infusion of 50 IU/kg

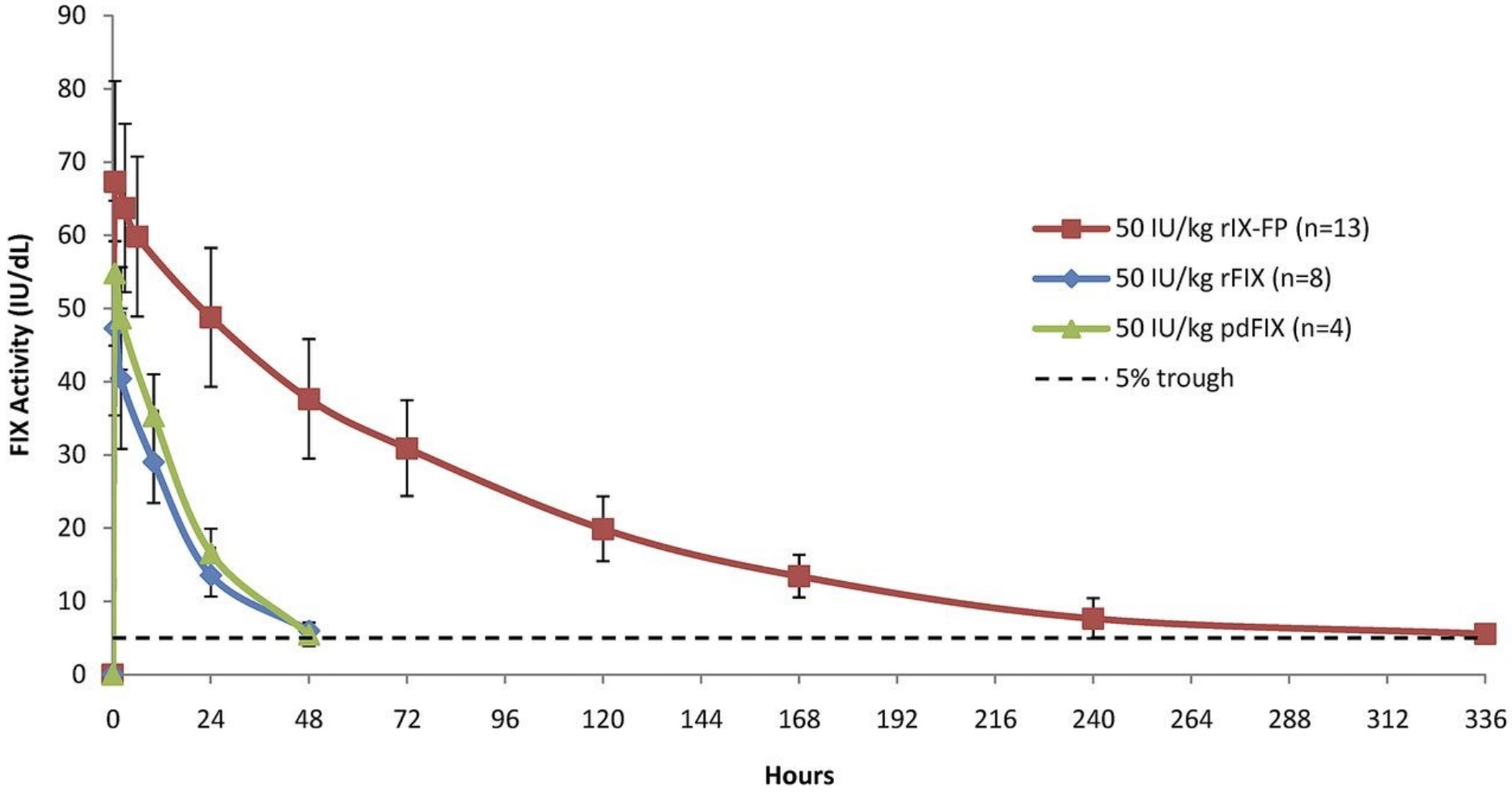
Powell et al. NEJM 2013

rIX-Albumin Fusion Protein

- **rIX-FP with proteolytically cleavable linker**
  - Albumin fused to the C-terminus of FIX
  - Cleavable linker between FIX and albumin derived from FIX activation region

