



Fred Hutch · Seattle Children's · UW Medicine

Bleeding Disorders

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Disclosures

Consulting Fees (e.g., advisory boards)

Chugai, Biomarin, CSL Behring, CRISPR Therapeutics, Genentech

Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents (e.g., speakers' bureaus)

Roche

Contracted Research

CSL Behring, Genentech, Spark

Objectives

- To discuss **von Willebrand disease**
 - Treatment option
 - Acquired von Willebrand syndrome
- To describe new treatment options for **congenital hemophilia**
- To recognize **acquired hemophilia** and describe potential 1st line treatment options
- To describe some **rarer factor deficiencies** and their treatment approaches

Von Willebrand Disease



Von Willebrand Factor

Quantity

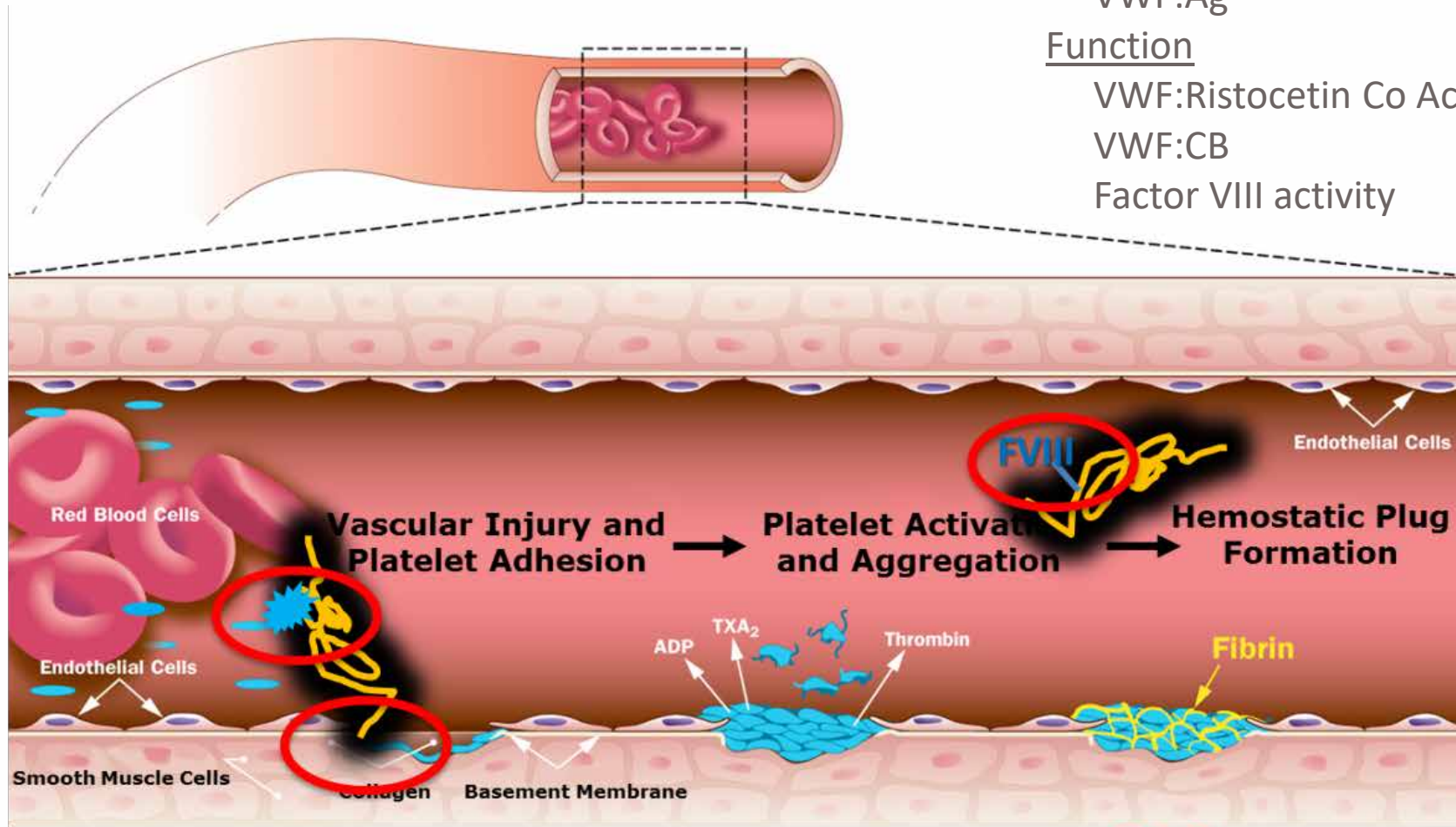
VWF:Ag

Function

VWF:Ristocetin Co Activity (RCo)/ VWF:Act

VWF:CB

Factor VIII activity



Collagen binding

Factor VIII binding

Platelet binding

Quantitative defects

- Type 1

- Type 2

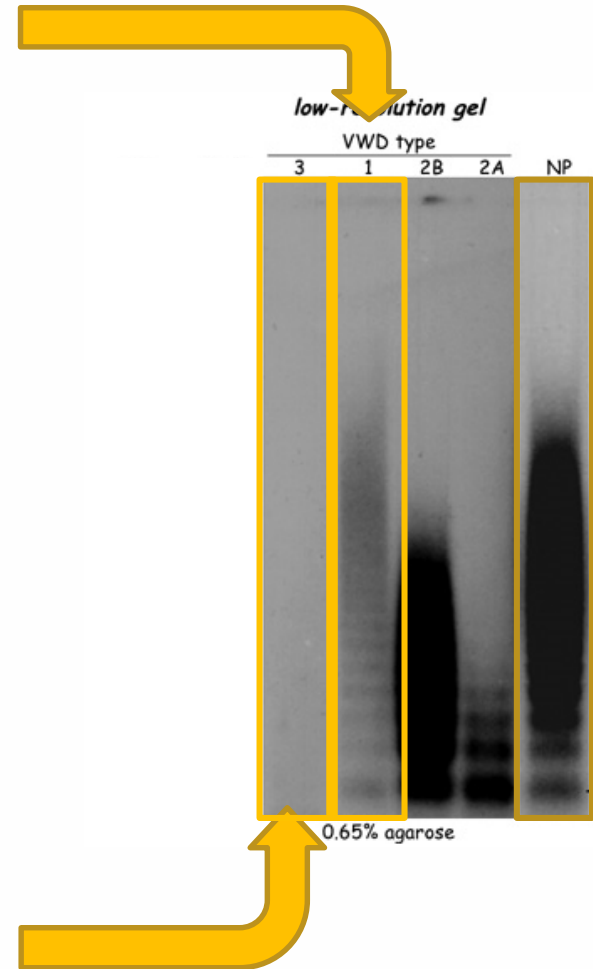
– 2A

– 2B

– 2M

– 2N

- Type 3



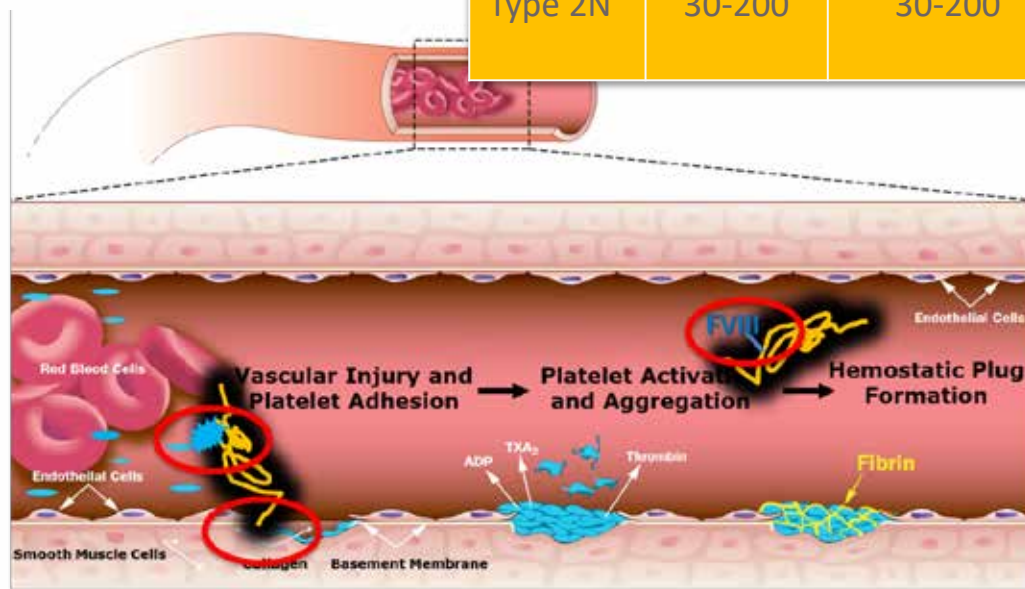
- Decreased VWF production
- Most common (75%)
- Mild bleeding symptoms

- Very decreased VWF production
- Very rare (<5%)
- Severe bleeding symptoms

Qualitative defects

- Type 2
 - 2A
 - 2B
 - 2M
 - 2N

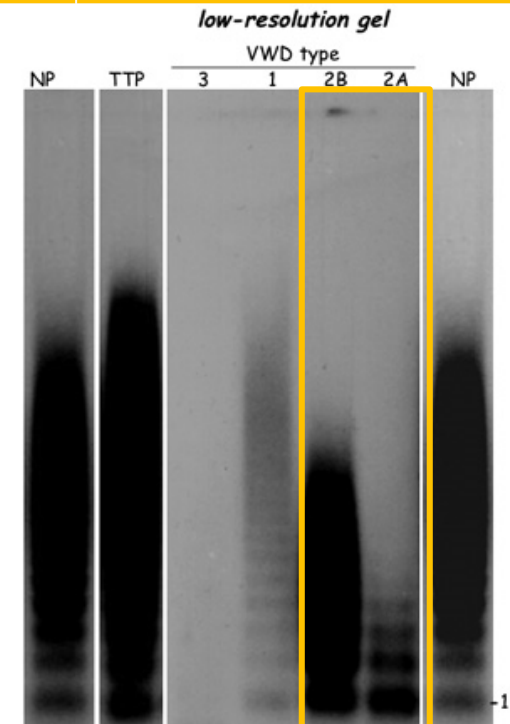
VWD type	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	Ratio of VWF:RCo/VWF:Ag	
Type 2A	<30*	<30-200*?	↓ or Normal	<0.5-0.7	Abnormal multimers Abnormal Ag/RCo ratio
Type 2B	<30*	<30-200*?	↓ or Normal	Usually <0.5-0.7	Abnormal multimers Abnormal Ag/RCo ratio Increased plt. binding
Type 2M	<30*	<30-200*?	↓ or Normal	<0.5-0.7	Normal multimers Abnormal Ag/RCo ratio
Type 2N	30-200	30-200	↓↓	>0.5-0.7	Normal multimers Normal Ag/RCo ratio Decreased FVIII binding



