Update: Bleeding

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@bloodman

OHSU GENERAL HEMATOLOGY

DISCLOSURE

Relevant Financial Relationship(s)

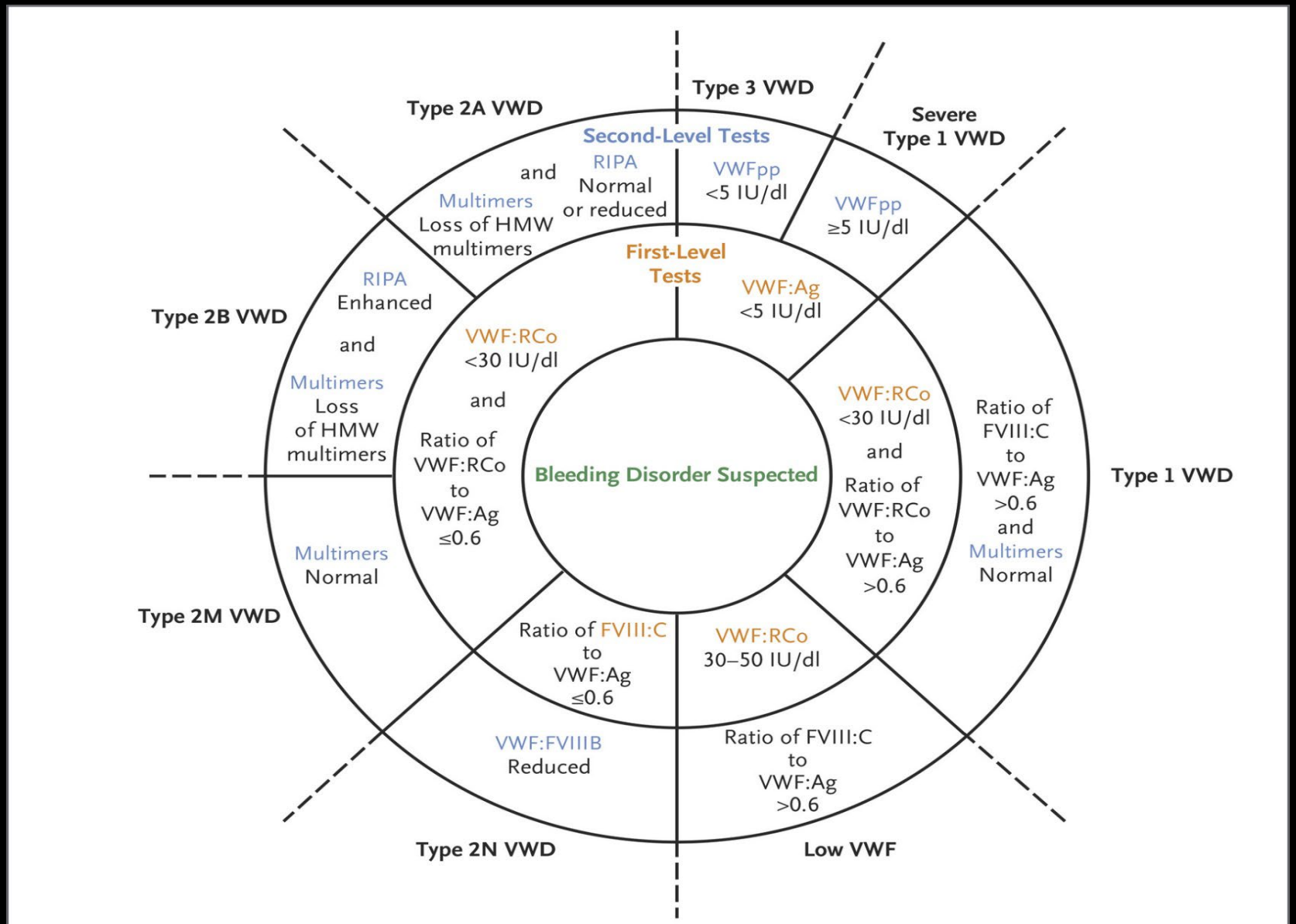
Speaker's Bureau – none

Talk

- New and future options for bleeding
  - Von Willebrand Disease
  - Hemophilia

Classification of VWD

- Type 1: Low concentrations of normal protein (quantitative defect) (80%)
- Type 2: Abnormal proteins (qualitative defect)
  - 2A: Failure to form HMW multimers
  - 2B: Enhance binding to GP 1b
  - 2N: Abnormal factor VIII binding site
- Type 3: No VWF
- Platelet type pseudo-VWF
- Acquired defects



N Engl J Med 2016; 375:2067-2080

Treatment by Types

- Type 1: DDAVP, VIII/vWF Concentrate
- Type 2A: DDAVP (10%) VIII/vWF Concentrate
- Type 2B: VIII/vWF Concentrate
- Type 2N: VIII/vWF Concentrate
- Type 3: VIII/vWF Concentrate
- Platelet type:???
- Tranexamic acid useful adjunct!

rVWF

- Products like Humate-P are VIII/VWF concentrates
- rVWF (Vonvendi) is just rVWF
  - No VIII!
- Need one dose of rVIII with first dose of rVWF
  - Or start a day before surgery
- Not for emergency bleeding!

2021 VWD guidelines on *diagnosis*

- **Panel suggests using the newer assays of VWF activity that evaluate platelet binding (e.g. VWF:GPIbM, VWF:GPIbR) over the VWF:RCo assay**
- **Use a VWF level of <0.3 regardless of bleeding and <0.5 if + bleeding (ABO specific ranges are not needed)**
- ***For people who have historical type 1 VWD but now have normal levels, reconsider the diagnosis but don't necessarily remove it***
- **For type 2B, use genetic testing over the RIPA test**

James PD, et al. Blood Advances. 2021.

2021 VWD guidelines on *management*

- For patients with VWD and severe and frequent bleeds, long-term prophylaxis is suggested
- DDAVP challenges should be done for those who will likely respond (note Stimate is still not available) (could maybe skip it for adults if levels >0.30)
- DDAVP contraindications: active CV disease, seizure disorders, type 1C and surgery, type 2B, pre-eclampsia
- For surgeries: get FVIII and VWF levels >0.5 for at least 3 days

James PD, et al. Blood Advances. 2021.

2021 VWD guidelines on *management*

- For minor surgery, get levels over 0.5 AND use TXA
- Type 1 VWD with VWF >0.3 and mild bleeding phenotype, just give TXA for minor mucosal procedures
- Use TXA or oral hormonal pill for heavy menstrual bleeding rather than DDAVP
- For women with VWD and who are pregnant and need an epidural, get levels 0.5-1.5
- Give women TXA during post-partum period

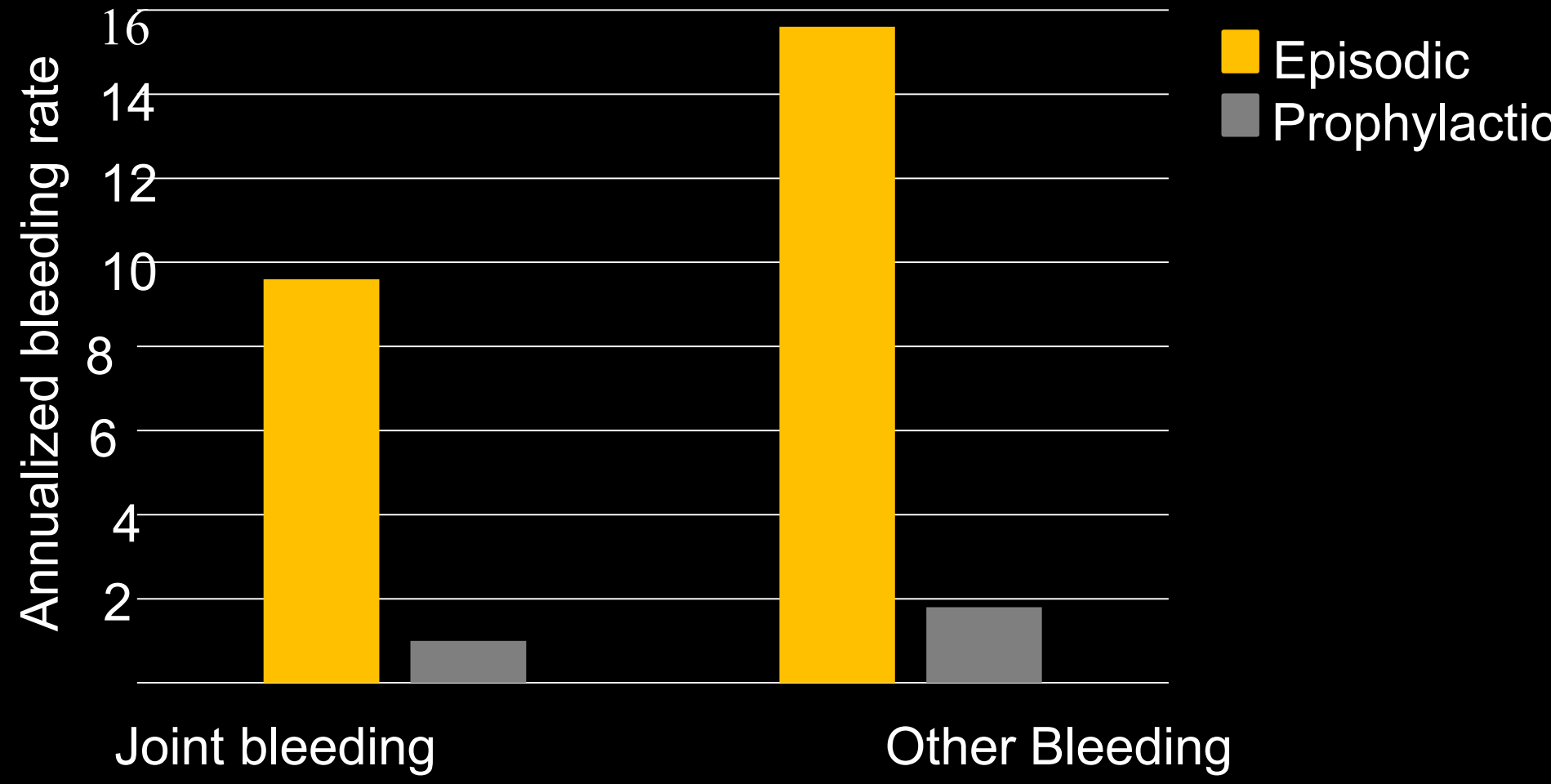
Hemophilia

- Extended half-life products
- Emicizumab
- Gene therapy

Hemophilia A (VIII)