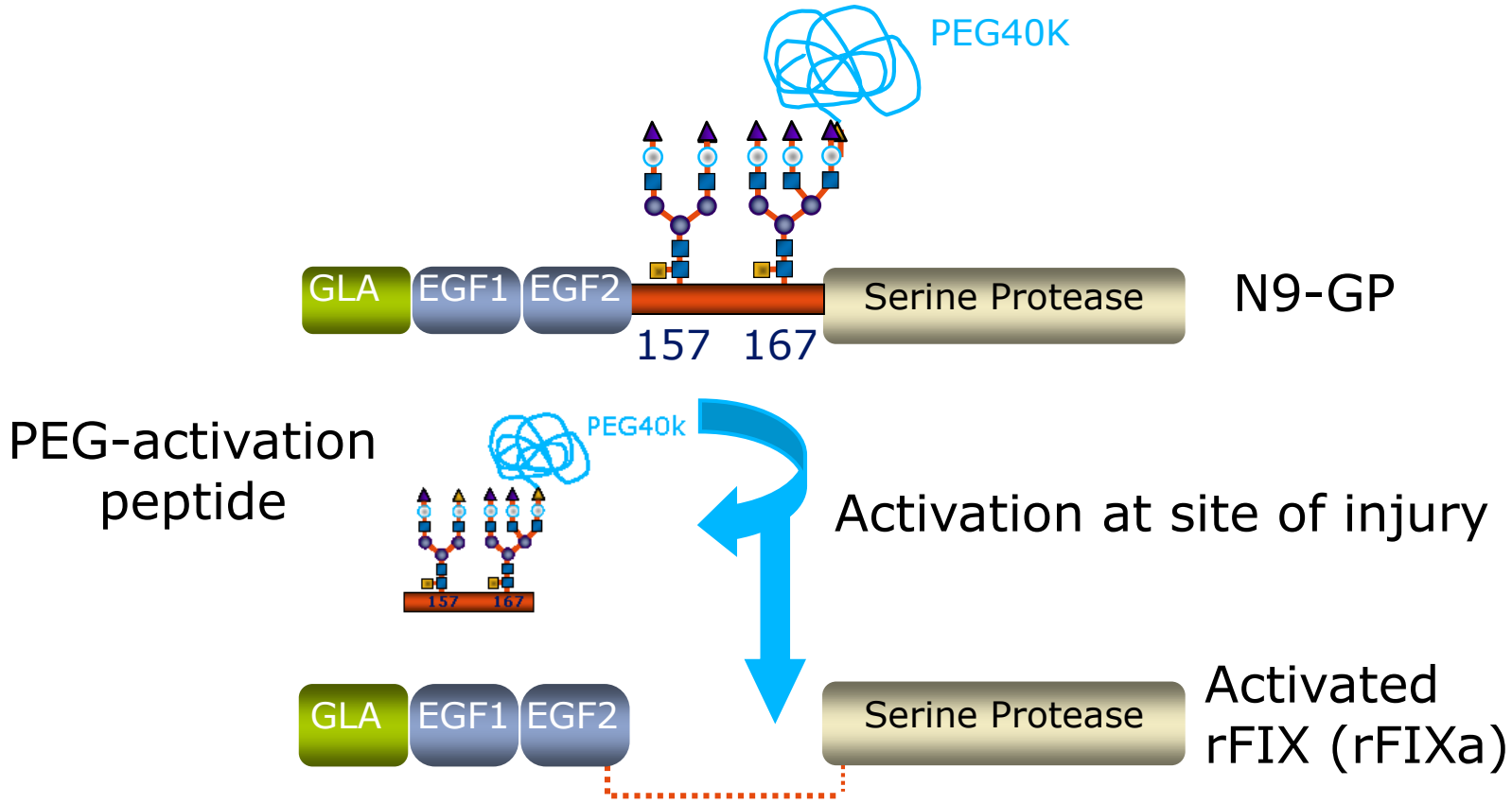


FIX activity level after the infusion of 50 IU/kg of rIX-FP and previous FIX product (PK population)

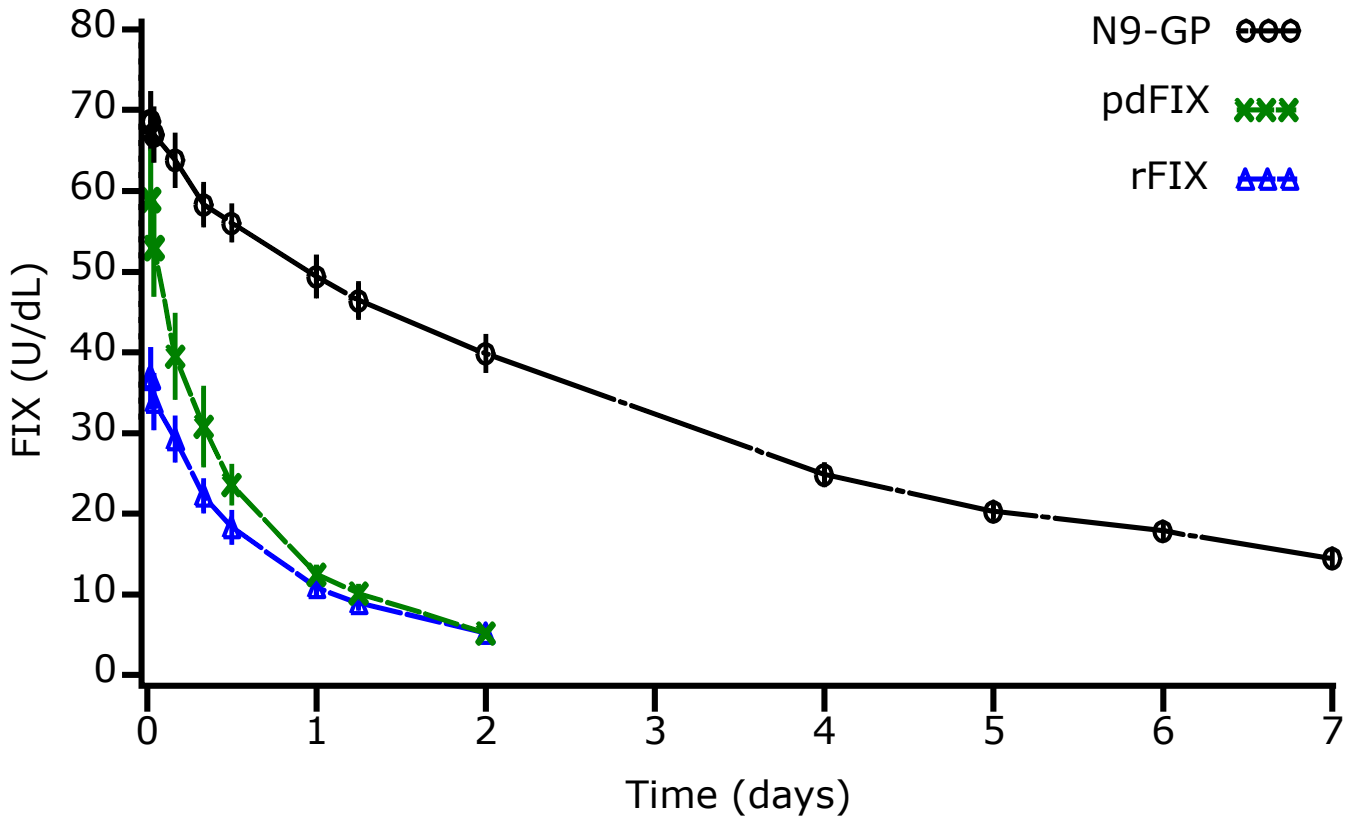


Santagostino E et al. *Blood* 2012; 120:2405-2411.