Collagen binding
Platelet binding

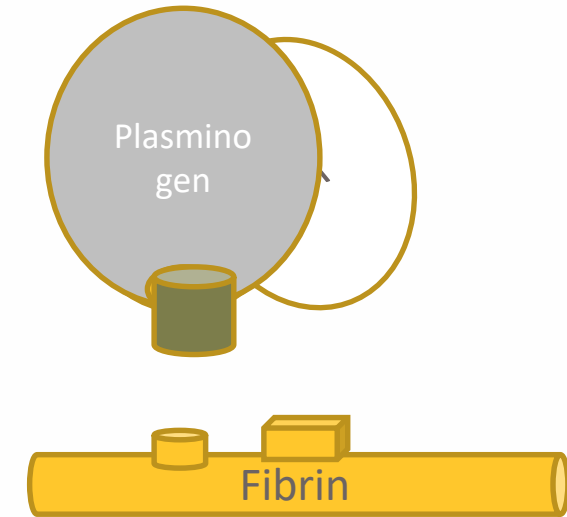
Factor VIII binding

Image adjusted from Victor S. Blanchette



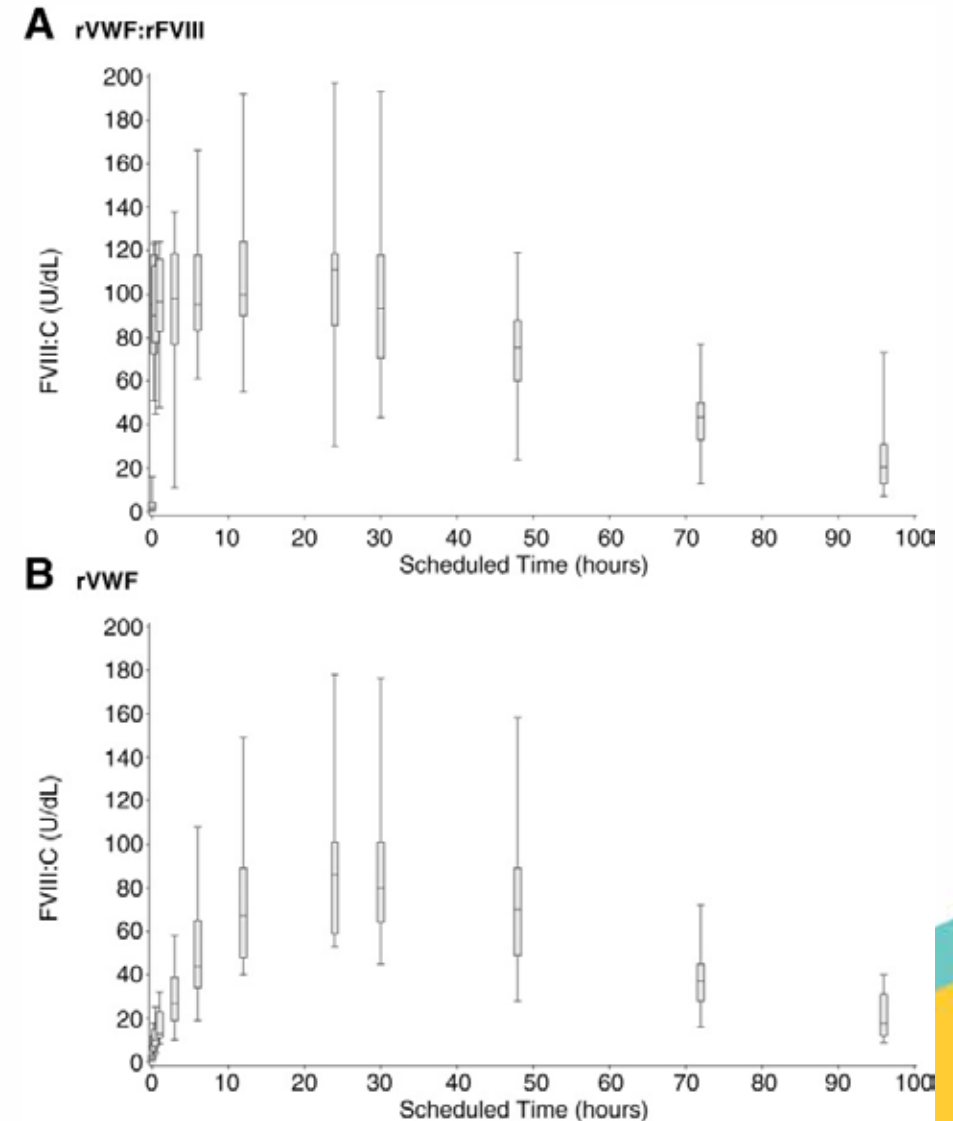
Treatment of VWD

- **Desmopressin (DDAVP, Stimate)**
 - Releases endogenous VWF and factor VIII
- **Antifibrinolytic**
 - ϵ -aminocaproic acid, tranexamic acid
 - Lysine analog
 - Binds to plasminogen and prevents conversion to plasmin and thus fibrin degradation



Treatment of VWD

- Factor concentrate
 - Plasma derived - all contain factor VIII as well
 - Recombinant von Willebrand factor (rVWF)
 - Phase III trial in severe VWD
 - 50 U/kg with or without FVIII
 - Terminal half life not affected by co-infusion of FVIII
 - Single infusion was effective in 81.8% of bleeds
 - 100% of bleeds (n=192) were controlled



Acquired von Willebrand syndrome (AVWS)

- Rare
 - underreported
- Paucity of data
 - largest data collection on the disorder today, the International Society of Thrombosis and Haemostasis International Registry on AVWS

AVWS due to decreased production

Decreased production of thyroid hormone



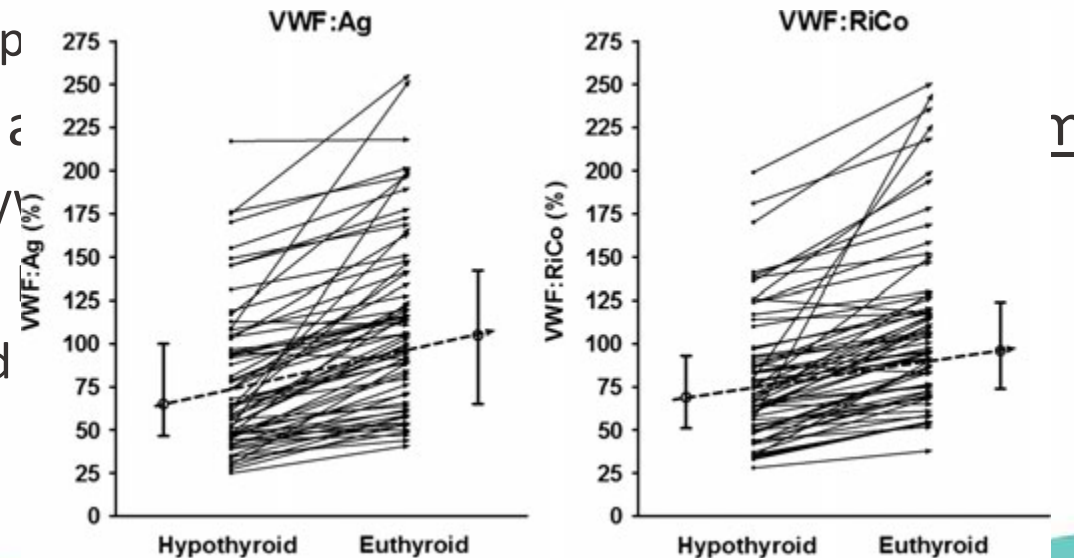
Decreased synthesis of von Willebrand factor

- Looks like a type 1 VWD (quantitative)

- Low VWF:Ag and VWF:Activity
- Normal multimers
- Low VWF p

- Study of 90 a

- 33% had V
- Most with
- Correlated

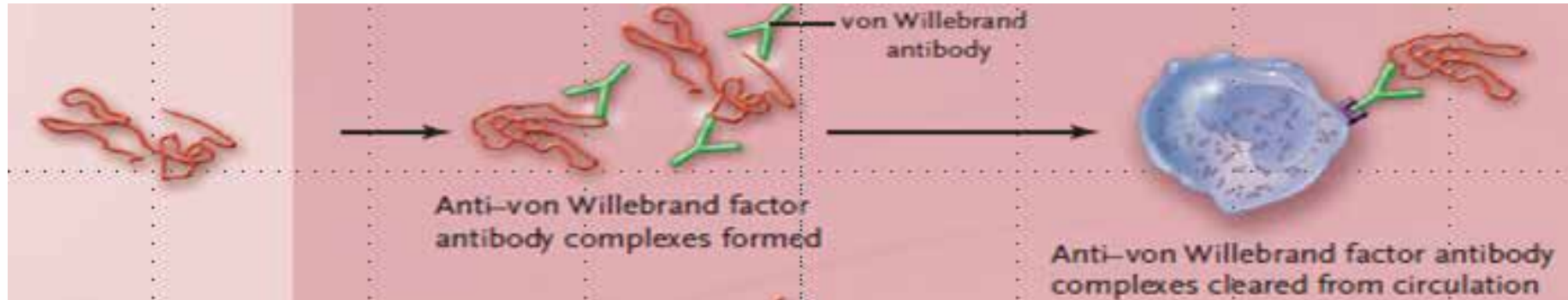


AVWS due to adsorption



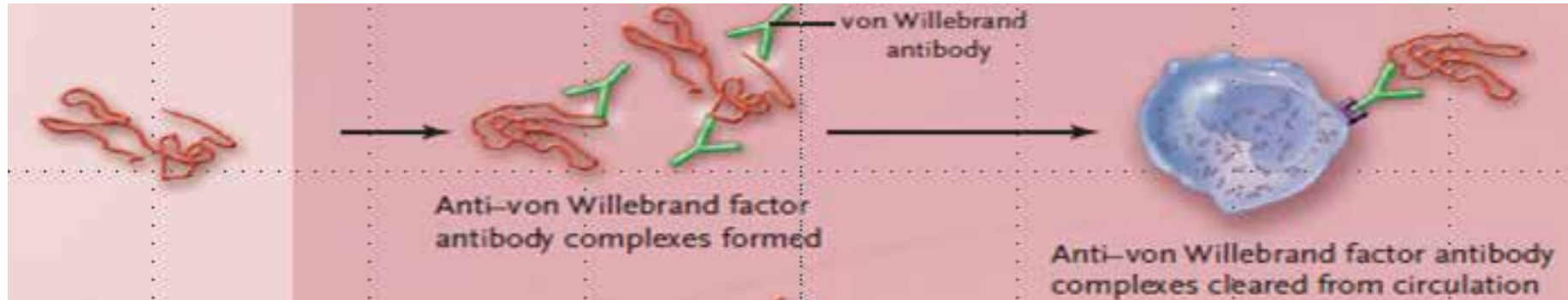
- Lymphoproliferative disorders (MM, WM, NHL, HCL), Myeloproliferative disorders (ET, PV), other thrombocytosis, malignancy
- Treat the underlying disease

AVWS due to antibodies



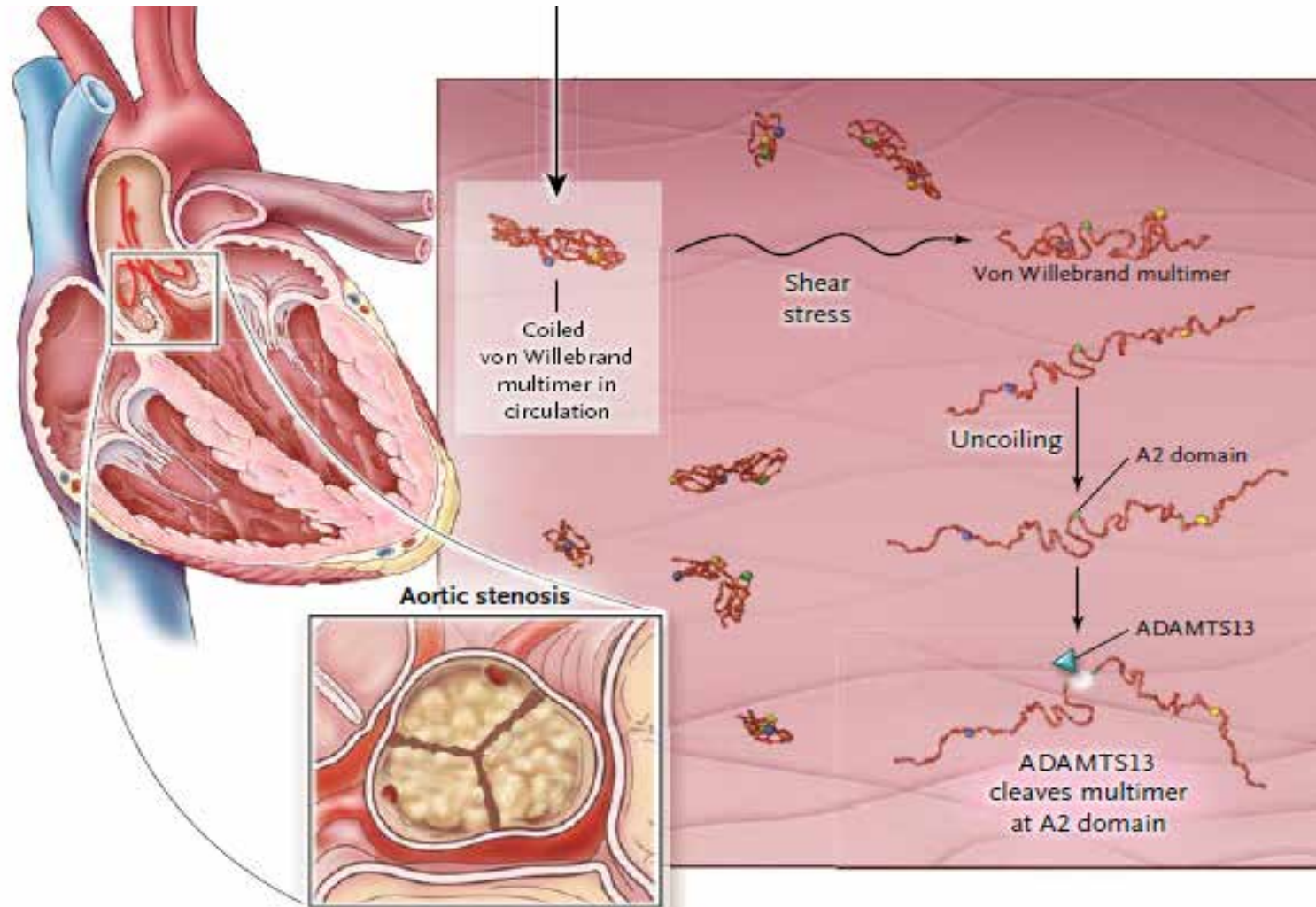
- Associated conditions:
 - monoclonal gammopathy of undetermined significance (MGUS)
 - lymphoproliferative disorders
 - systemic lupus erythematosus
- Detection of actual antibodies remains challenging and not well standardized