- Most common (~80%)
- Sex-linked
- 30% of patients have inhibitors
- Prophylaxis is standard
  - Prevents joint damage
  - Improves quality of life

Bleeding Rate
Episodic versus Prophylactic



Manco-Johnson, *NEJM*, 2007

Prophylaxis Guidelines

Prophylaxis intensity	Hemophilia A	Hemophilia B
High- dose prophylaxis	25- 40 IU FVIII/kg every 2 days	40- 60 IU FIX/kg twice per week
Intermediate- dose prophylaxis	15- 25 IU FVIII/kg 3 days per week	20- 40 IU FIX/kg twice per week
Low- dose prophylaxis (with escalation of dose intensity, as needed)	10- 15 IU FVIII/kg 2- 3 days per week	10- 15 IU FIX/kg 2 days per week

Carcao et al, *Haemolphilia* 2020

Hemophilia A: Standard FVIII Products

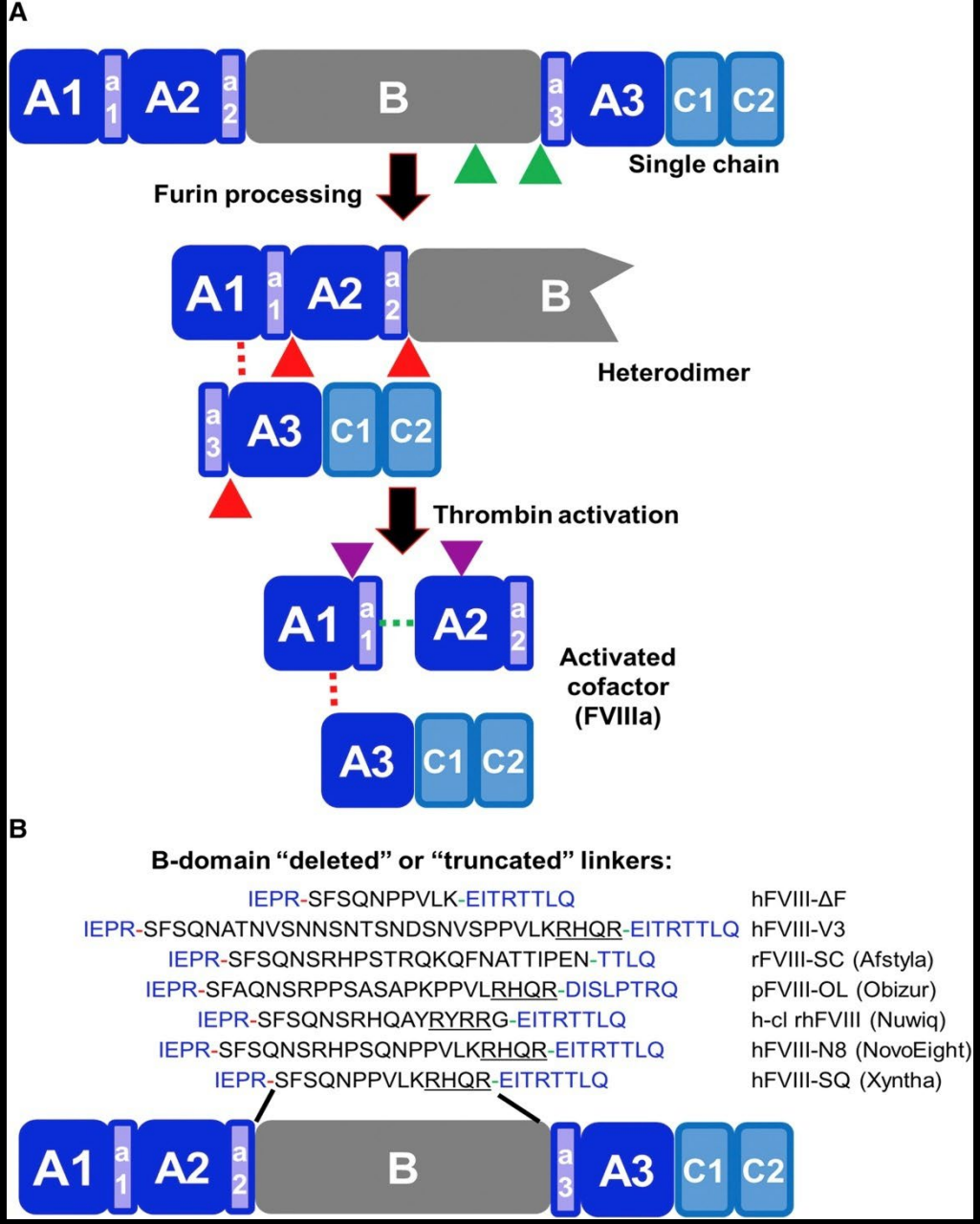
Product name	Half-life (hours)*	Characteristics
Standard half-life products ¶		
Advate	9 to 12	Recombinant
Hemofil M	15	Plasma-derived; mAb-purified
Kogenate FS	11 to 15	Recombinant
Koate (previously called Koate DVI)	16	Plasma-derived; chromatography purified
Kovaltry	12 to 14	Recombinant
Novoeight	8 to 12	Recombinant
Nuwiq	12 to 17	Recombinant
Recombinate	15 Δ	Recombinant
Xyntha	8 to 11	Recombinant

UpToDate

Factor VIII Dosing

- $\frac{(\text{Desired Factor VIII concentration - current level}) \times \text{weight (kg)}}{2}$

- (level desired/2)*kg
- Bad Bleed: 50 units/kg



Molecular Therapy - Methods & Clinical Development 2019 12184-201DOI: (10.1016/j.omtm.2018.12.007)

Extended Half-Life FVIII Products

FVIII EHL product	B-domain modification	Additional modifications	Half-life (hrs, mean
Afstyla	Yes (truncated)	Single-chain	14.2 +/- 3.7
Adynovate	No	PEGylation	14.7 +/- 3.8
Nuwiq	Yes	-	17.1 +/- 11.2
Eloctate	Yes	Fc-fusion	19.7 +/- 2.3
Jivi	Yes	PEGylation	19
N8-GP	Yes (truncated)	PEGylation	19

- Half-life now ~14-20 hours
- Reduce FVIII infusions by ~30%

VWF-VIII Fusion

- Bypass need for VWF “protection”
- Levels of 17% after one week
- Maybe weekly prophylaxis?
- In trials

Management of Bleeding Patient on EHL

- Use standard half-life products and base off levels
- If severe bleeding and no levels 50 units/kg of rVIII

Hemophilia B (IX)

- Less common (~20%)
- Sex-linked
- ~5% of patients have inhibitors
- Prophylaxis is standard

Hemophilia B: Standard FIX Products

Product name	Half-life (hours)*	Characteristics
Standard half-life products		
AlphaNine SD	18 ¶	Plasma-derived; solvent/detergent treated
BeneFIX	16 to 19	Recombinant
Ixinity	24 Δ	Recombinant
Mononine	23 ¶	Plasma-derived; mAb purified
Rixubis	23 to 26	Recombinant

Factor IX Doses

- (Desired Factor IX concentration - current level) x weight (kg)
  - With recombinant products need "fudge" factor of 1.2

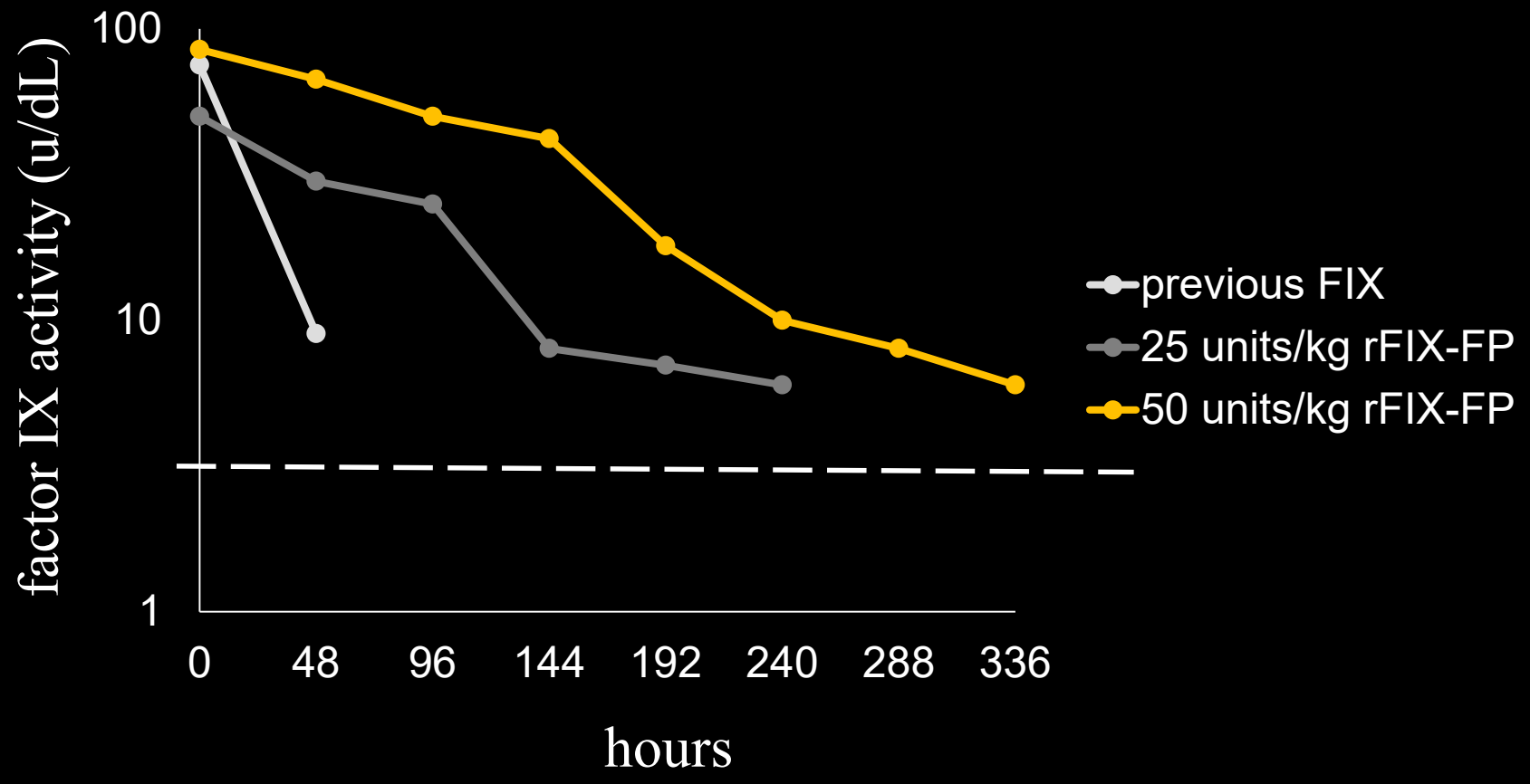
- Or level desired*kg
- Severe: 100 units/kg (120 units/kg)