GlycoPEGylated rFIX (N9-GP)



Pharmacokinetic Comparison of N9-GP to previous FIX Products



Negrier C et al. *Blood* 2011; 118:2695–2701.

Comparison of derived PK parameters between N9-GP and previous FIX products

PK parameters	N9-GP Mean (N=15)	rFIX Mean (N=7)	pdFIX Mean (N=8)	Ratio N9-GP/FIX
$t_{1/2}$ (hours)	92.7	19.3	17.8	5.00
Incremental recovery (U/dL per U/kg)	1.33	0.69	1.12	rFIX: 1.94 pdFIX: 1.20
CL (mL/hour/kg)	0.70	6.99	5.48	0.11
Vz (mL/kg)	94.2	195	141	0.57
AUC (mL/kg)	71.3	7.15	9.1	rFIX: 10.13 pdFIX: 7.69
Time to 1% activity (days)	22.5	4.5	4.0	
Time to 3% activity (days)	16.2	2.8	2.7	

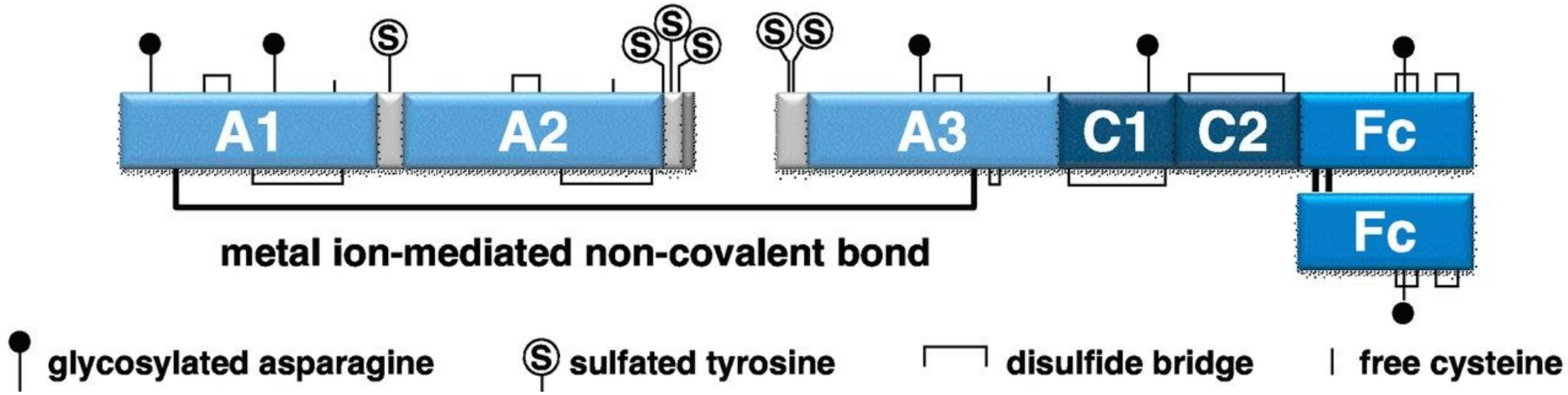
The time to 1% and 3% activity was estimated *post-hoc*

Negrier C et al. *Blood* 2011; 118:2695–2701.

Conclusions for EHL FIX

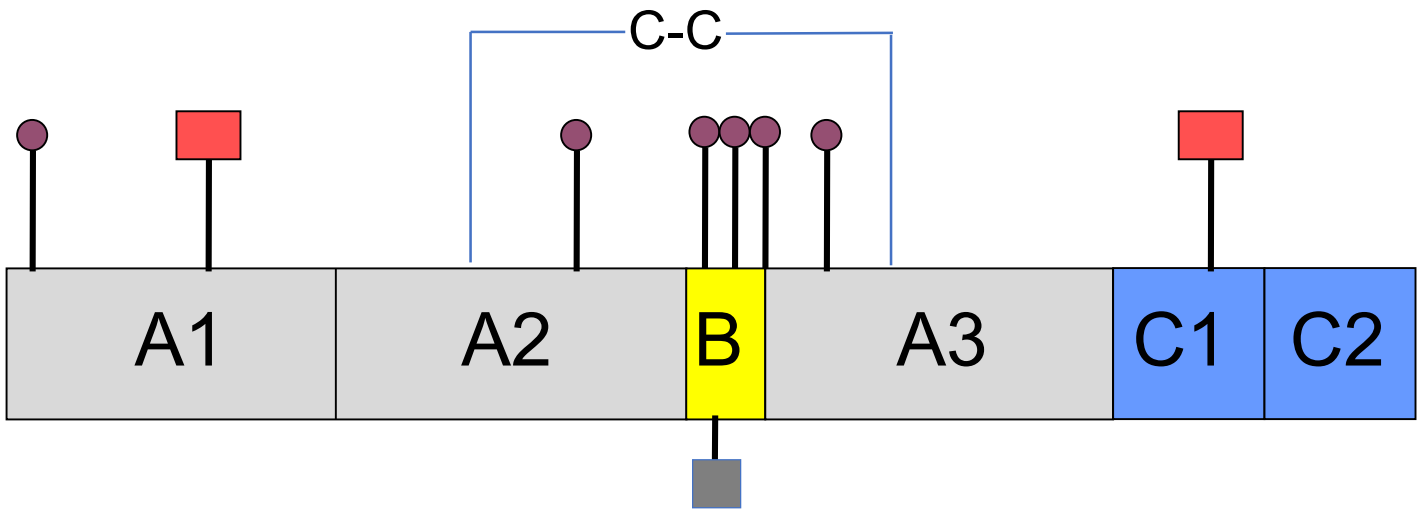
- Higher FIX trough levels
- At least as good or even better protection against bleeding
- Less frequent infusions
- Decrease of FIX units used by ~40%