AVWS due to antibodies



- Immunosuppression
 - Intravenous immunoglobulin¹
 - Corrects laboratory abnormalities within 24-48 hours
 - Alleviates bleeding symptoms in IgG-MGUS but not IgM-MGUS.
 - Response can be seen for about 21 days and periodic re-dosing can achieve long-term control
 - Prednisone and other immunosuppressant and rituximab
 - Varying results

AVWS associated with cardiovascular abnormalities



AVWS associated with cardiovascular abnormalities

- Etiology
 - acquired valve and other structural abnormalities
 - hypertrophic cardiomyopathy
 - intra-cardiac devices
- About 20% of adults with congenital heart disease have AVWS
Laboratory
 - Often normal VWF:Ag, VWF:RCo, or VWF:CB levels
 - But reduced VWF:RCo/Ag and VWF:CB/Ag ratio

AVWS associated with cardiovascular abnormalities

- Mitral valve regurgitation:

Variable	Mild (<i>N</i> = 13)	Moderate (<i>N</i> = 14)	Severe (<i>N</i> = 26)	<i>P</i> -value
HMWM loss	1 (8)	9 (64)	22 (85)	< 0.001*
PFA-CADP (s)	84 (73–96)	156 (104–181)	190 (157–279)	< 0.001
VWF multimers > 15	0.21 (0.18–0.23)	0.15 (0.14–0.18)	0.12 (0.10–0.14)	< 0.001
VWF multimers > 10	0.50 (0.46–0.54)	0.43 (0.37–0.45)	0.37 (0.32–0.44)	< 0.001
VWF:Act (%)	109 (93–124)	101 (61–133)	83 (77–140)	0.56
VWF:Ag (IU dL ⁻¹)	123 (97–146)	116 (76–167)	107 (93–195)	0.67
VWF:Act/VWF:Ag	0.92 (0.83–0.97)	0.85 (0.76–0.89)	0.79 (0.75–0.82)	< 0.001
BNP (pg mL ⁻¹)	48 (27–60)	112 (72–193)	156 (77–329)	< 0.001
BNP/ULN	0.42 (0.31–0.55)	1.10 (0.79–1.61)	1.92 (1.04–3.78)	< 0.001

AVWS associated with cardiovascular abnormalities

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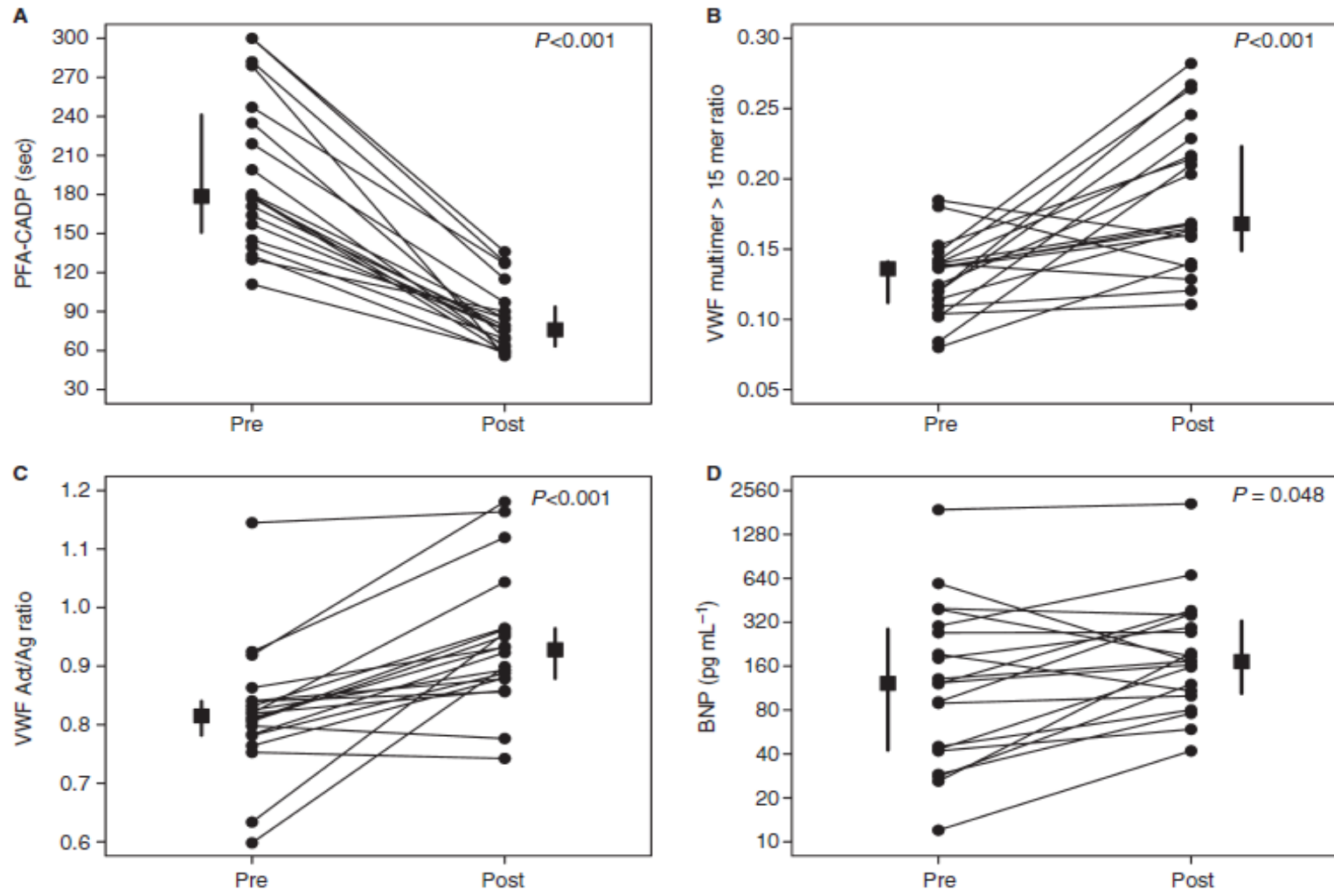
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AVWS associated with cardiovascular abnormalities

Effect of mitral valve repair



Hyde's Syndrome

Correspondence in NJEM 1958 by EC Heyde

Gastrointestinal Bleeding in Aortic Stenosis

In Blacksmith study in hypertrophic cardiomyopathy

8/20 (40%) had AVM's

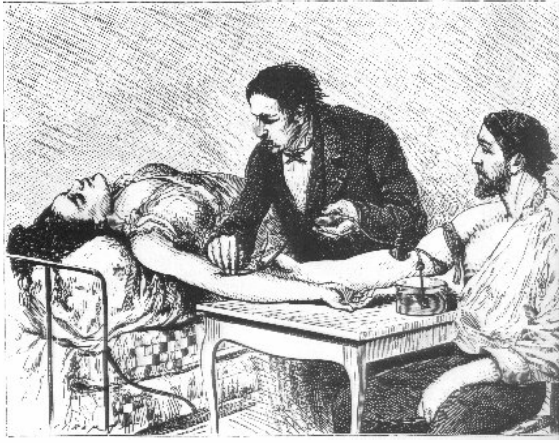
Etiology is poorly understood

normal vascular aging and an impairment of platelets to maintain vascular endothelium

Bleeding symptoms resolve after valve replacement

Congenital Hemophilia

Transfusions are critical to keep a patient safe and healthy. We have a variety of options to help you manage your patient's care.



**First Blood Transfusion
for Hemophilia**

First Plasma Transfusion

**Cryoprecipitate discovered
by Dr. Judith Pool**

First Factor Concentrates

First Monoclonal Factor Concentrates

First Recombinant Factor Concentrates

**Prophylaxis
In U.S.**

1803 1823 1840 1936 1964 1960/70's 1987 1993 2007 2014 2017

The biggest challenges for hemophilia #1

Factor replacement is standard of care

Prophylactic factor given several times weekly for severe hemophilia

As needed for moderate/mild hemophilia

Has to be given **IV**

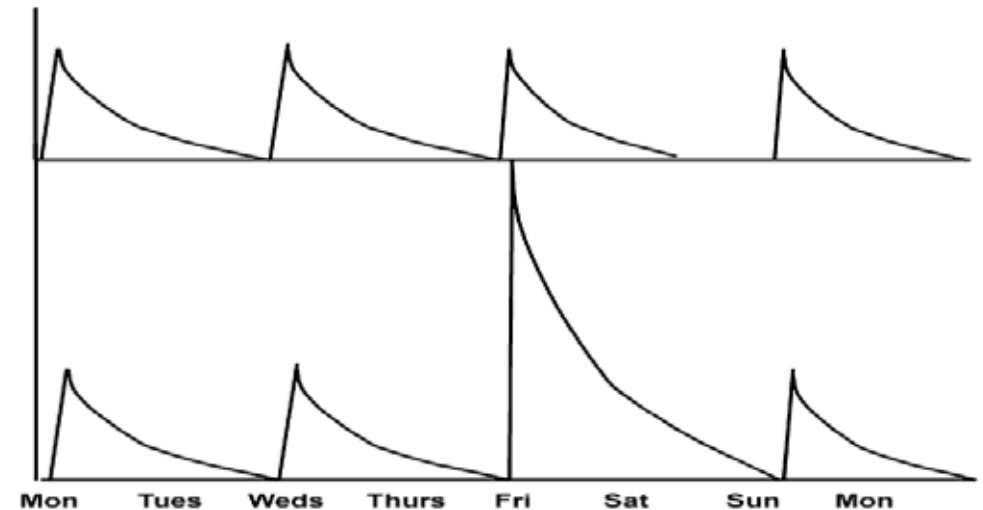
Factor has a relatively **short half life**

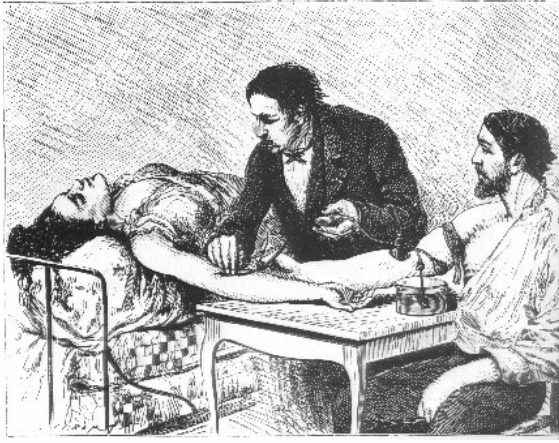
~ 6-10 hours for factor VIII

~12-18 hours for factor IX

Has to be given frequently

Difficult to achieve troughs to maintain an active lifestyle





Extended half-life factors (EHL)



1803

1823

1840

1936

1964

1960/70's

1987

1993

2007

2014

2017

First Blood Transfusion
for Hemophilia

First Plasma Transfusion

Cryoprecipitate discovered
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First Factor Concentrates

First Monoclonal Factor Concentrates

First Recombinant Factor Concentrates

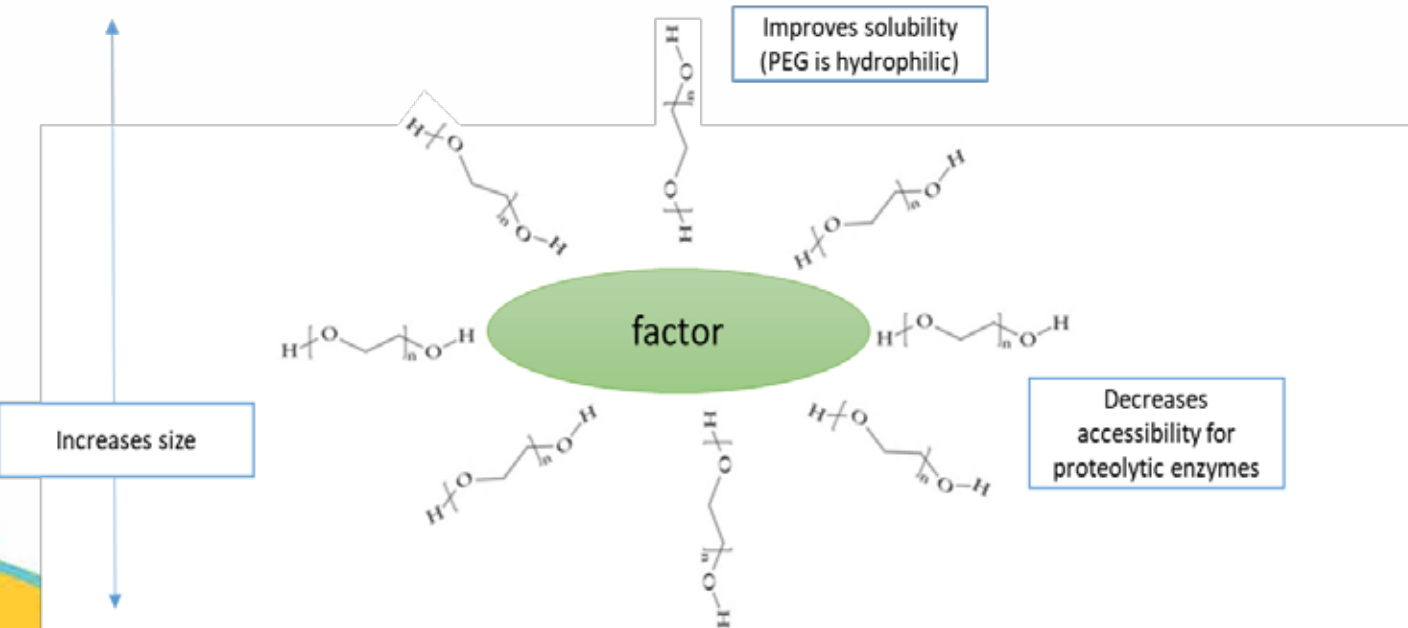
Prophylaxis
In U.S.