Extended Half-Life FIX Products

FIX EHL product	EHL modification	Half-life (hrs)
Alprolix	Fc-fusion	82
Rebinyn	PEGylation	93
Idelvion	Albumin fusion	102

Can extend prophylaxis to weekly or even every other week

rFIX-FP (Idelvion) Pharmacokinetics



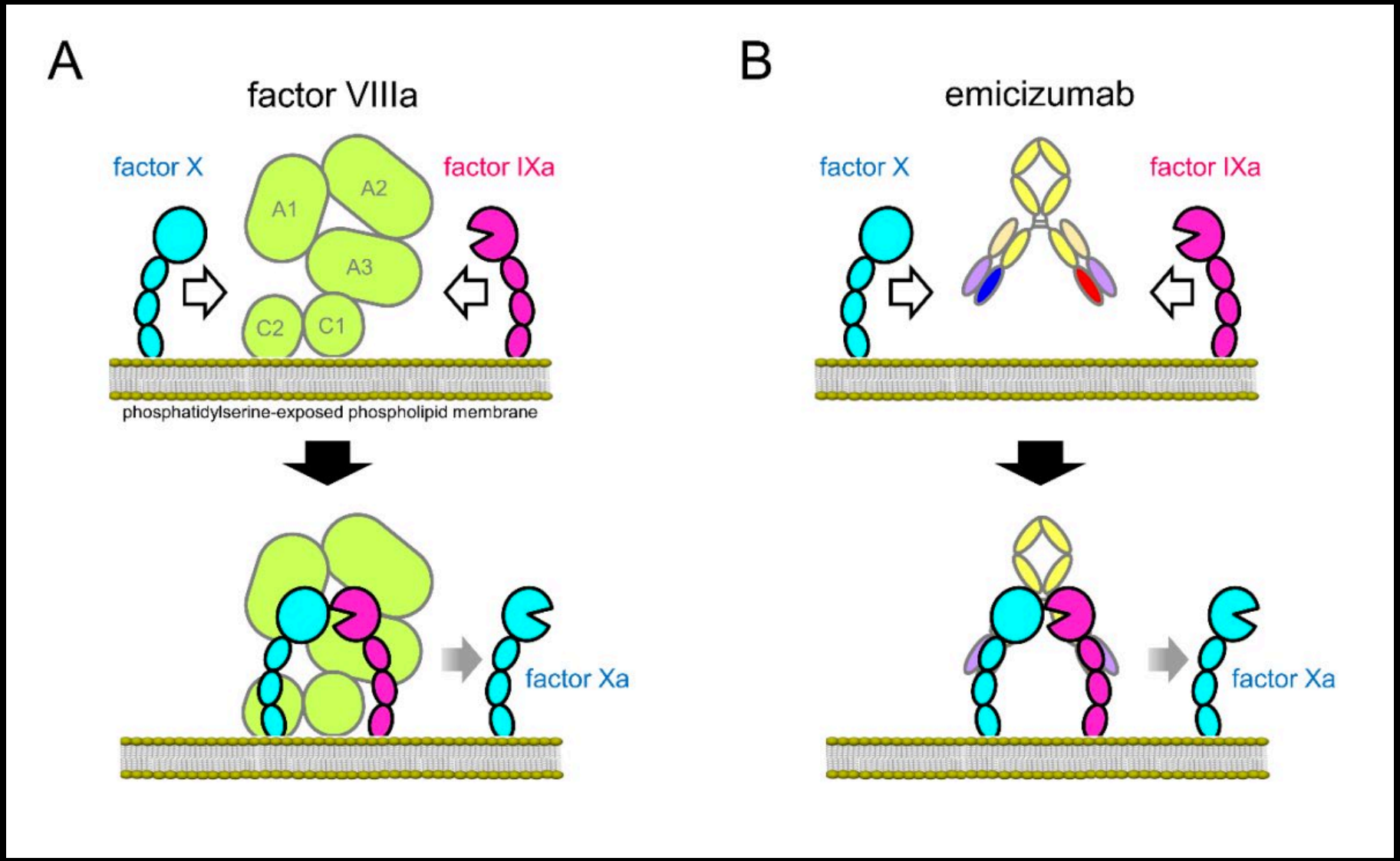
Santagostino, *Blood*, 2016

Management of Bleeding Patient on EHL

- Use standard half-life products and base off levels
- If severe bleeding and no levels 100 units/kg of IX

Emicizumab

- Novel monoclonal protein
- Major breakthrough in Hemophilia A

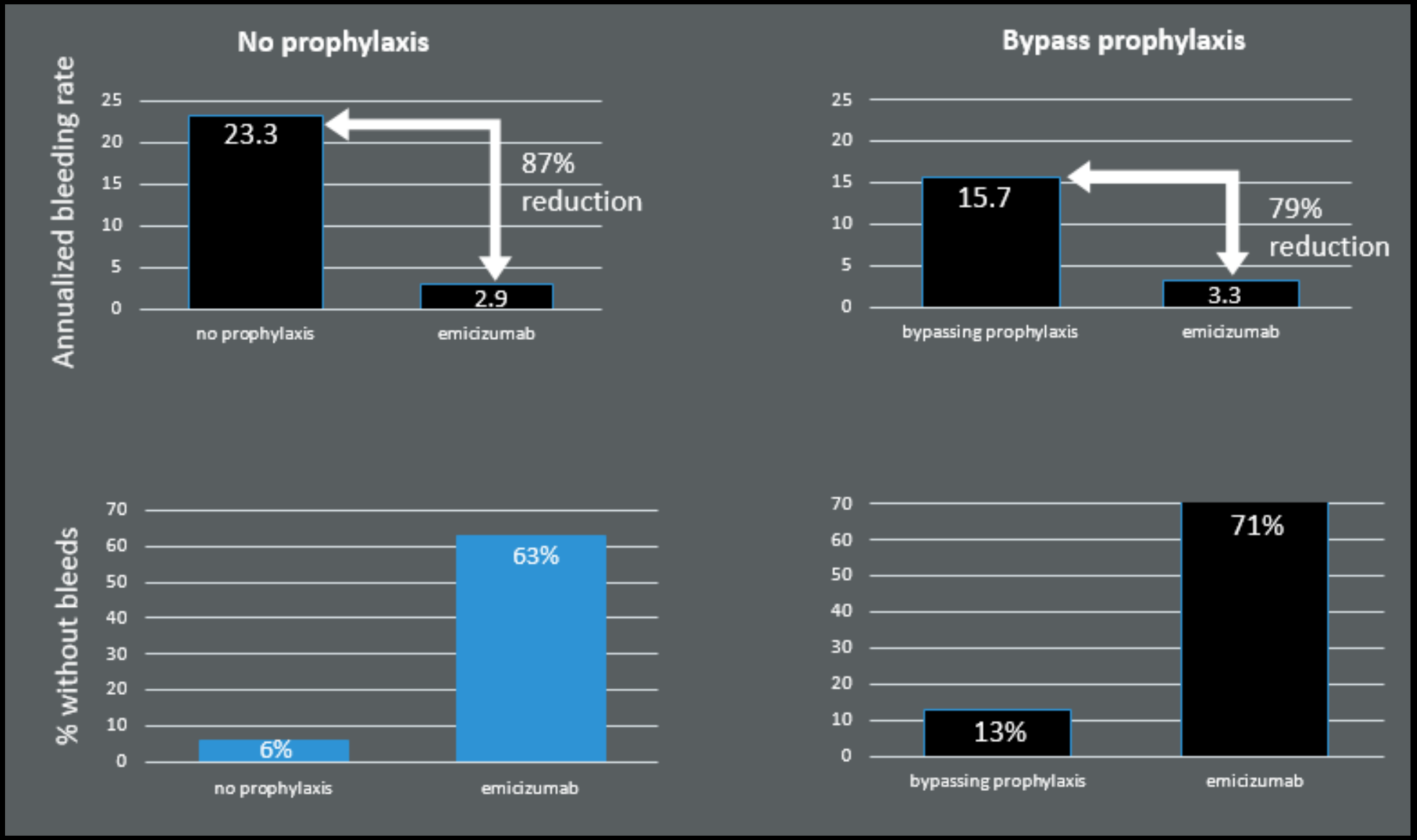


N Engl J Med 2016;374:2044-53.