Factor VIII EHL Products



Eloctate – FVIIIFc fusion

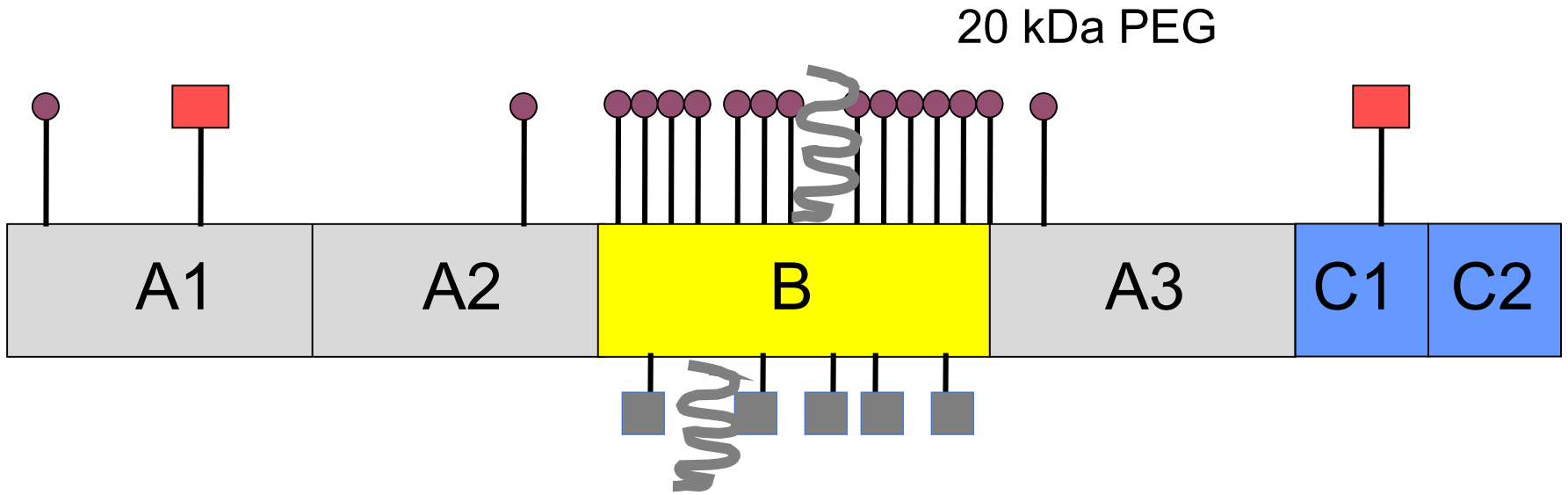
(HEK293)



Chinese hamster ovary - (CHO)

Covalently linked single chain FVIII - truncated B domain

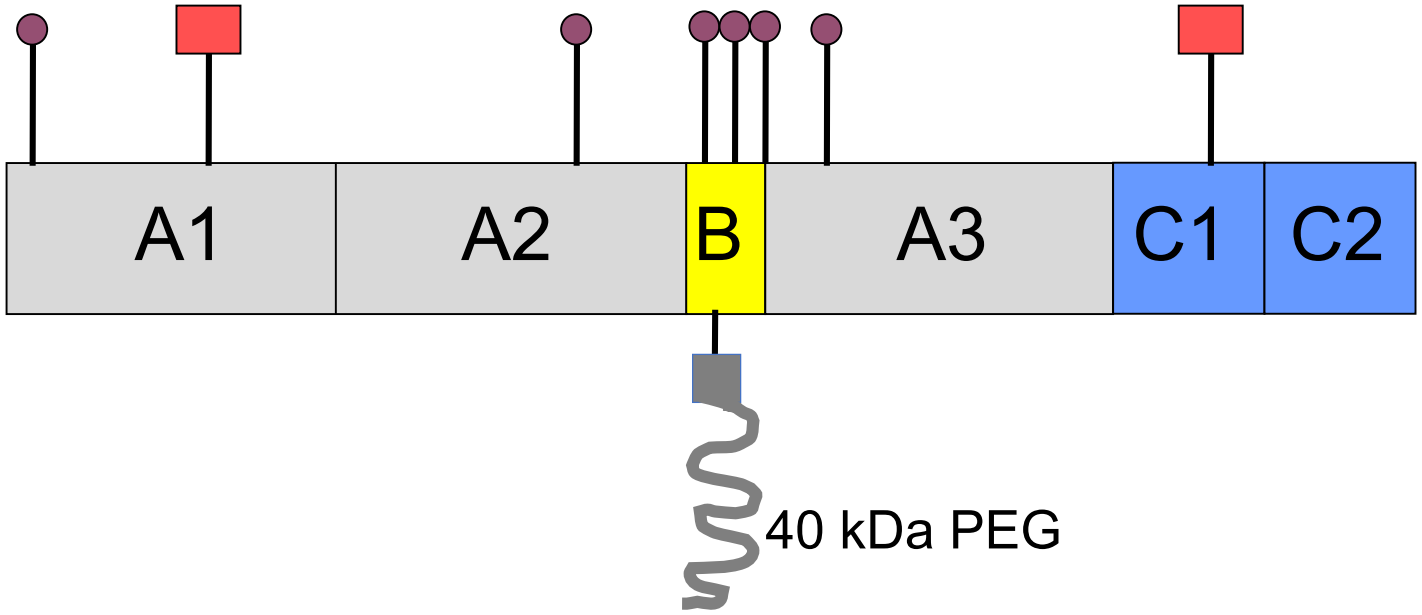
CSL - Afstyla



Chinese hamster ovary - (CHO)