Bi-specific Ab

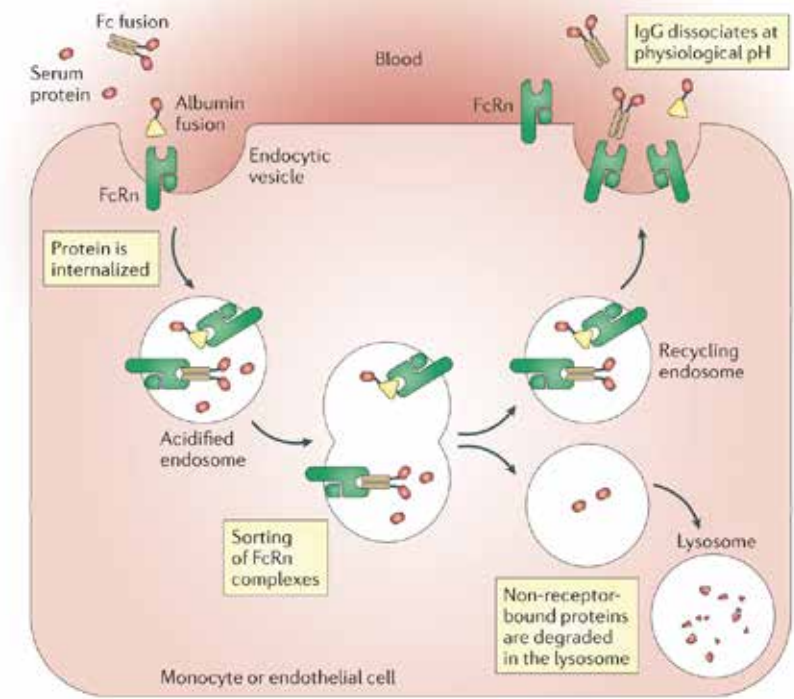
**Gene
therapy**

Mechanism of extended half-life factors

Pegylation

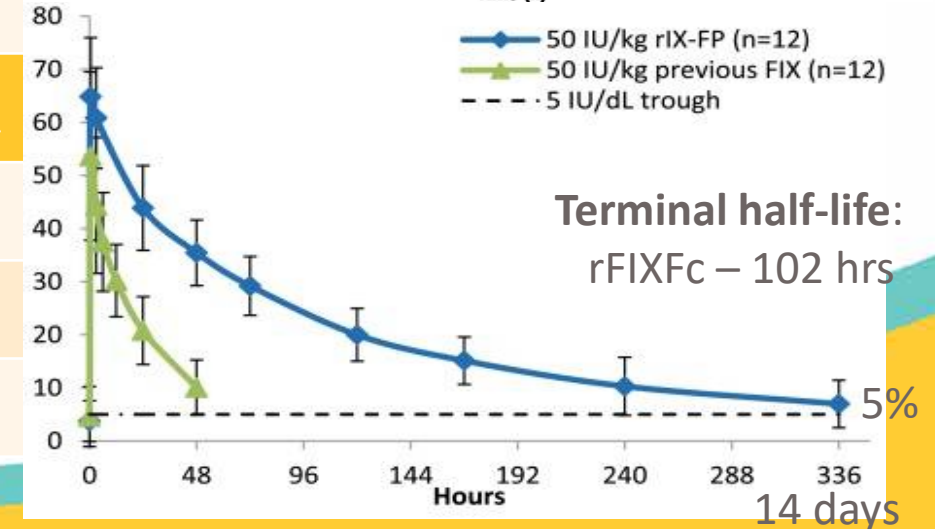
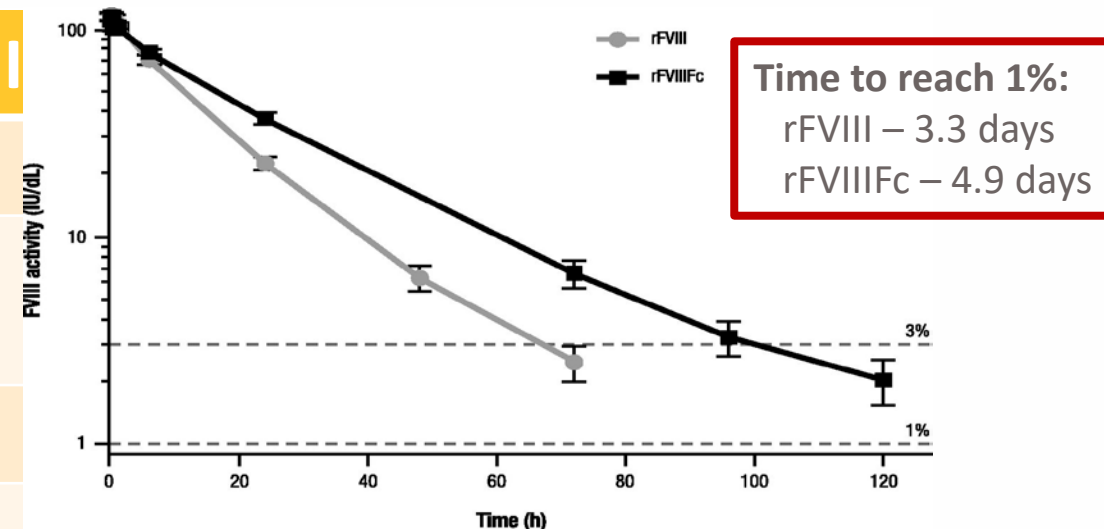


Fc or albumin fusion



Products with phase III data in the U.S.

Factor VIII	
rFVIII Fc (Eloctate)	1.5 fold
rFVIII pegylated (BAX855, Adynovate)	1.5 to 2-fold
N8-GP (Esperoct)	2-fold
BAY94-9027 (Jivi)	1.8-fold
Factor IX	
rIX Fc (Alprolix)	2.4 fold
rIX-FP (Idelvion)	> 5 fold
N9-GP (Rebinyn)	> 5 fold

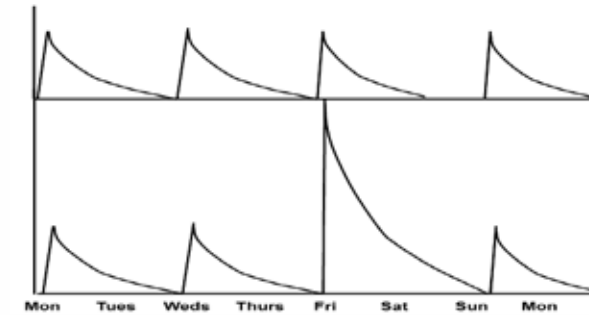
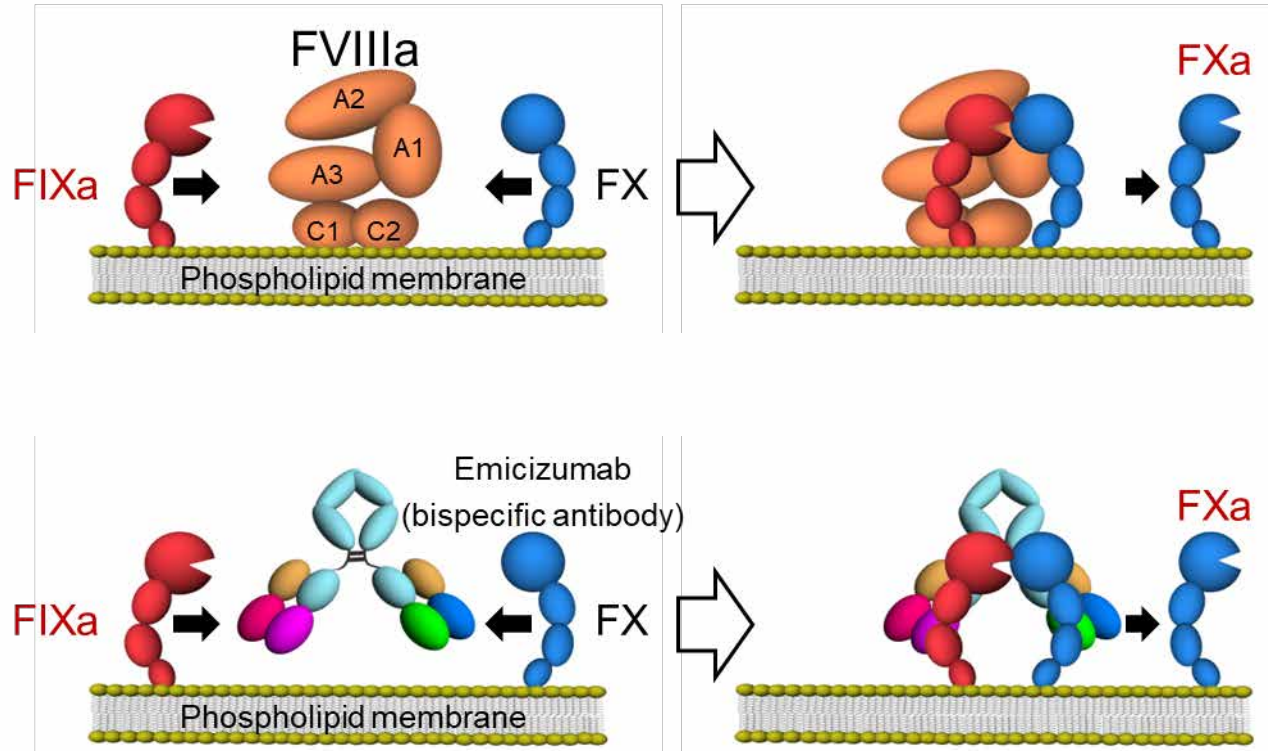


The biggest challenges for hemophilia #2

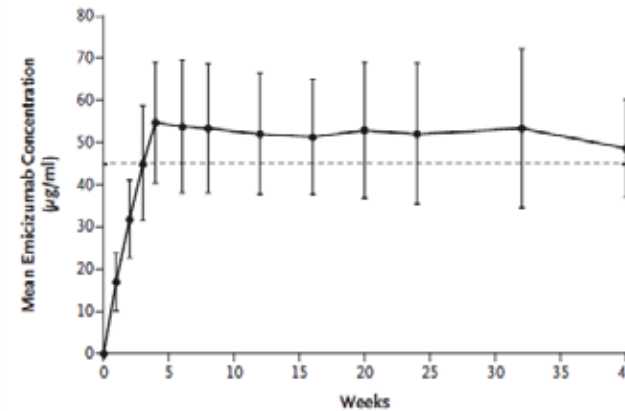
Antibody (**inhibitor**) formation is the most problematic side effect of factor replacement

- 30% of people with severe hemophilia A develop antibodies
- High titer inhibitors do not respond to FVIII replacement
 - Need to treat bleeding with **bypassing agents**
 - recombinant factor VII activated (rFVIIa)
 - activated prothrombin complex concentrate (aPCC, contains factor II, VII, IX, X)
 - Need lengthy **immune tolerance therapy (ITT)** to eradicate inhibitor
 - Daily high dose factor VIII infusion for months

Concept of FVIIIa-Mimetic Bispecific Antibody



IV
 $T_{1/2} \sim 8$ hours



SQ
 $T_{1/2} \sim 28$ days

- SQ every 1-4 weeks
- Hemophilia A ONLY
- With and without inhibitors

FVIIIa=activated factor VIII; FIXa=activated factor IX; FX=factor X.

Kitazawa T et al. *Nat Med.* 2012;18:1570-1574; Sampei Z et al. *PLoS One.* 2013;8:e57479; Muto A et al. *J Thromb Haemost.* 2014;12:206-213; Shima M et al. *N Engl J Med.* 2016;374:2044-2053.

Emicizumab approval

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2017 Jul 10.