Emicizumab

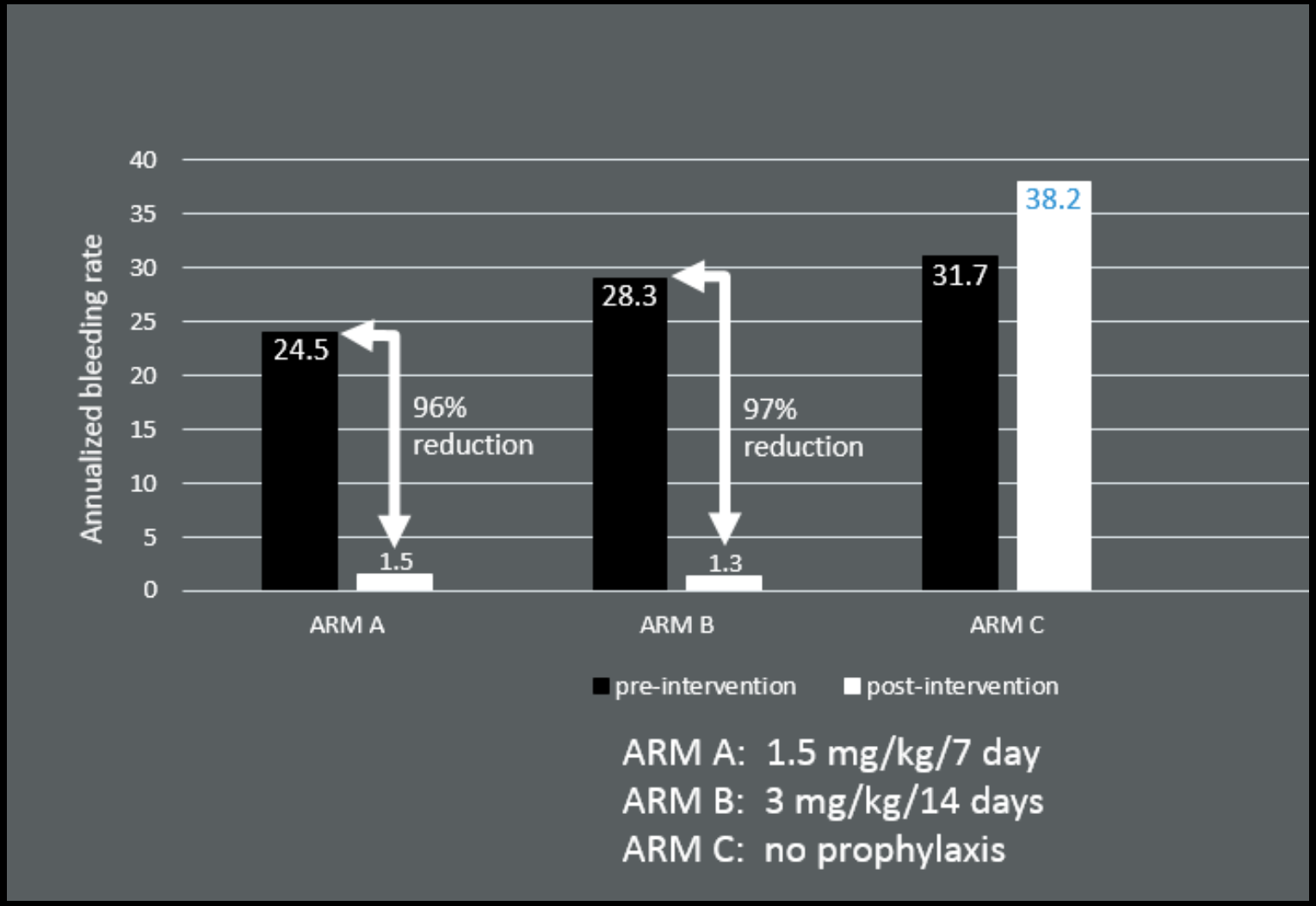
- Two major clinical trials
  - Hemophilia A with factor inhibitor
  - Hemophilia A with no factor inhibitor

Inhibitor Patients

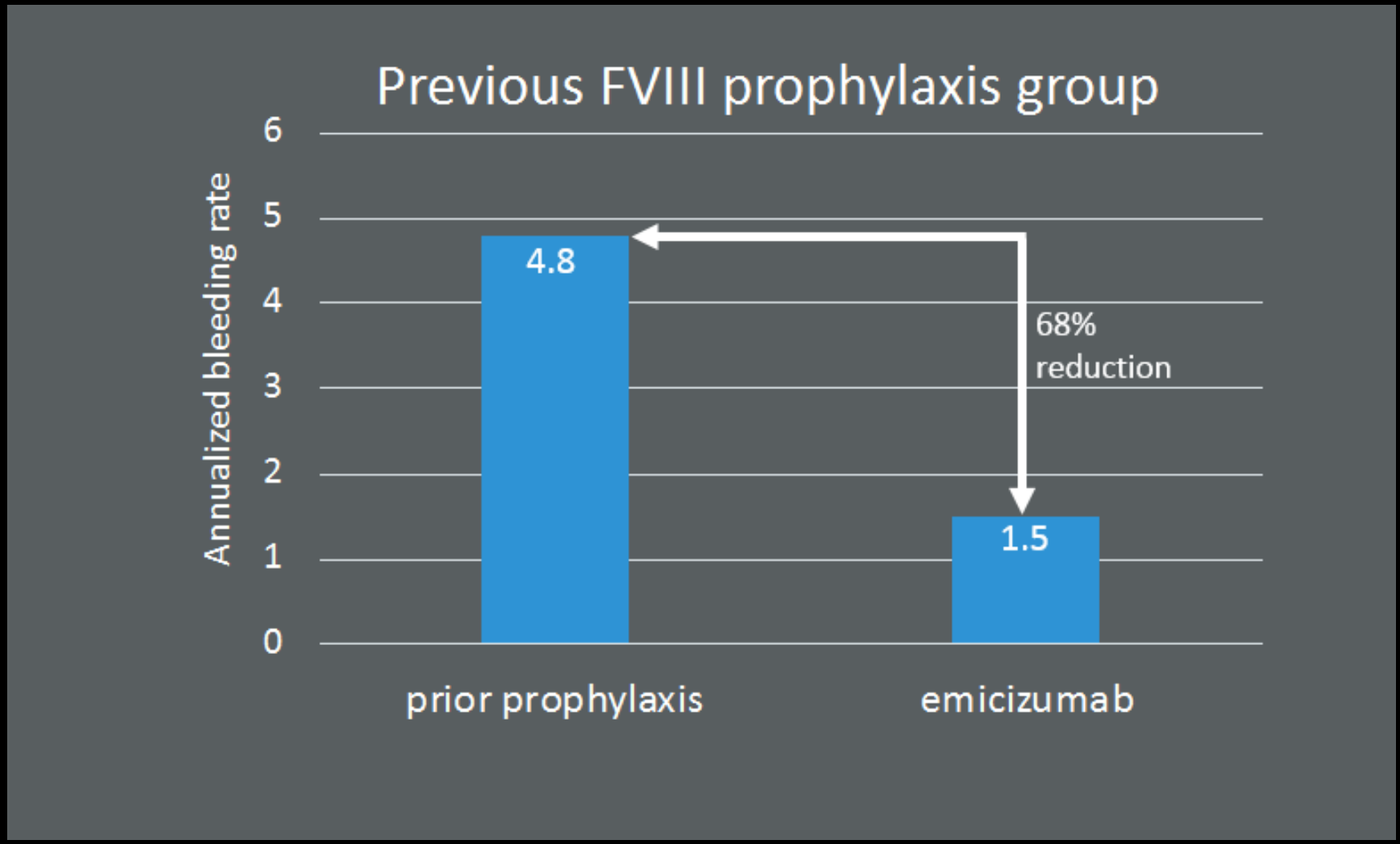


N Engl J Med 2017; 377:809-818

No Inhibitors



N Engl J Med 2018; 379:811-822



N Engl J Med 2018; 379:811-822

Emicizumab

- Very effective in reducing bleeds
- Safe!
  - Thrombosis seen in early trials with high dose FEIBA use

FDA Approval

- Hemophilia A with (Nov 2017) and without inhibitors (Oct 2018)
- Dosing
  - Loading dose: 3 mg/kg weekly x 4 weeks
  - Maintenance dose:
    - 1.5 mg/kg weekly
    - 3 mg/kg every other week
    - 6 mg/kg every 4 weeks

Burn Point

- aPTT and standard Factor VIII levels not valid in patients on Emicizumab!!
- Need specialized lab assay to measure factor VIII

Acute Bleeding: Inhibitors

- rFVIIa at dose of 90-120 mcg/kg
- Frequency should be no more than every 2 hours
- Vast majority of bleeding should be controlled with a maximum of three doses
- Use of FEIBA should be avoided if possible
  - Initial dose should be 50 units/kg
  - Should not exceed 100 units/kg/day