Full length FVIII – Random 20 kDa PEGylation

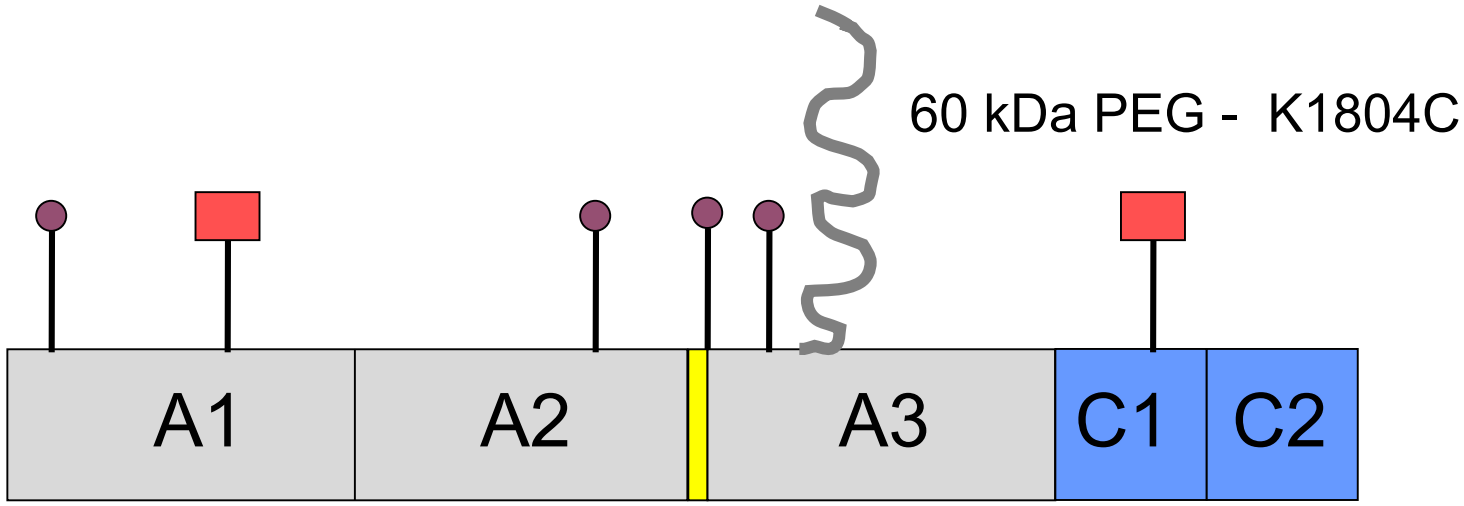
Adynovate – Baxalta/Shire



Chinese hamster ovary - (CHO)

Truncated B domain – GlycoPEGylated 40 kDa PEG

Novo Nordisk - NN7088 - N8-GP or turoctocog alfa pegol



Baby Hamster Kidney – BHK

B domain deleted FVIII – Site-specific 60 kDa PEGylation

Bayer - BAY94-9027, damoctocog alfa pegol

Extended Half-Life FVIII Products (13-19 hrs)

Eloctate	Bioverativ	Fc fusion	HEK293	BDD
Adynovate	Baxalta/Shire	Random PEGylation 20 kDa x 2	CHO	Full-length
Bay 94-9027	Bayer	Site-specific PEGylation 60 kDa at K1804C	BHK	BDD
Afstyla	CSL-Behring	Covalently linked heavy-light chain	CHO	BD truncated
N8-GP	Novo Nordisk	Site-specific 40 kDa PEG to O-linked glycan	CHO	BD truncated

Clotting Factor Half-Life Extensions

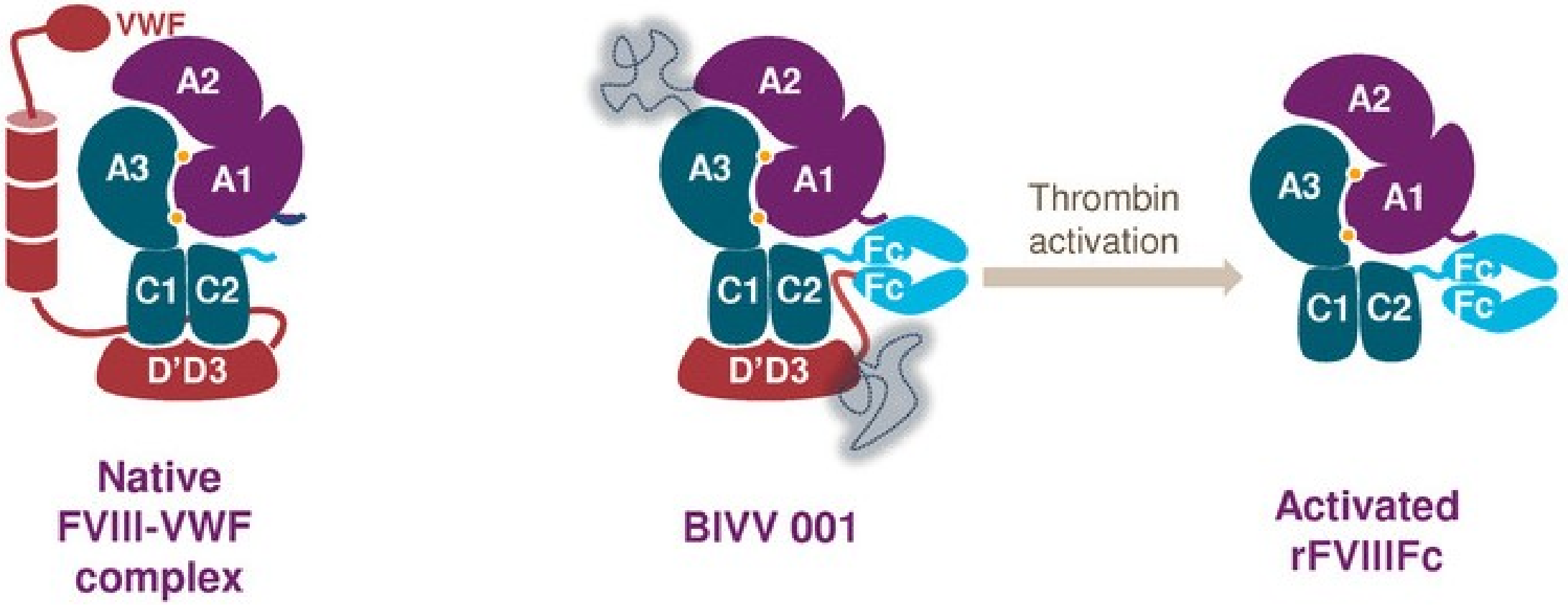
Factor IX 3 to 5-fold → 1 infusion Q7-14 days