ORIGINAL ARTICLE

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D.,
Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D.,
Guy Young, M.D., Elena Santagostino, M.D., Ph.D.,
Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D.,
Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc.,
Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

FDA Approval in USA for on November 16, 2017

to prevent or reduce the frequency of bleeding episodes in **adult and pediatric** patients with hemophilia A who have developed antibodies called **Factor VIII (FVIII) inhibitors**

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 30, 2018

VOL. 379 NO. 9

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

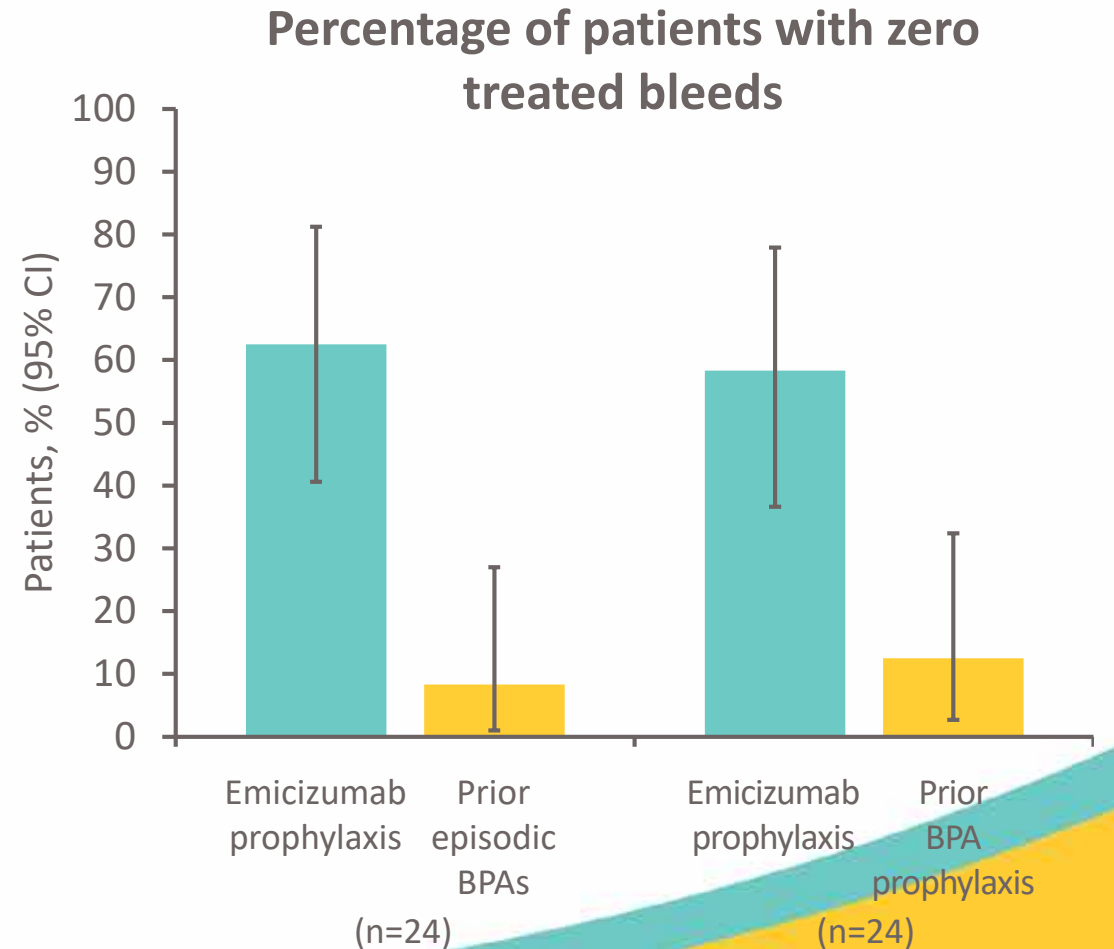
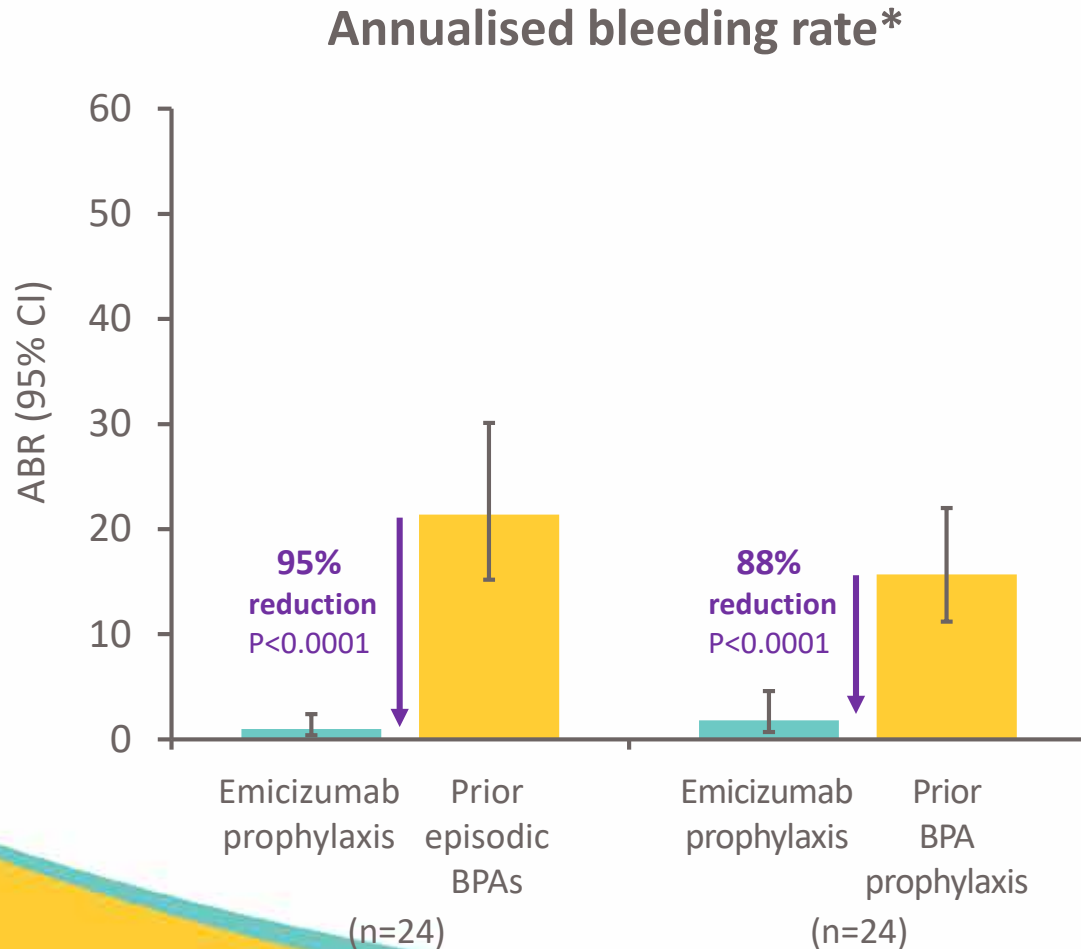
J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres

FDA Approval in USA for on October 4, 2018

for **prophylaxis** to prevent or reduce the frequency of bleeding episodes in **adult and pediatric** patients (ages newborn and older) with hemophilia A **with or without** **factor VIII (FVIII) inhibitors**

Intra-individual comparison

Comparing BPA prophylaxis to Emicizumab - ≥ 12 years old



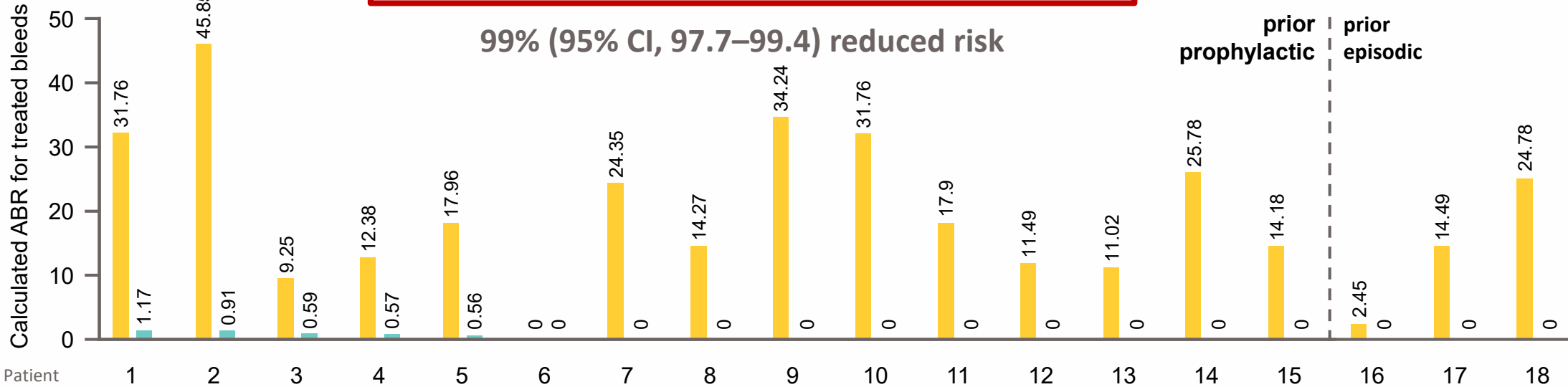
*Negative binomial regression model.
ABR, annualised bleeding rate; BPA, bypassing agent.

Efficacy of Emicizumab – Inhibitor <12 yo (HAVEN 2)

Intra-individual comparison

	Prophylactic/episodic BPAs	Emicizumab 1.5 mg/kg QW
ABR	19.9	0.2

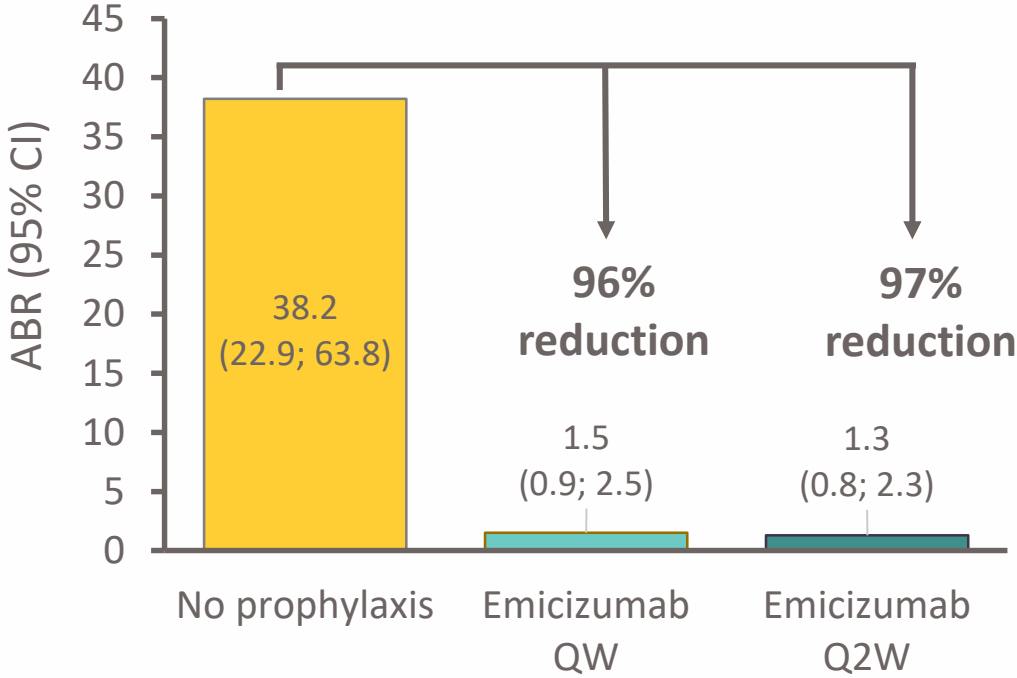
99% (95% CI, 97.7–99.4) reduced risk



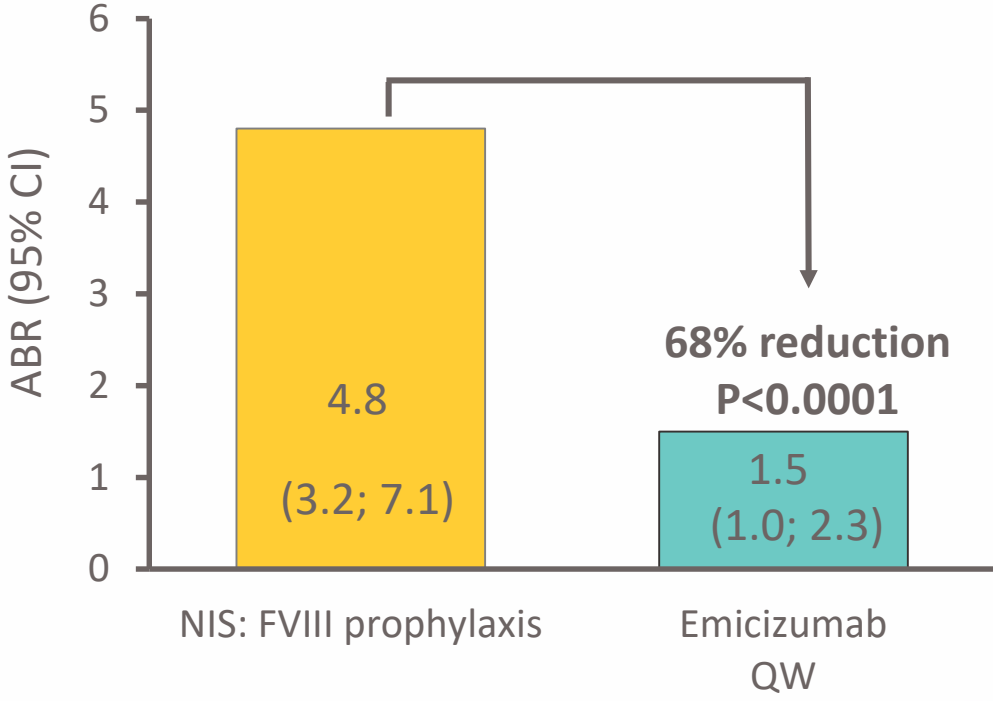
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Duration of efficacy period (days)	115	239	79	118	122	61	120	128	128	138	102	159	232	255	309	149	252	280
Number of treated bleeds	10	30	2	4	6	0	8	5	12	12	5	5	7	18	12	1	10	19
Number of treated bleeds (Efficacy)	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Efficacy of emicizumab – Non-Inhibitor (HAVEN 3)