Acute Bleeding: Without Inhibitors

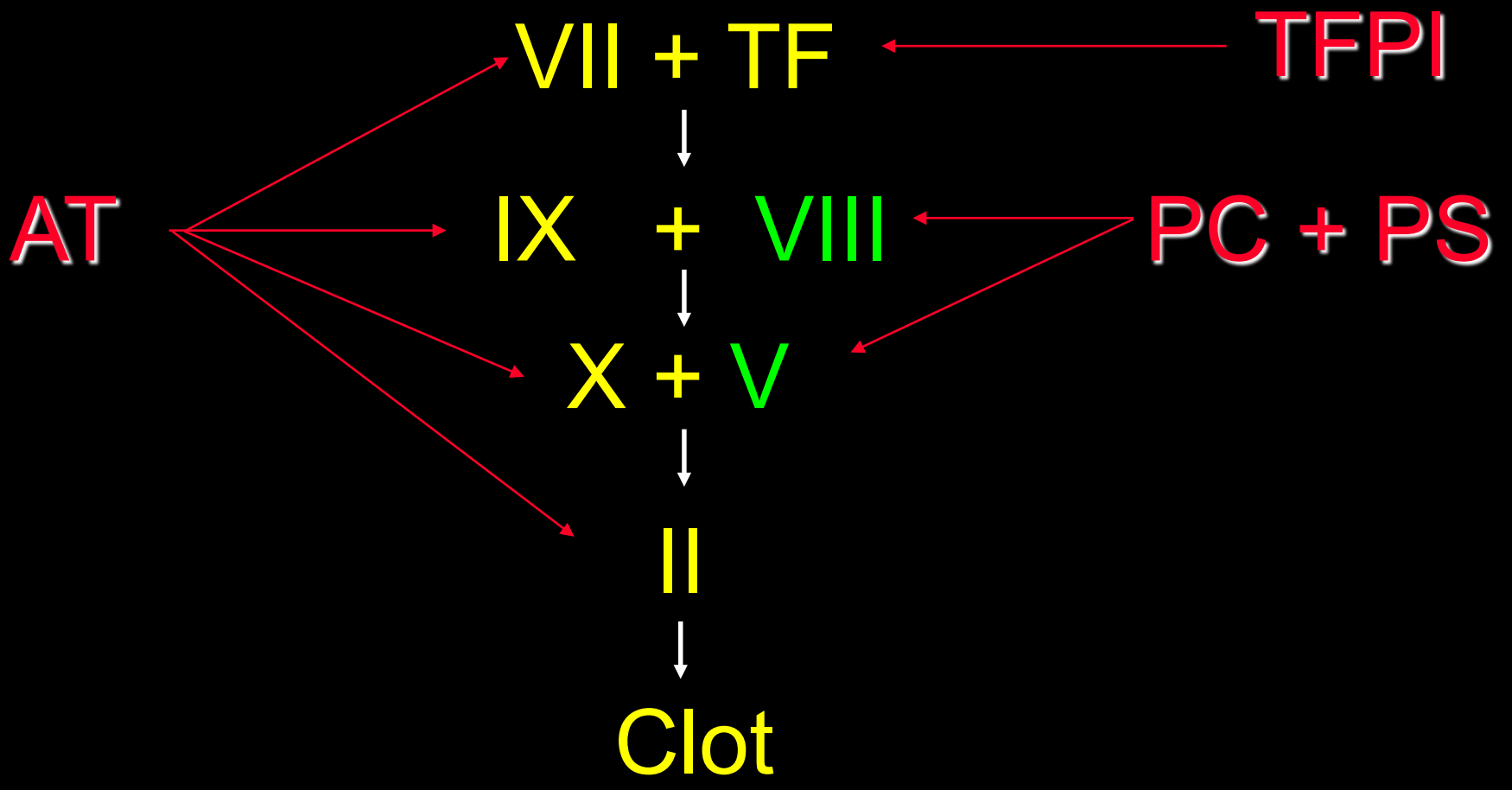
- Factor VIII concentrates for treatment of breakthrough bleeding.
- Standard dosing should be used
- Need special levels

Inhibiting Inhibitors

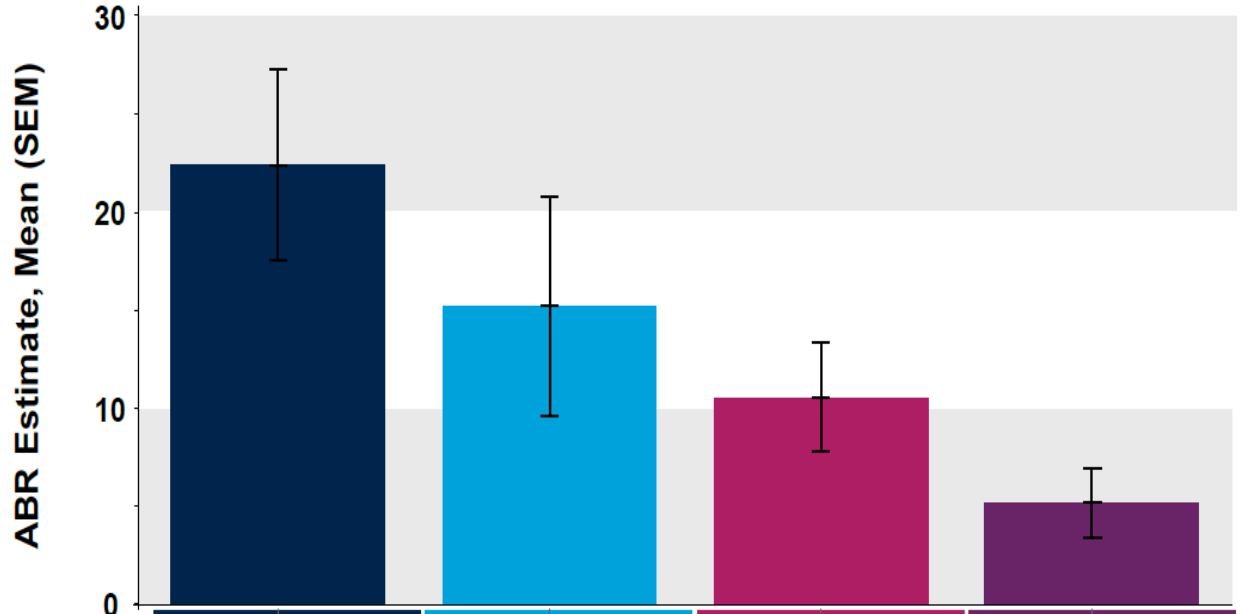
- Blocking natural anticoagulants reduces bleeding
  - TFPI
    - Antibodies
  - Antithrombin
    - siRNA
  - Activated Protein C
    - Antibodies
    - Recombinant inhibitors

Me trying to learn the Coagulation Cascade for the 827th time

Natural Anticoagulants



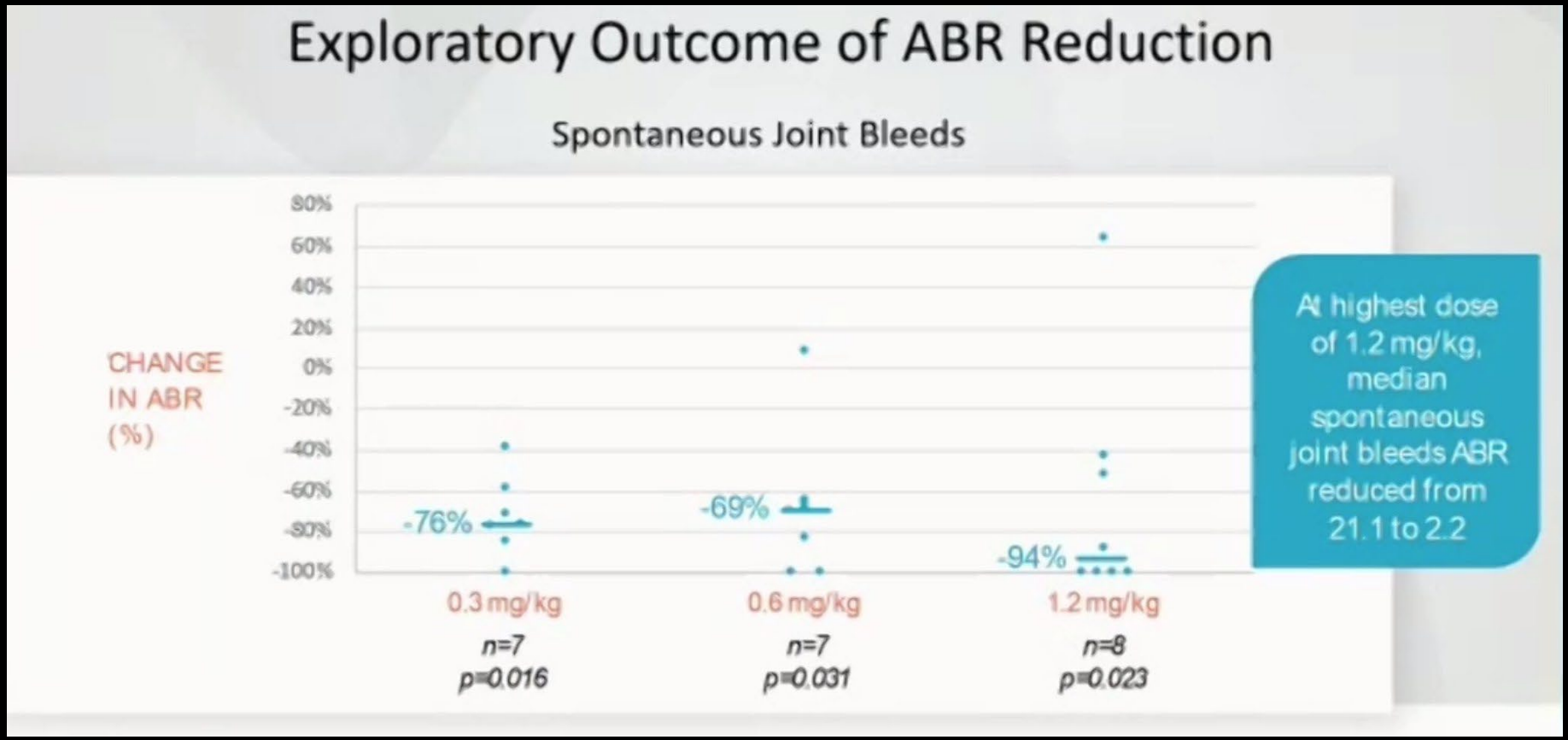
Fitusiran (AT) Bleeding Events



	AT Lowering <25%	AT Lowering 25-50%	AT Lowering 50-75%	AT Lowering >75%
Patients†	30	27	25	16
Cumulative Days	733	1119	1203	1128
Cumulative Bleeds	47	40	36	11
ABR‡, Mean (SEM)**	22 ± 5	15 ± 6	11 ± 3	5 ± 2
ABR, Median	10	0	6	1

Pasi, WFH, 2016

aPC Blockade



But….