(Santagostino et al Blood 2012)
(Negrier et al Blood 2011)
(Shapiro et al Blood 2012)

Factor VIII 1.5 to 1.8-fold → 1 infusion Q3-4 days

(Powell et al Blood 2012)
(Coyle et al JTH 2014)
(Mahlangu et al Blood 2014)

FVIII half-life limited by dominance of VWF



BIVV001 Novel FVIII.Fc-VWF D'D3 Molecule

Late Breaking Abstract WFH Congress Glasgow 2018

BIVV001 Preliminary Results

EXTEN-A Phase 1/2A Clinical Study

4 adult severe hemophilia A pts - single infusion of BIVV001 at 25 IU/kg

FVIII half life of 37 hrs

Mean residual FVIII levels

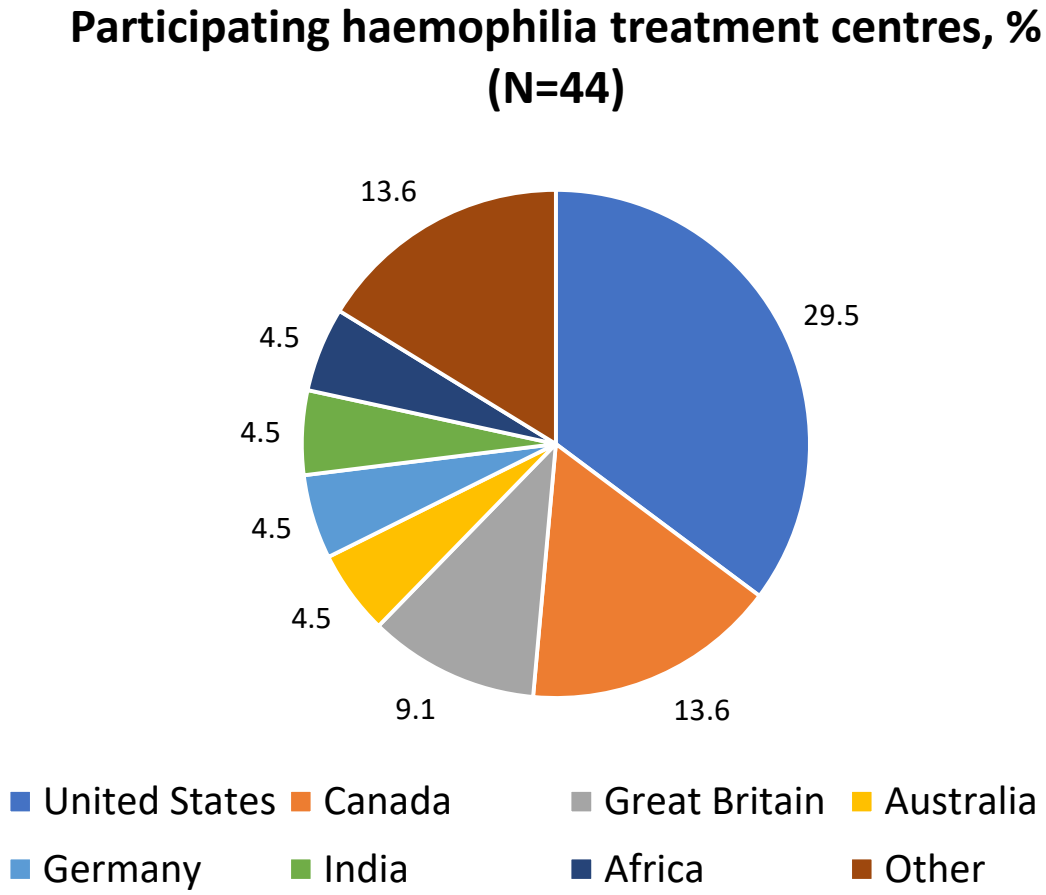
13% at 5 days

5.6% at 7 days

Late Breaking Abstract WFH Congress Glasgow 2018

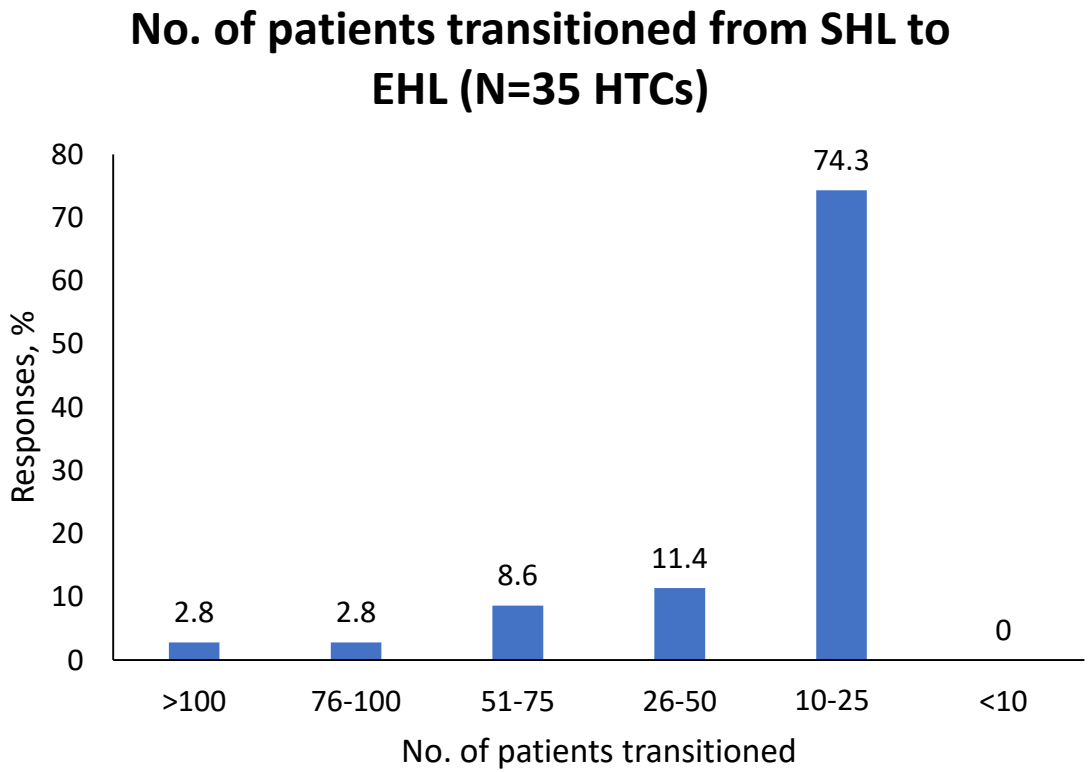
ISTH-SCC survey: use of pharmacokinetics for EHL product treatment in clinical practice