On demand FVIII



Prophylactic FVIII



HAVEN 1: Overall Safety with Emicizumab

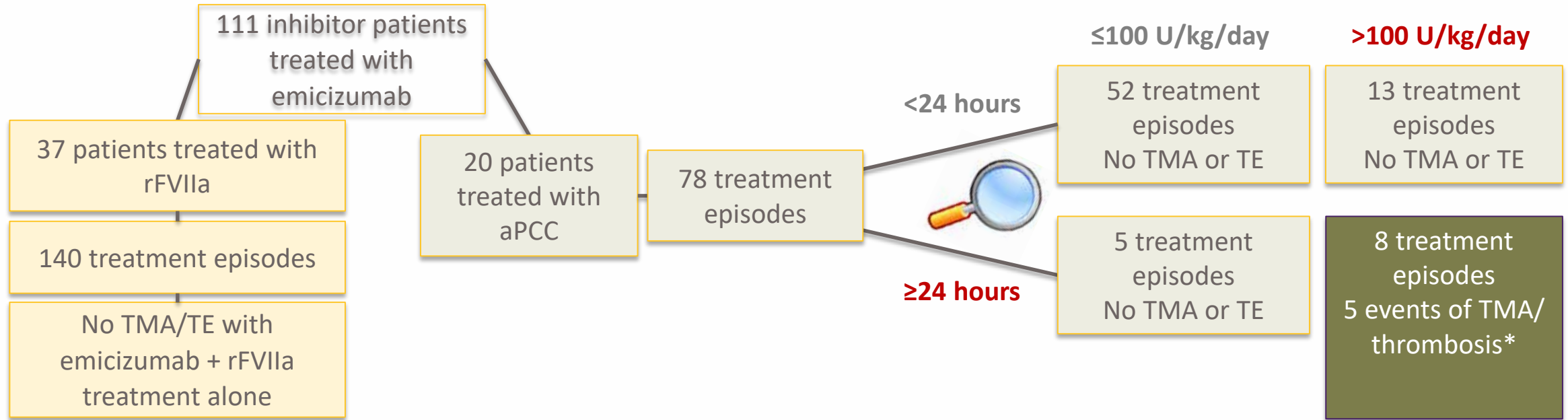
	Total (N=103)
Total number of adverse events (AEs), n	198
Total patients with ≥ 1 AE, n (%)	73 (70.9)
Serious AE*	9 (8.7)
Thrombotic microangiopathy (TMA)**	3 (2.9)
Thrombotic event	2 (1.9)
Death**	1 (<1)
AEs leading to withdrawal	2 (1.9)
Grade ≥ 3 AE	8 (7.8)
Related AE	23 (22.3)
Local injection site reaction	15 (14.6)

← Serious adverse

← Most common

*Additional serious AEs included one event each of: iron deficiency anaemia, sepsis, haemarthrosis, muscle haemorrhage, gastric ulcer haemorrhage, headache and haematuria. **Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal haemorrhage. Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision

HAVEN 1: assessment of interaction between emicizumab and aPCC

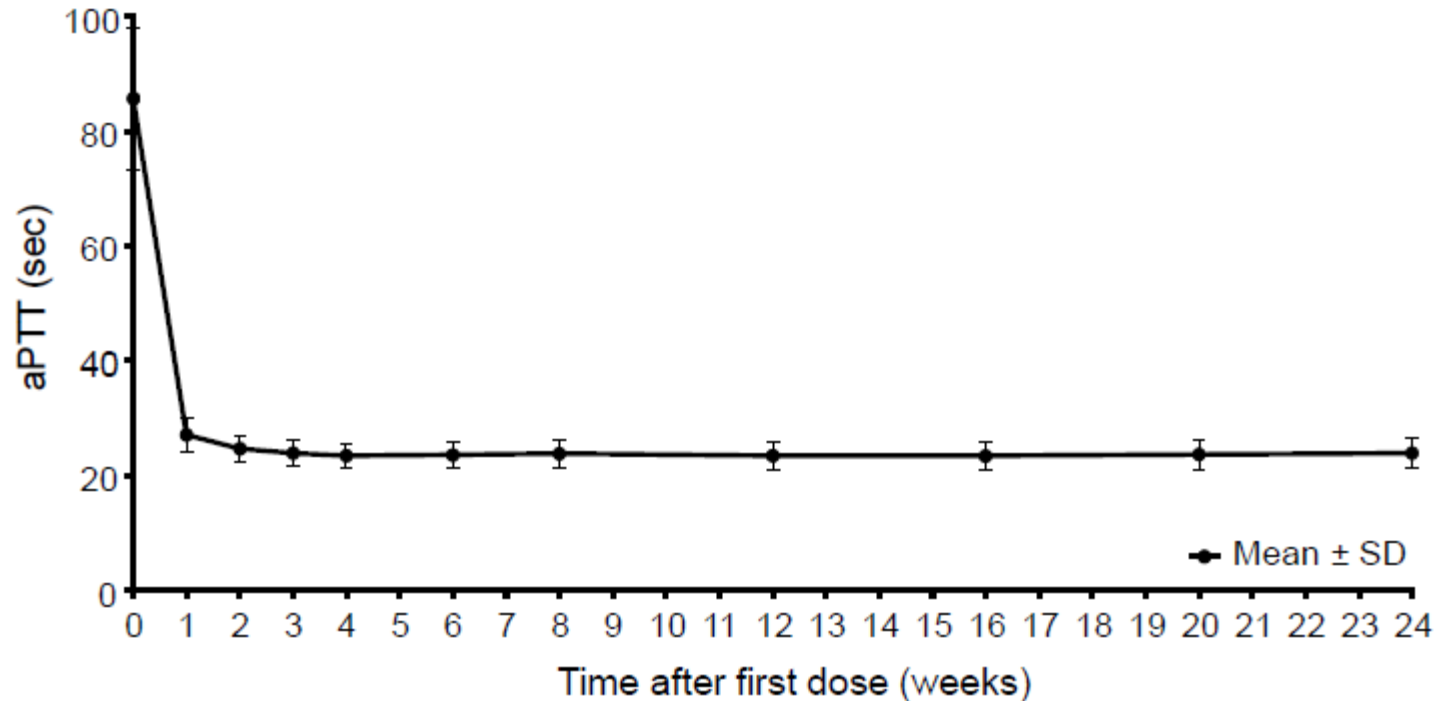


- aPCC contains activated and non-activated coagulation factors, including FII, FVII, **FIX** and **FX**, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date

*Two patients also received rFVIIa prior to/during the event
Updated data cutoff – April 21, 2017, including 8 additional patients

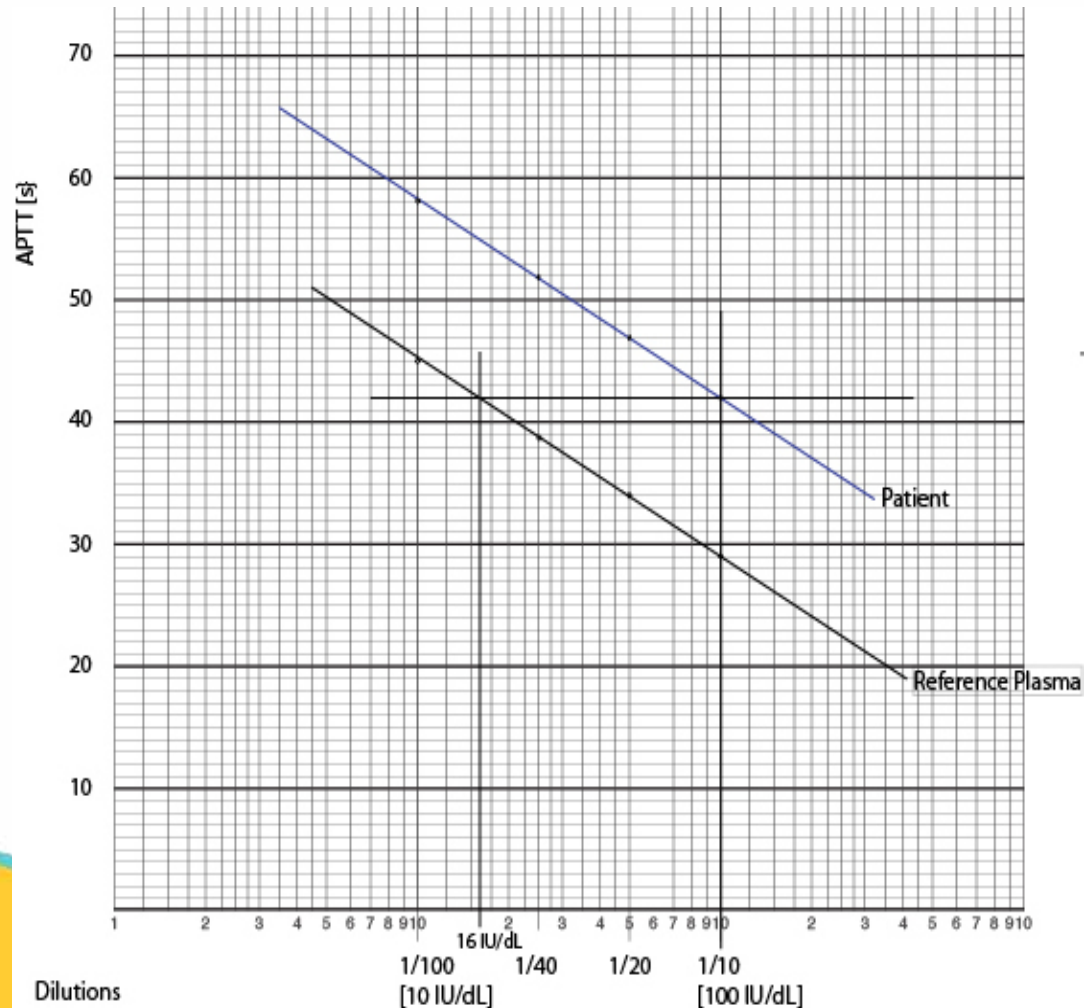
Emicizumab has a strong effect on aPTT

aPTT over time



- aPTT is **not an accurate measure of hemostatic potential** in the presence of emicizumab

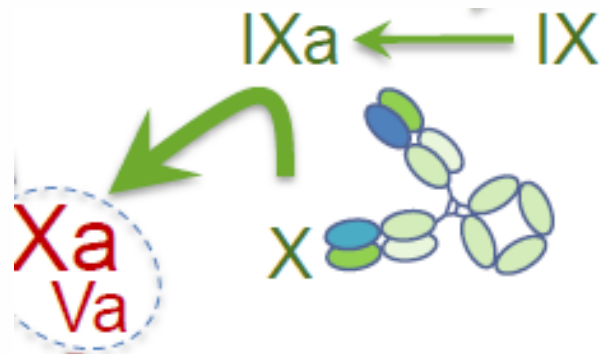
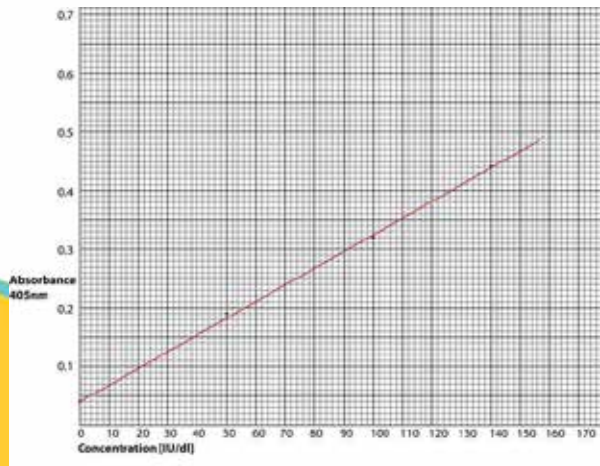
Effect on one stage assay (OSA) factor VIII assay...