- Thrombosis – including fatal - has been an issue in clinical trials
- Need right balance of inhibition

Fitusiran: Thrombotic Risk and AT Level

AT level is a predictor of thrombosis risk:

AT Level	Incidence Thrombosis/100 pt-yr
AT < 10%	5.91
AT 10-20%	1.49
AT > 20%	0

Goal: **Maintain AT level above 20% to prevent thrombosis.**

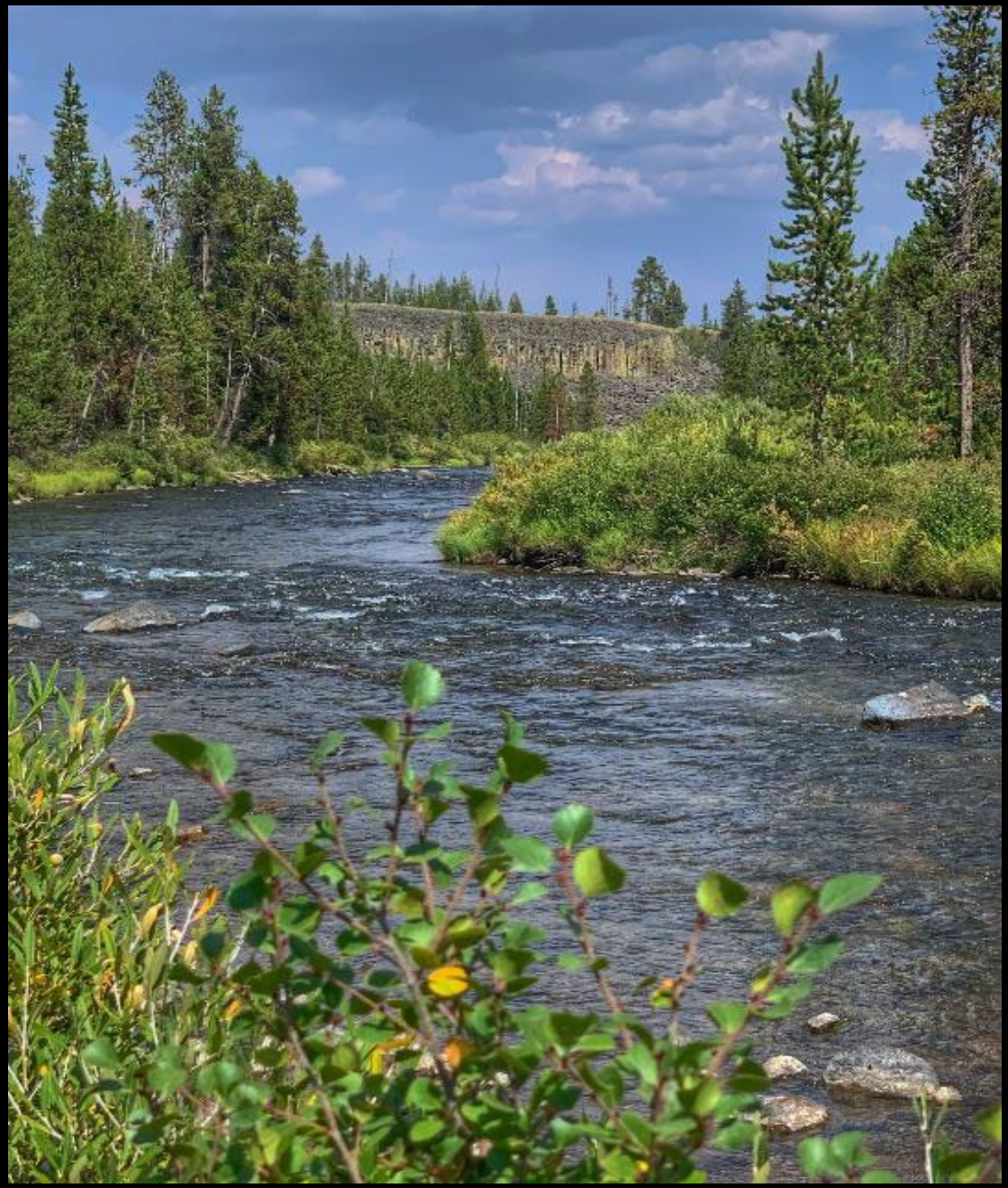
Will that also be an effective dose to prevent bleeds?

Phase I Trial: Safety & Mitigation Procedures

Breakthrough bleeds:	Use low doses of factor and bypass agent FVIII: 10-20 IU/kg FIX: 20-30 IU/kg FVIIa: 45 mcg/kg aPCC: 30 IU/kg Keep a diary of factor treatment Call if continuing dosing is required Avoid antifibrinolytics when using factor or bypass agent
Surgery:	For procedure, schedule at nadir: 2 weeks after dose Use low-dose VIII, IX, rVIIa pre, post surgery for hemostasis
Educate patients:	Symptoms, risks of thrombosis

Bottom Line

- Interesting concept
- Allows for infrequent dosing
- Balance of thrombosis vs bleeding major issue



Gene Therapy

- Hemophilia ideal disease for gene therapy
  - Low levels of gene expression would provide protection
  - Easy to measure lab and clinical endpoints
  - Biology of Factor VIII and IX understood

Hemophilia Severity

	Factor VIII/IX Activity	Spontaneous Bleeding	Bleeding After Trauma
Unaffected	>40%	No	-
Mild	6-40%	Rare	Yes
Moderate	1-5%	Occasional	Yes
Severe	<1%	Frequent (Hemarthrosis)	Yes

Factor VIII: Gene Therapy

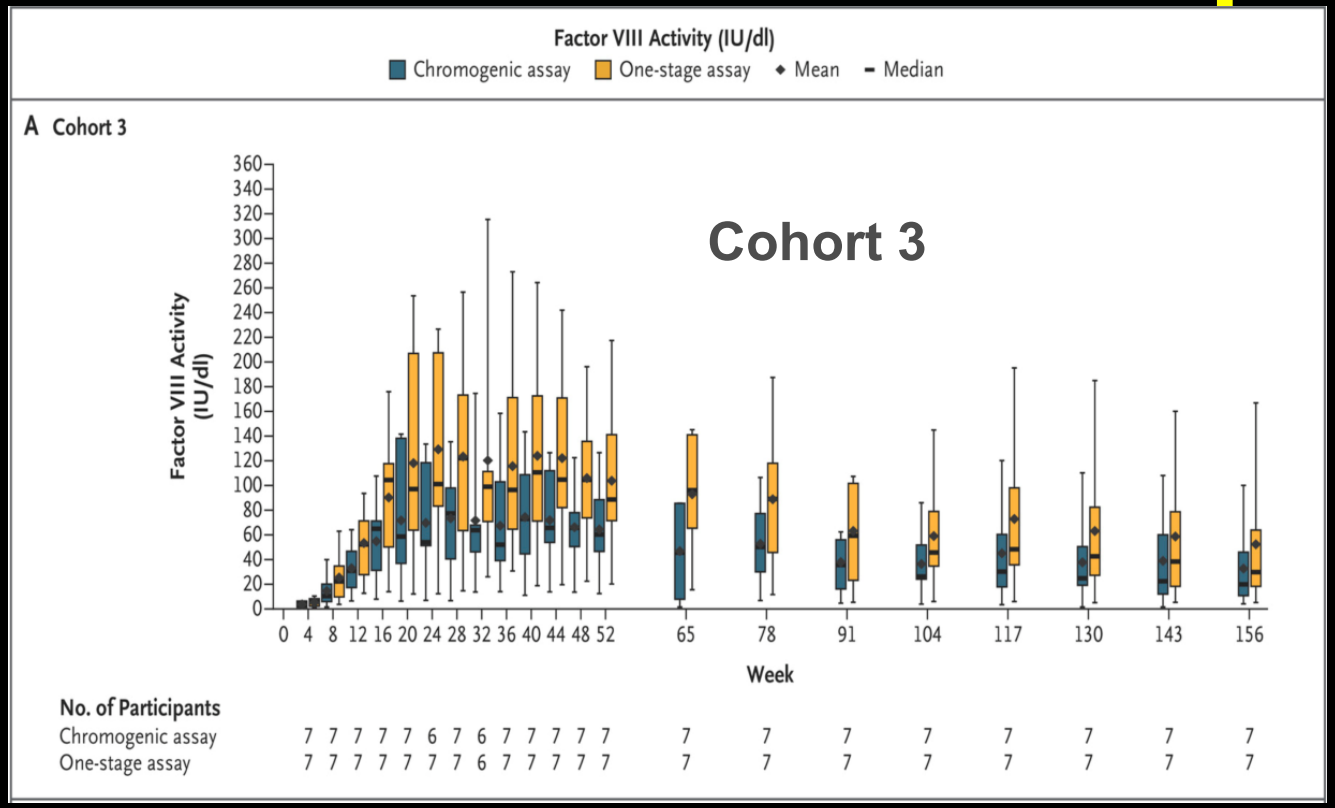
- Factor VIII is BIG! (2351 AA)
  - Too big to be fit into vectors
  - B domain is deleted
- Liver specific promoter inserted
- Recombinant adenovirus vector
- Administered IV

Hemophilia A Trials

Sponsor	Generic/ product name	NC no.	Phase	N	Dose of vector (/kg BW)	Expression level short term (1-6 mo)*	1 y (IU/dL or %)	>2 y (IU/dL or %)	Duration and stability
Hemophilia A									
Biomarin Pharmaceuticals	Valoctocogene roxaparvovec (AAV5 BMN 270)	NCT02576795	1/2	7	6×10^{13}	Gradual increase up to 24 wk	60 (median) 64 (mean) CSA	36 (median) 26 (mean)	Expression declining after 1 y to 33 (mean) and 20 (median) after 3 y
BioMarin Pharmaceutical	Valoctocogene roxaparvovec (AAV5 BMN 270)	NCT03370913	3	134	6×10^{13}	n.a.	23.9 (median) 42.9 (SD 45.5) CSA	n.a.	No long-term data available
Spark Therapeutics	SPK-8011, AAV LK03-co-BDD-F8	NCT03003533	1/2	7	2×10^{12}	16-49 (n = 5), response < 5 in 2 patients	n.a	5.2-19.8 (n = 5)	Two patients lost expression
Sangamo Therapeutics/ Pfizer	Giroctocogene fitelparvovec SB-525, AAV6-co-BDD-F8 (ALTA-Study)	NCT03061201	1/2	5	3×10^{13}	Increase to normal range within 5 wk	50.2 (median steady state) 80.1 mean (SD 93.3)	n.a.	
Bayer	BAY2599023 (DTX 201) AAVhu37-GET-8 study	NCT03588299	1/2	2	2×10^{13}	12 and 72	n.a	n.a	Follow-up too short for evaluation of durability

Blood 138: 923–931.