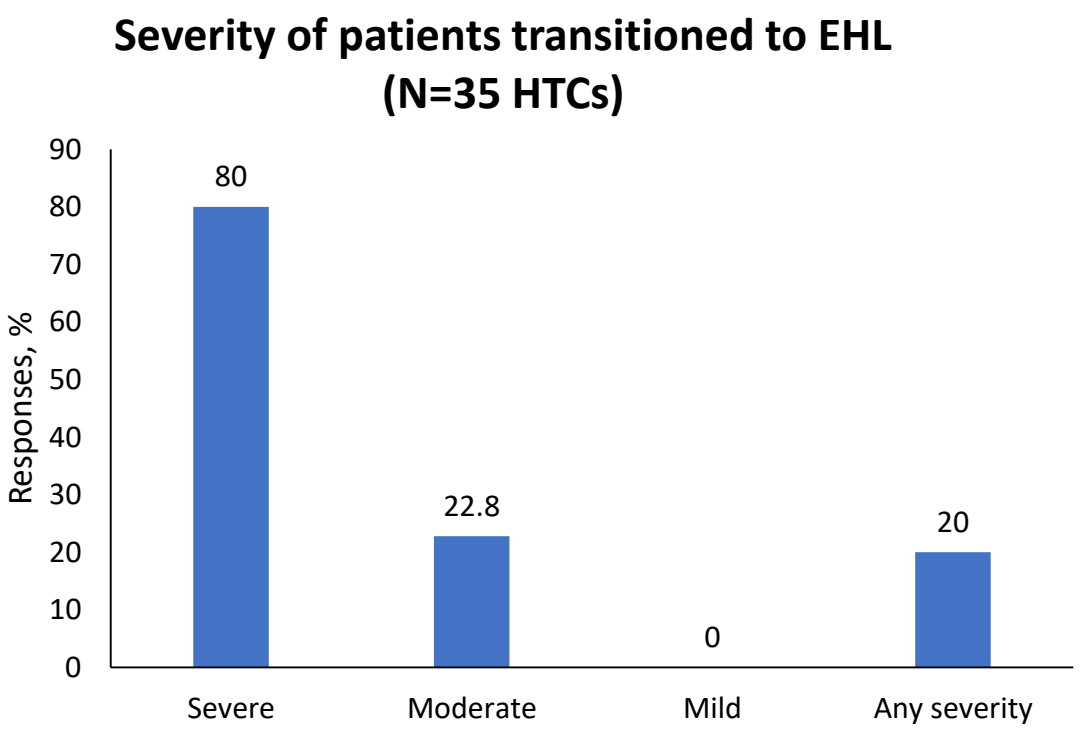
- Online 13-question survey distributed to members of the ISTH-SSC FVIII and FIX committee
- 44 centers provided sufficient data for analysis



N, number of survey respondents
EHL, extended half-life; PK, pharmacokinetic; SHL, standard half-life.
Ragni MV et al. *J Thromb Haemost.* 2018;doi: 10.1111/jth.14153 [Epub ahead of print].

ISTH-SCC survey: overview of patient transition from SHL to EHL products





37 centres (84.1%) transition patients from SHL to EHL

Reasons for not transitioning to EHLs (N=6) were EHL not available (50.0%), EHL not reimbursed (16.7%), yet to transition to EHL (16.7%), and not applicable (16.7%)

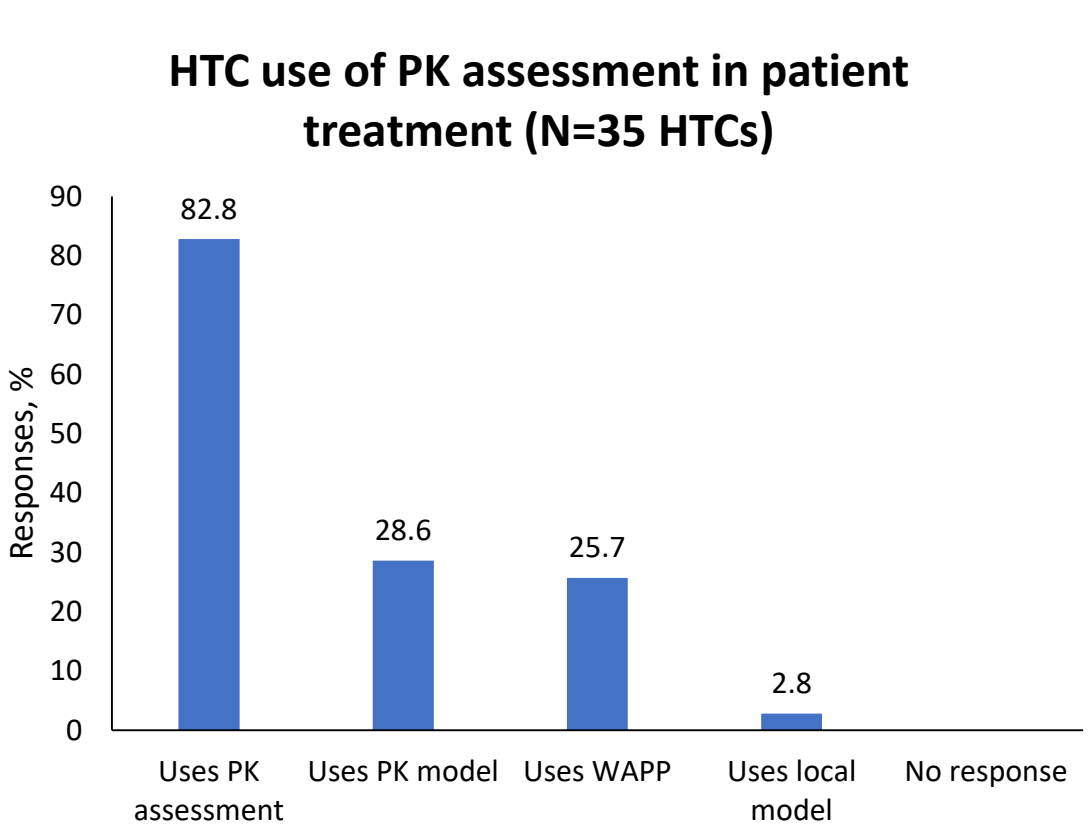
Patients transitioned (N=35) were all ages (60.0%), adults, >18 years (20.0%), and adolescents, >12 years (8.6%)