- OSA is based on aPTT
- **Not a reliable assay** to measure FVIII on emicizumab

Chromogenic Factor VIII Assay

- Incubation step to generate FXa -> determine the amount of FXa produced
- Amount of FXa is measured by its action on a highly specific chromogenic substrate -> color intensity produced is directly proportional to the amount of Fxa -> directly proportional to the amount of FVIII

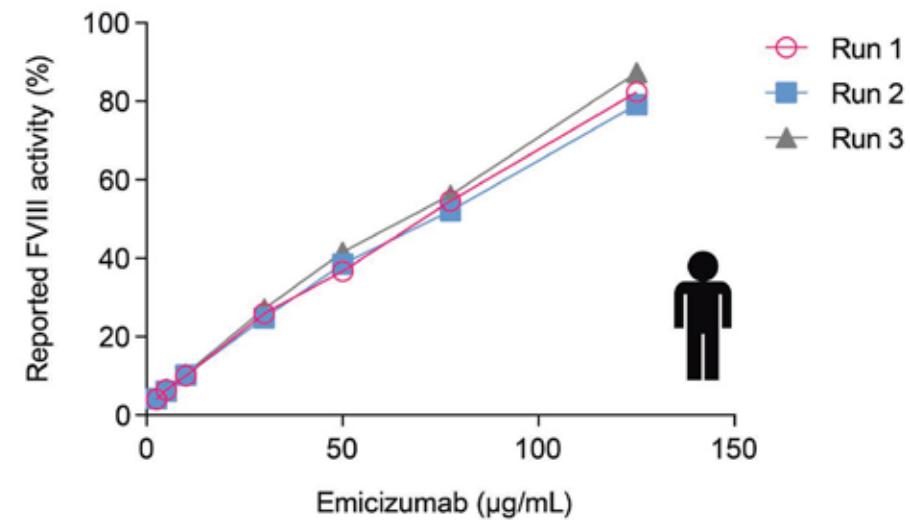


Works with **human** or **bovine** reagent

Effect of emicizumab on chromogenic factor VIII activity

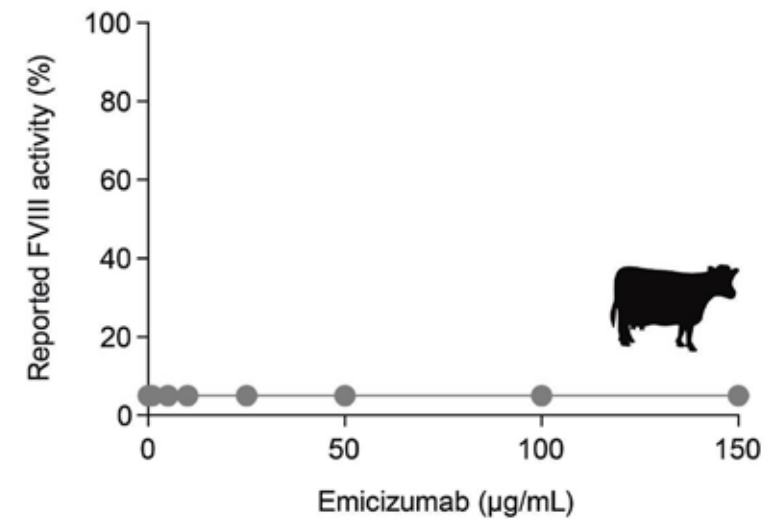
Human reagent

– detects emicizumab



Bovine reagent

– does NOT detect emicizumab

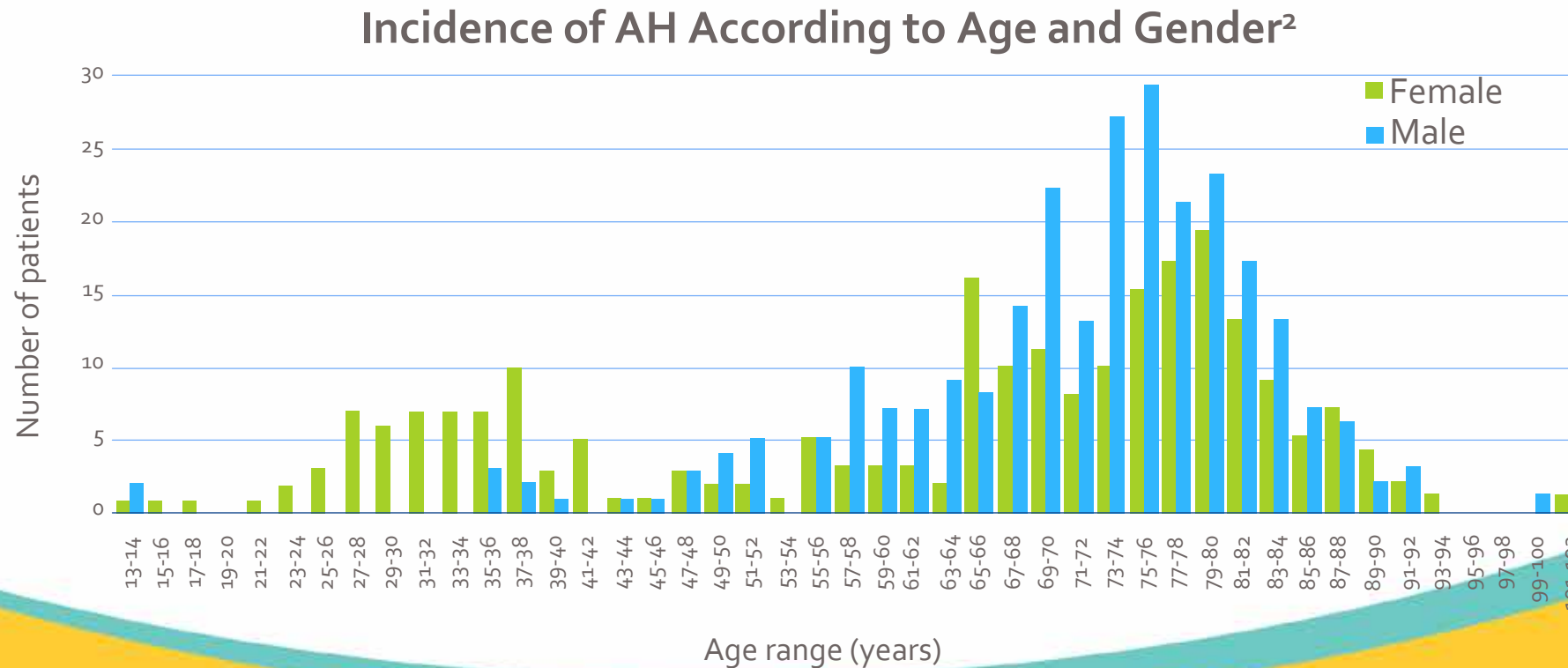


Acquired Hemophilia A

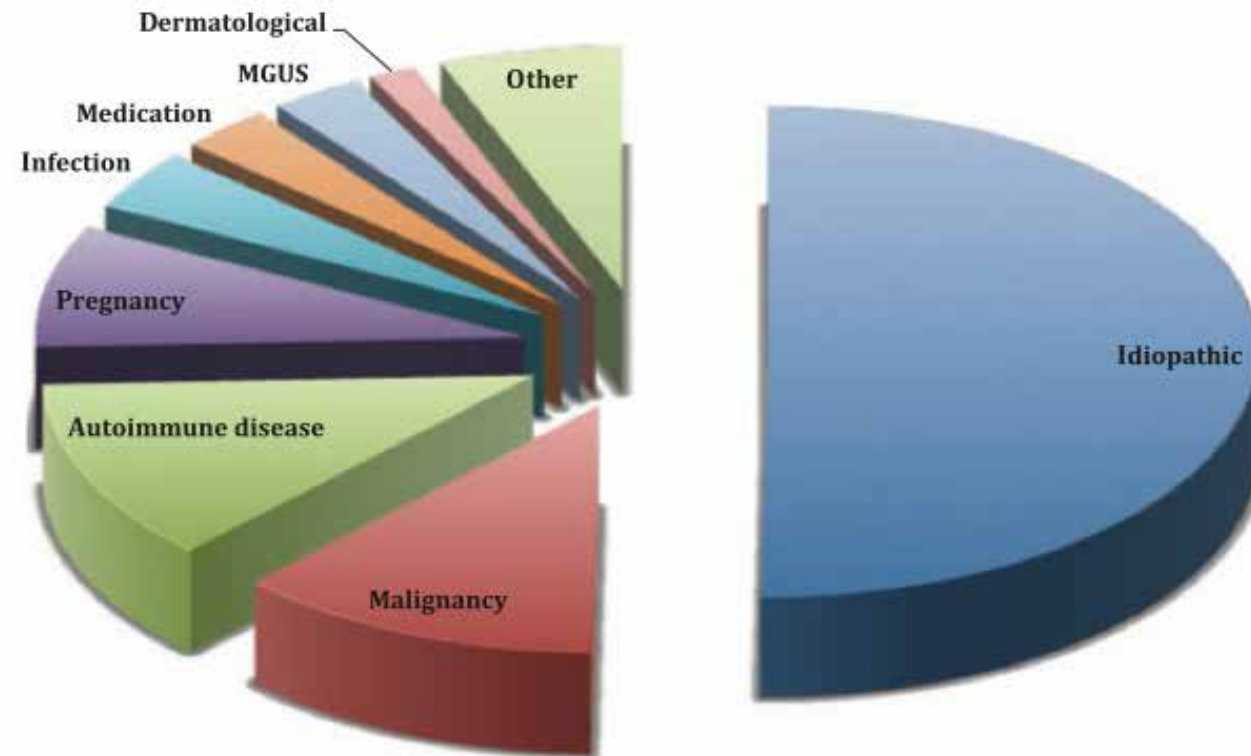
Diagnosis: PT/APTT should be elevated and reversible
with FFP or cryoprecipitate-depleted plasma

Epidemiology of Acquired Hemophilia

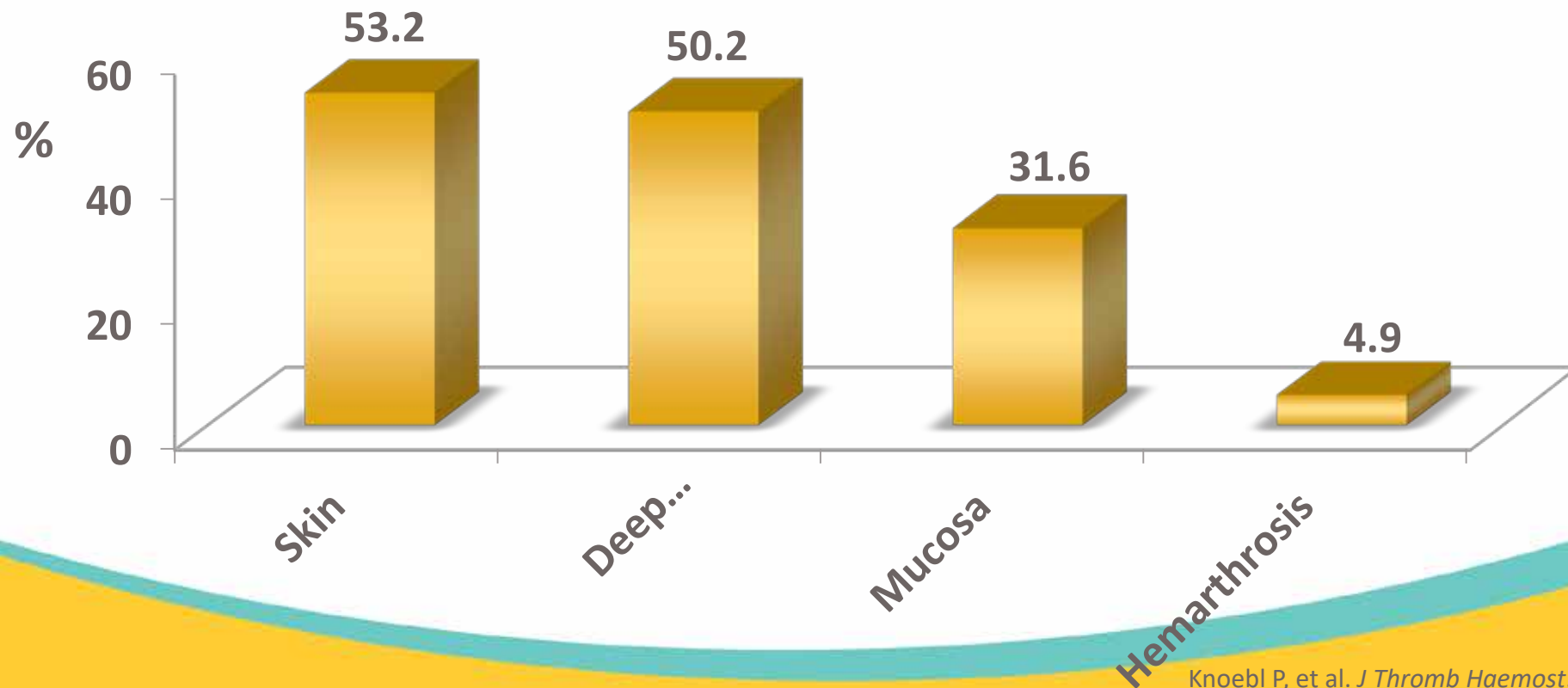
- Rare bleeding condition caused by an autoantibody (inhibitor) to coagulation factor VIII (FVIII)
 - Incidence: 1.5 cases per million/year¹