Factor VIII Example



Mean Factor VIII Activity Levels

Cohort	Viral Therapy	Yr. 1	Yr. 2	Yr. 3
3	6×10^{13} vg/Kg	64 IU/dL	36 IU/dL	33 IU IU/dL
4	4×10^{13} vg/Kg	21 IU/dL	15 IU/dL	

N Engl J Med 2020;382:29.

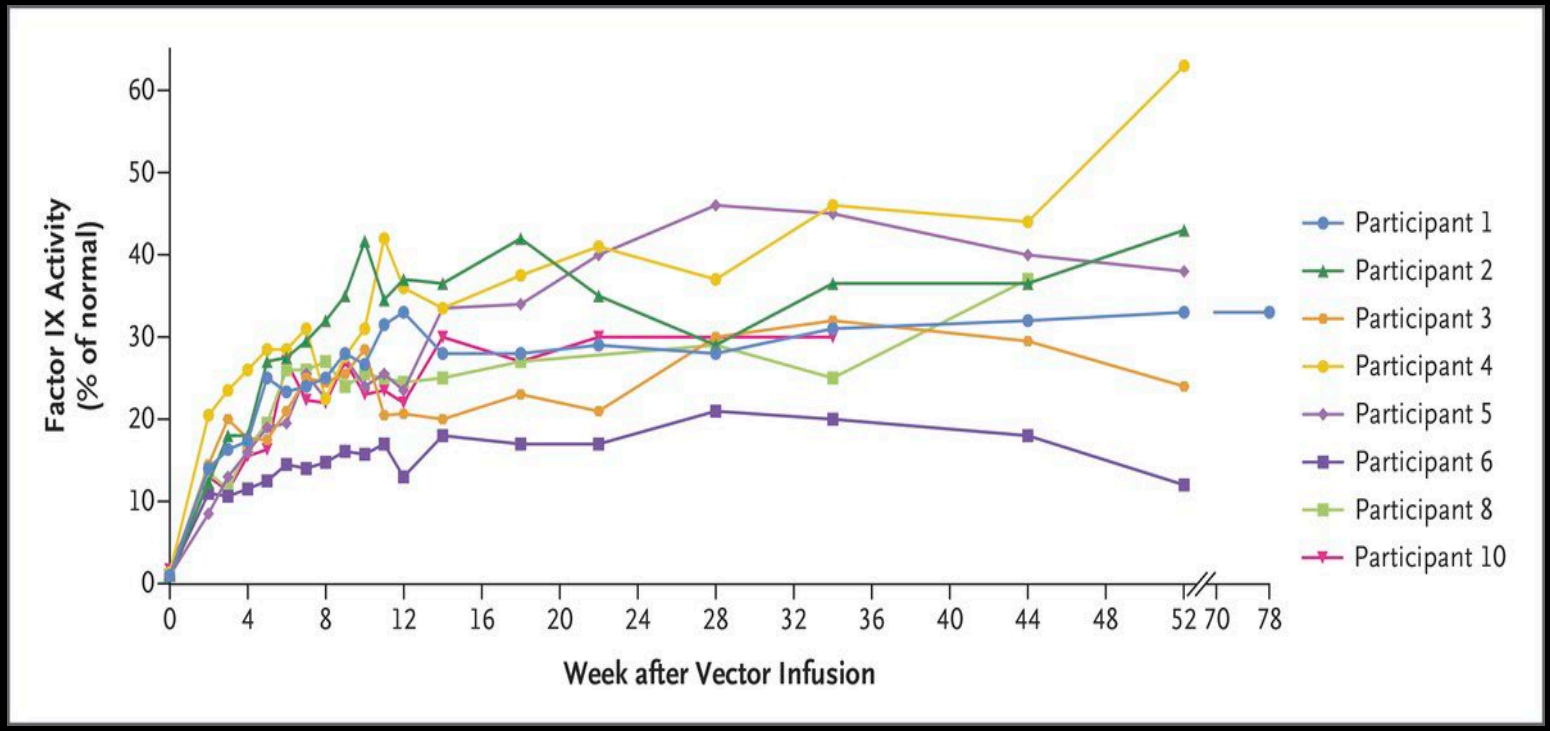
Factor IX

- Small molecule (607 AA)
- Factor IX Padua
  - 10x activity of wild type IX

Sponsor	Generic/ product name	NC no.	Phase	N	Dose of vector (/kg BW)	Expression level short term (1-6 mo)*	1 y (IU/dL or %)	>2 y (IU/dL or %)	Duration and stability
Baxalta/Takeda	AAV8-coF9-Padua Bax 335	NCT01687608	1/2	2	3×10^{12}	45.3 (mean peak levels) (range 32-59) (OSA)	n.a.	20 (one patient)	Transient, short-term expression in 7; loss of expression in 6 out of 7
UniQure BioPharma	AAV5-hFIX (AMT-060)	NCT02396342	1/2	5	2×10^{13}	6.9 (mean) (95% CI, 2.6-11.3) (OSA)	n.a.	7.4 (95% CI 4.2-10.6)	Stable expression over 5 y
Spark Therapeutics/ Pfizer	Fidanacogene elaparvovec SPK-9001, mutant AAV8-coF9-Padua Factor IX-long study	NCT03307980	1/2	10	5×10^{11}	33.7 mean (SD 18.5) Range 14-81 (OSA)	n.a.	n.a.	
UniQure Biopharma	Etranacogene dezaparvovec AAV5-hFIXco-Padua (AMT-061)	NCT03489291	2b	3	2×10^{13}	47 (mean) (range 33.2-57.0) (OSA)	n.a.	n.a.	No long-term data available
Freeline Therapeutics	FLT180a (B-AMAZE)	NCT03369444	1	2	1.5×10^{12}	160 (67-253) Mean (range at 26 wk)	n.a	n.a.	Studies continued with lower dose
UniQure Biopharma	AAV5-hFIXco-Padua (AMT-061)HOPE-B	NCT03569891	3	54	2×10^{13}	37.2 (mean) 19.6 SD Range 1-97 (OSA)	n.a.	n.a	No long-term data available
Hemophilia B									
UCL/St JudesCRH	AAV8 FIX-WT	NCT00979238	1	6	2×10^{12}	1.4-7.2 (range) (OSA)	5.1 mean (SD 1.7)		Stable expression over 8 y
Ultragenics Pharm	DTX101, AAVrh10FIX	NCT02618915	1/2	3	5×10^{12}	12-20 (range) reached within 3-8 wk	Gradual decrease to baseline		Transient, short-term expression

Blood 138: 923–931.

Gene Therapy: Factor IX



N Engl J Med 2017;377:2215.

Gene Therapy: Issues

- Many patients need steroids to keep factor production up
  - All trials give with infusion
  - Some need steroids > 6 months
- AAV antibodies frequent
  - May be “immunoabsorbed”
- Duration of benefit is unclear
- Carcinogenesis

Etranacogene Dezaparvovec

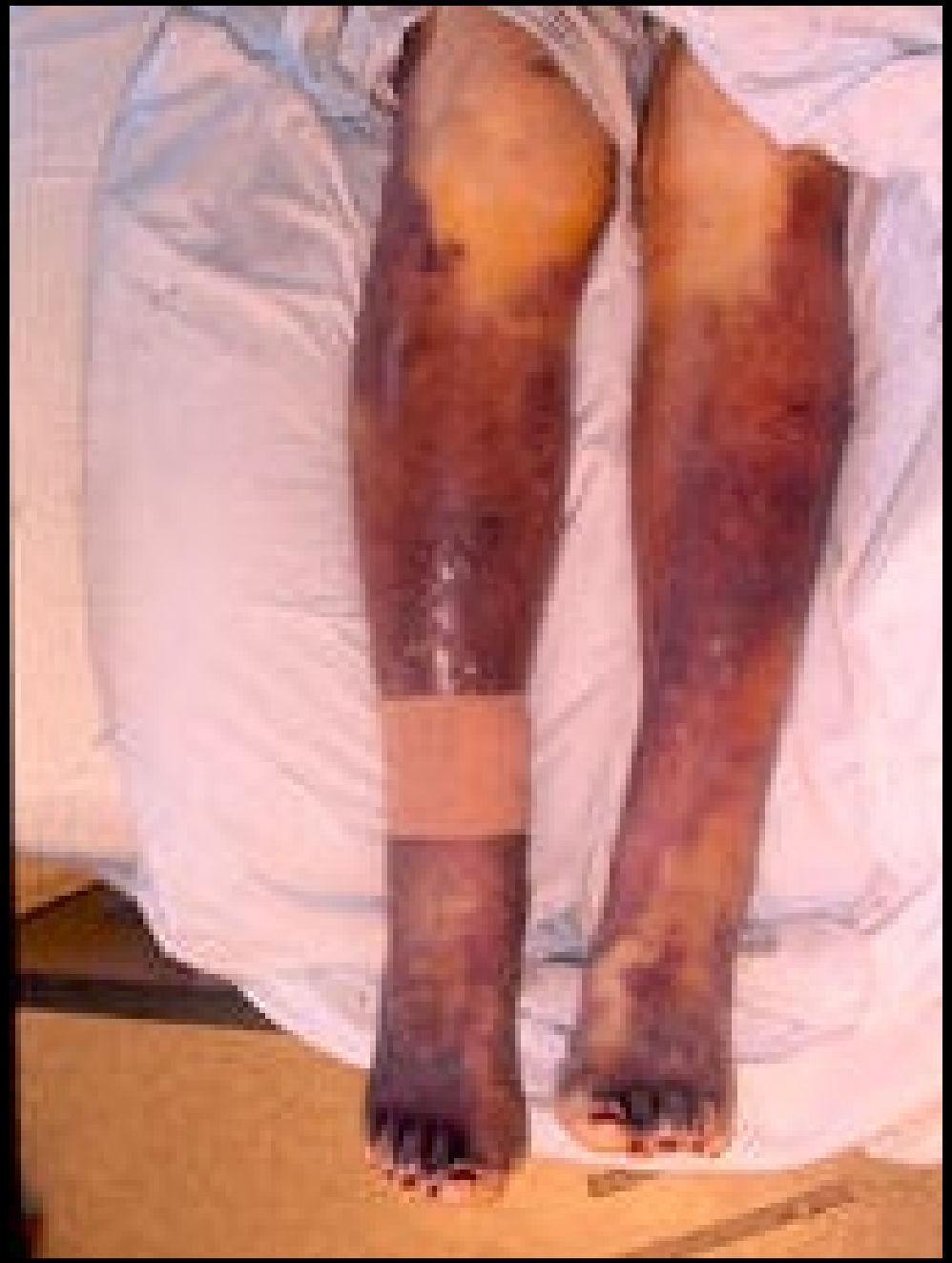
- FDA approved FIX gene therapy
- Can be administer in hemophilia centers
- Cost: ~ 3,500,000