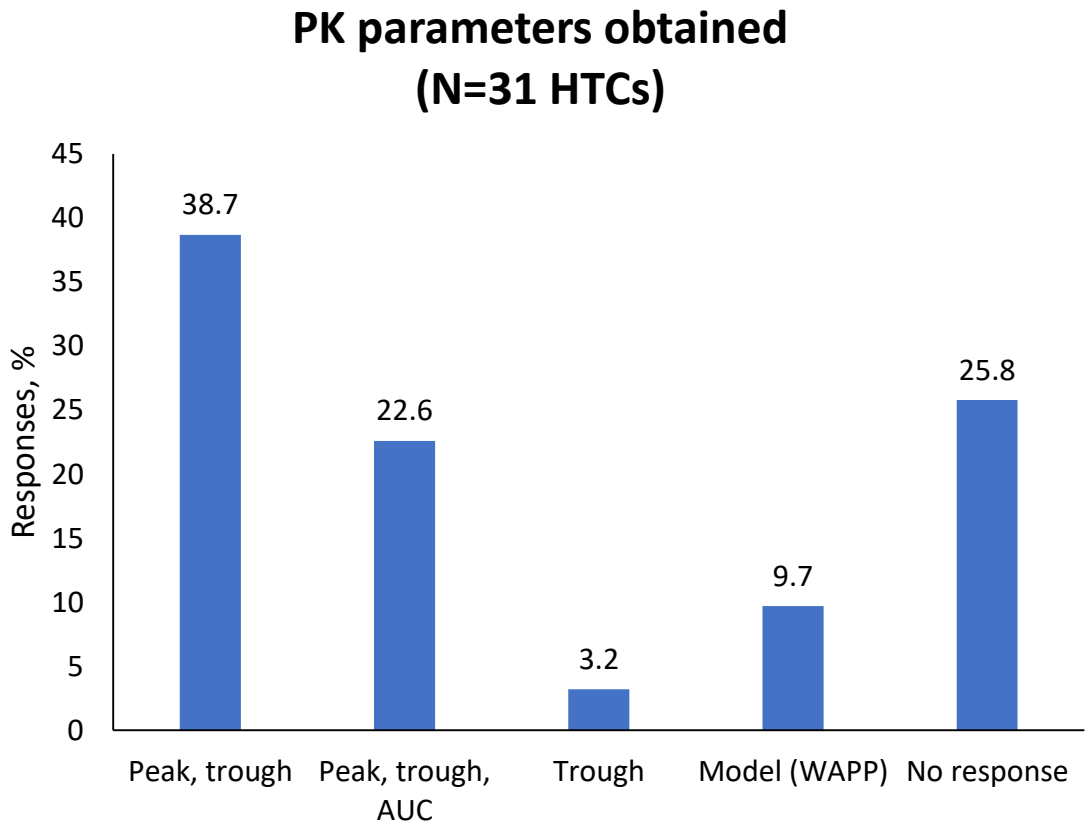
N, number of survey respondents.

EHL, extended half-life; HTC, haemophilia treatment centre; SHL, standard half-life.

Ragni MV et al. *J Thromb Haemost.* 2018;doi: 10.1111/jth.14153 [Epub ahead of print].

ISTH-SCC survey: use of pharmacokinetics in patients transitioned from SHL to EHL products





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Ragni MV et al. *J Thromb Haemost.* 2018;doi: 10.1111/jth.14153 [Epub ahead of print].

ISTH-SSC recommendations for implementing EHL products in clinical practice[1,2]

- PK-guided dosing of factor concentrates provides for more individualized prophylaxis and treatment in patients with hemophilia
- A sampling strategy for population PK analysis should include a minimum of 2 to 4 post-infusion time-points
- PopPK tools such as WAPPs-Hemo or OPTI-CLOT, which utilize a Bayesian approach to estimate individual PK profiles, provide a more practical approach to generating individual PK data, as compared with a classical PK approach
- Further studies are needed to assess the impact of integrating PK data into medical decision making on patient outcomes, factor utilization, bleeding events, quality-of-life, and compliance

WAPPs-Hemo, Web Accessible Population Pharmacokinetic Service for Hemophilia; OPTI-CLOT, Patient Tailored Pharmacokinetic-Guided Dosing of Clotting factor concentrate and DDAVP in bleeding disorders.

1. Ragni MV et al. *J Thromb Haemost.* 2018;doi: 10.1111/jth.14153 [Epub ahead of print]. 2. Iorio A et al. *J Thromb Haemost.* 2017;15(12):2461-2465.

Summary & Conclusions

Products with Extended half-lives will be beneficial to patients

- Less frequent injections - 3x per week to 1x per week
- Improved treatment adherence
- Enhanced prophylaxis outcomes

Their introduction is frequently monitored with PK assessment

Queen's University

Queen's University, Kingston, Canada

Queen's University