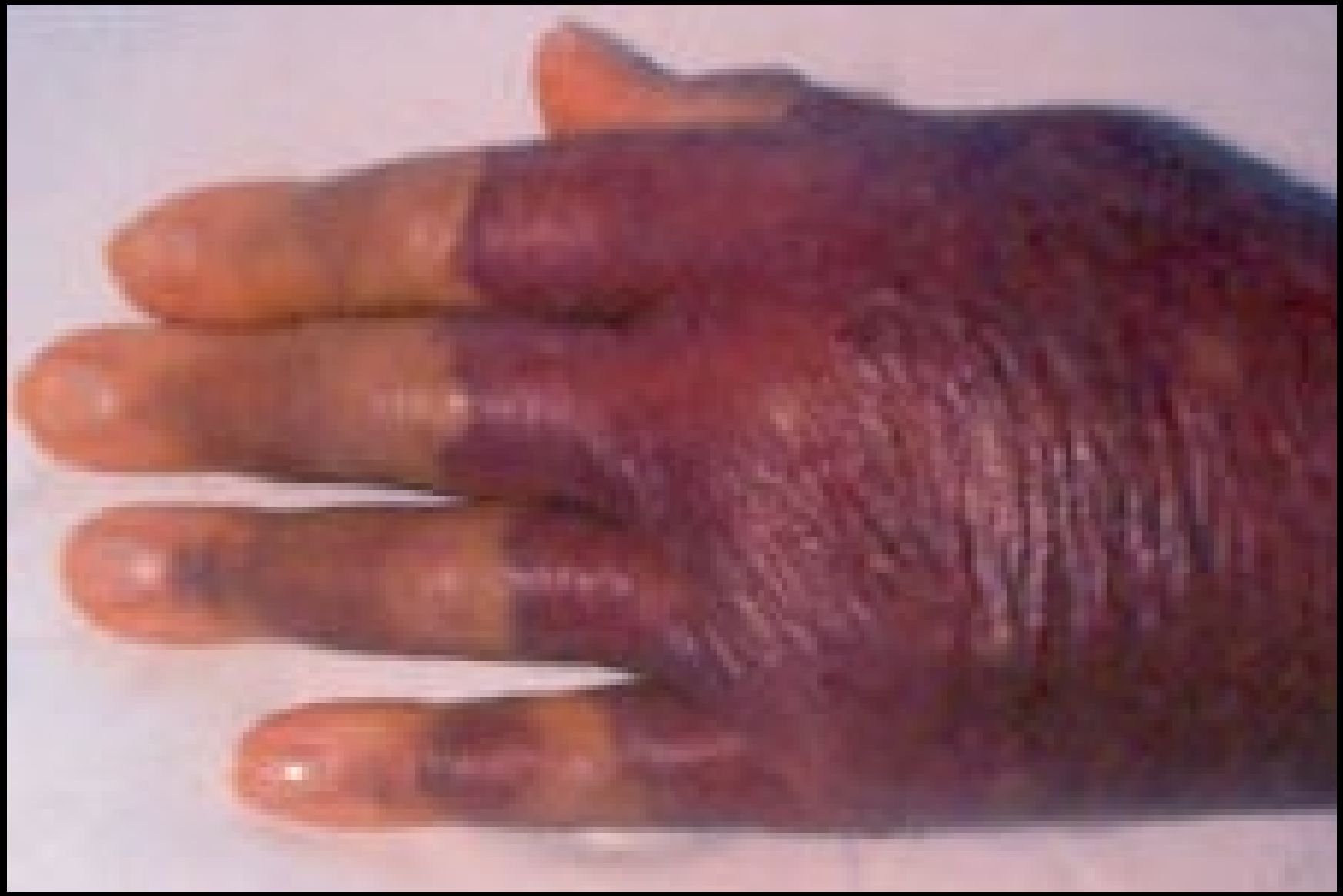
Acquired Factor Inhibitors

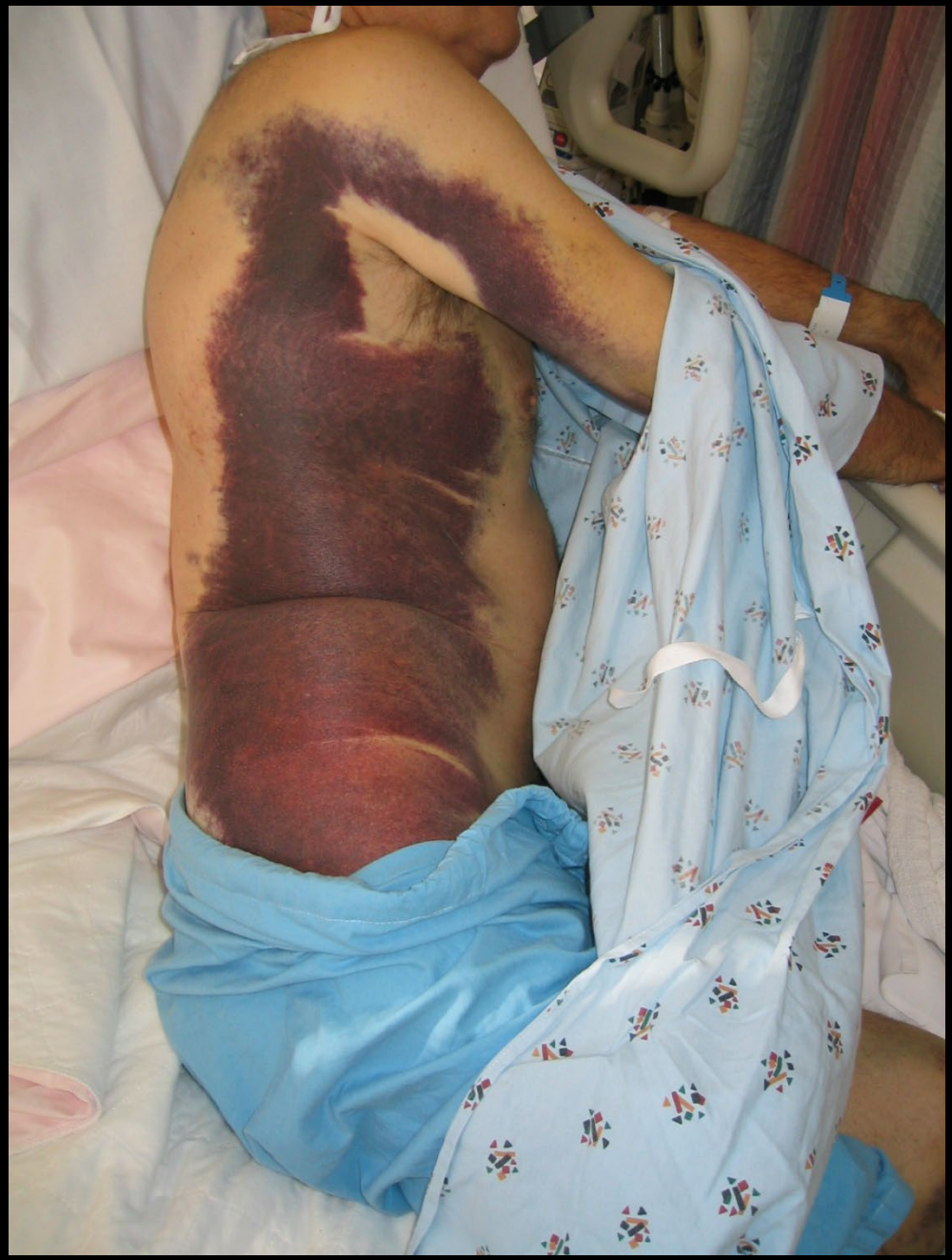
- Rare but spectacular cause of bleeding
- Specific inhibitory antibody forms to coagulation factor
- Underlying disease
  - Autoimmune disease
  - Cancer
  - Older age

Acquired Factor Inhibitors

- Most common is factor VIII
- Presentation: sudden onset of bruising and bleeding, excessive bleeding from surgery sites







Acquired Factor VIII Inhibitors

- Dx: elevated aPTT that corrects (or near corrects) at time zero but prolongs with incubation
  - Measurement of specific factor levels

Therapy for Coagulation Inhibitors

- Two goals
  - Drive away antibodies
  - Correct coagulation defects

Drive Away Antibodies

- Steroids
  - 60 mg daily
- Cyclophosphamide
  - 100mg po daily
- Rituximab
  - 1000mg x 2 14 days apart

Correct Coagulation Defects

- Infused VIII is ineffective
- Porcine factor VIII
- Activated prothrombin complex concentrates
- rVIIa

RVIIa

- 90 ug/kg ~ q2-3 until hemostasis
  - Then every 6 for 24 hrs?
- Risk of thrombosis minimal

FIEBA

- 50 units/kg 6 hrs
- Contraindicated if patient getting emicizumab

Obizur

- Porcine Factor VIII
  - 200 units/kg load then 100 units/kg bid
- Can develop inhibitors

Emicizumab

- Increasing use in acquired inhibitors
- Started at 3mg/kg weekly
- Quicly effective
- Difficult to monitor VIII levels

Conclusions

- Lots of action in this field!
- Extended half-life products and emicizumab major impacts
- Anti-natural anticoagulant therapy
  - Promising but risky
- Gene therapy
  - Lots of trials