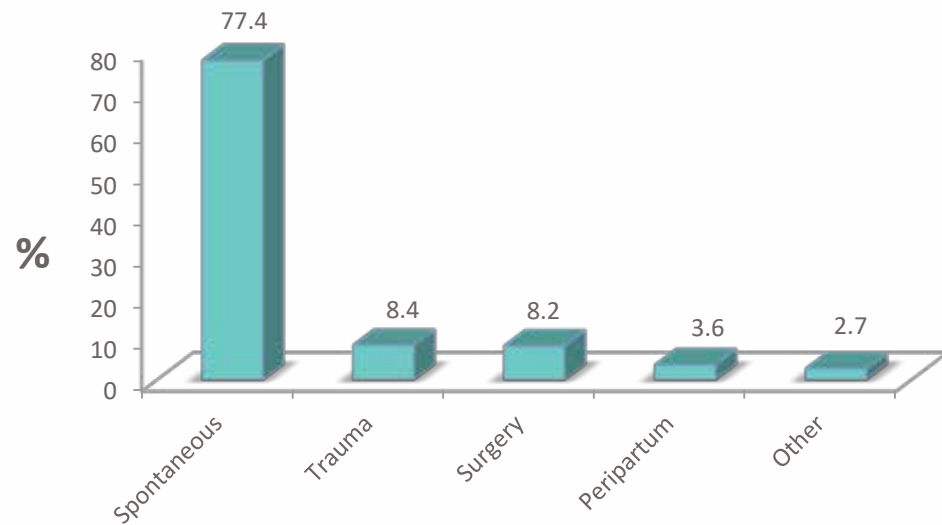
Associated Conditions



Bleeding Pattern in AHA

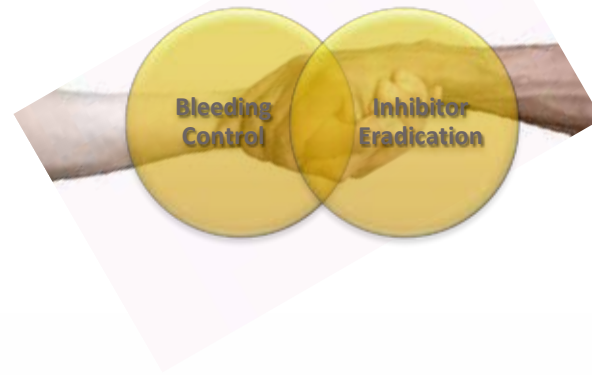


Bleeding Severity in AHA

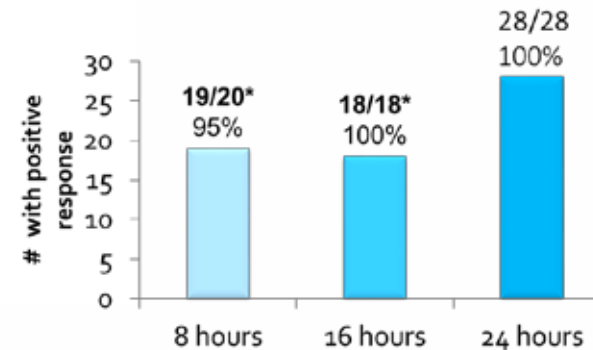
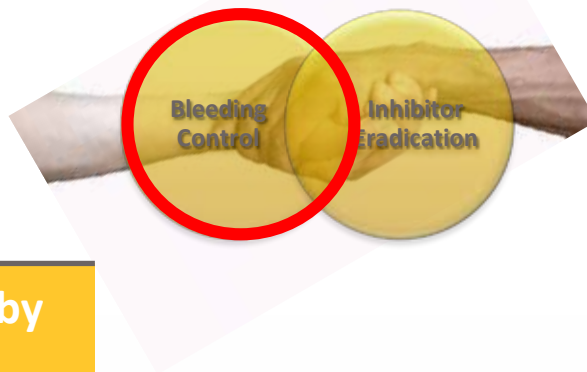


73% severe
Mortality - 8% to 22%

Principles of Treatment



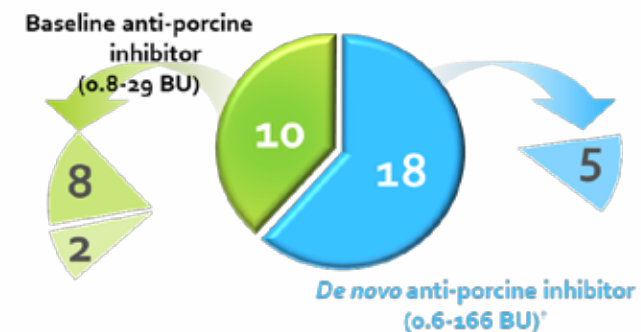
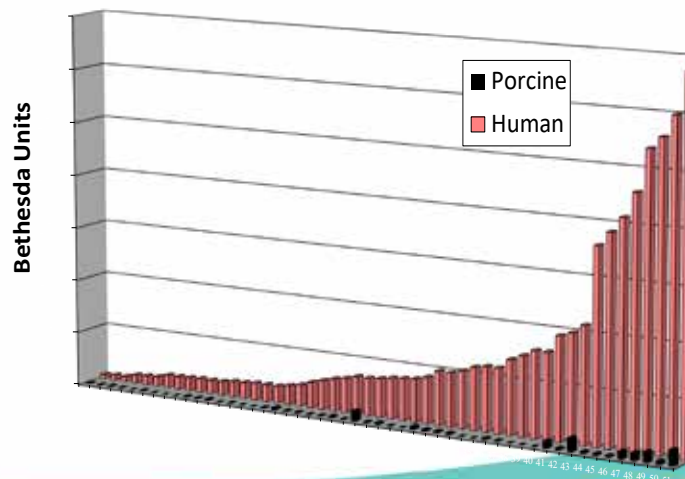
Principles of Treatment



Rates of Control for First Bleeding Episodes by First-line Therapy

	First-line Bleeding Control	
	n	%
Bypassing Agent	219	91.8
- Recombinant factor VIIa	159	91.2
- Activated prothrombin complex concentrate (aPCC)	60	93.3
Replacement Therapy	69	69.6
- FVIII	55	70.1
- DDAVP	14	64.3

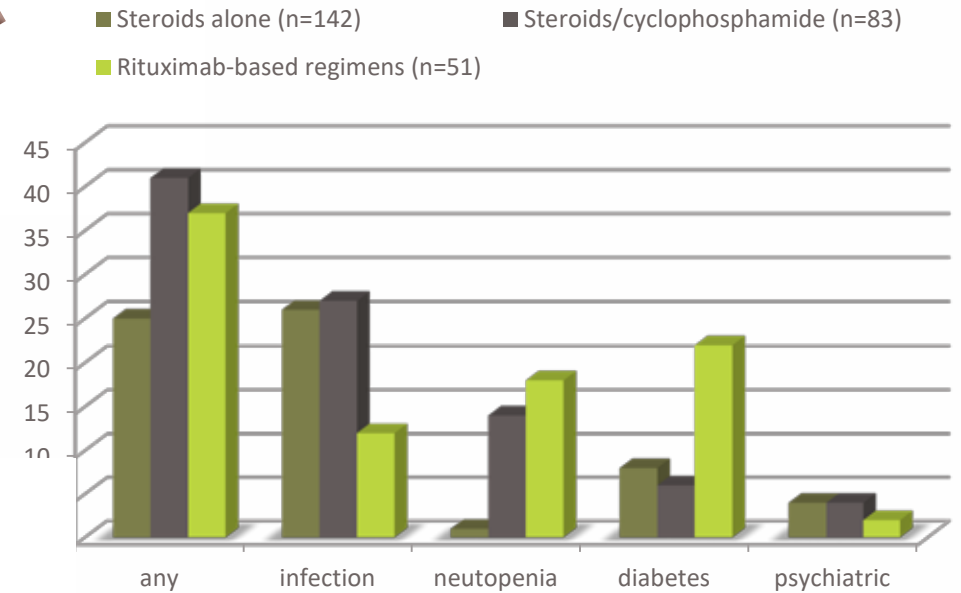
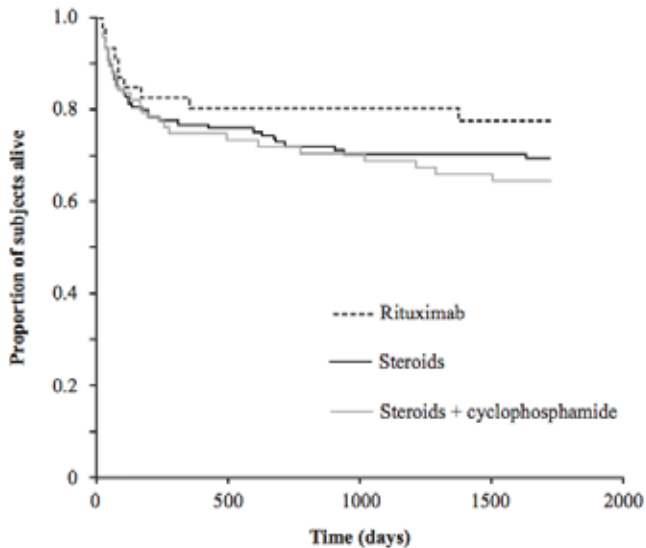
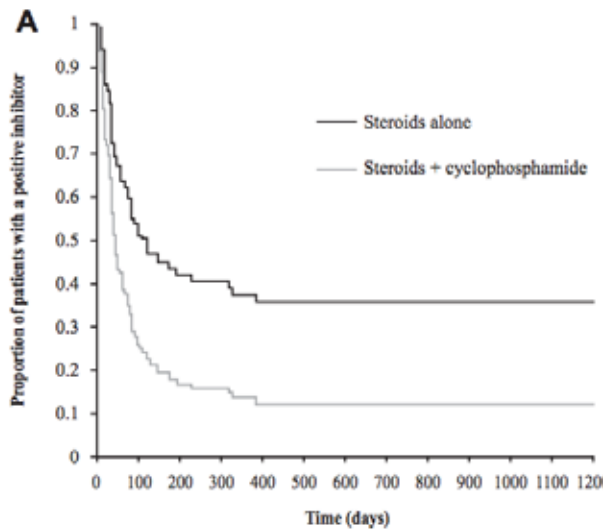
Porcine factor VIII concentrate



Immunosuppressive therapy (IST)



- Autoantibodies rarely disappear spontaneously
- Higher risk of mortality if they persist



- Rate of complications from IST is about 30%
- Mortality as high as 16-30%

Other Clotting Factor Deficiencies



Factor V Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
 - 75% quantitative, 25% qualitative
- Acquired as a result of autoantibody formation
 - Spontaneously or secondary to exposure to bovine thrombin or medications
 - autoimmune disorders, human immunodeficiency virus, bacterial infections, malignancy, and medications such as beta-lactam or aminoglycoside antibiotics

Treatment

- 25% of FV is stored within platelet alpha granules
- FFP or platelet transfusion
- There is no factor V concentrate

Factor VII Deficiency

Pathophysiology

- Inherited – autosomal

Clinical

- Bleeding correlates poorly with factor level
 - less likely if FVII > 10%
 - patient with undetectable levels can be asymptomatic
- Excessive bleeding after invasive procedures, intracranial, umbilical cord, joint and muscle bleeding

Treatment

- rFVIIa concentrate 15 to 30 mcg/kg every 12 hours
- Goal to keep FVII > 15-20%

Factor X Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
- Acquired associated with amyloidosis

Clinical

- Bleeding correlates well with factor level, usually < 10%
- Excessive bleeding after invasive procedures, intracranial, umbilical cord, joint and muscle bleeding

Treatment

- Half-life of factor X is 40 to 60 hours
- FFP or prothrombin complex concentrate (Factor II, VII, IX, X)
- High-purity, human plasma-derived FX concentrate (pdFX; Coagadex[®])
- Goal – to keep FX>20%

Factor XI Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
 - Higher prevalence in Ashkenazi Jews (8-9% are heterozygous)
- Acquired associated with liver dysfunction, DIC, factor XI inhibitors (allo or auto)

Clinical

- Poor correlation between plasma level and bleeding
- Not usually spontaneous bleeding but bleeding provoked by trauma or surgery (especially mucosal surfaces)

Treatment

- Half-life of factor XI is 50 to 80 hours
- Fresh Frozen Plasma - 10 - 20 mL/kg, followed by 5 - 10 mL/kg every 24 to 48 hours
- Antifibrinolytic agents, fibrin sealant (fibrin glue), desmopressin (DDAVP), and low dose recombinant activated factor VII (rFVIIa)
- Factor XI concentrates not available in the United States

Factor XIII Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
- A or B subunit deficiency (A more severe)
- Factor XIII A subunit in anchoring the cytotrophoblast
 - Unlikely to have successful pregnancy without replacement

Clinical

- Bleeding correlates well with factor level, bleeding usually if < 5%

Treatment

- Half-life of factor XIII is 11-14 days
- FFP or cryoprecipitate
- Factor XIII concentrate
 - Recombinant factor XIII A subunit (Tretten)
 - Plasma derived factor XIII (Corifact)

International registry of 104 patients with factor XIII deficiency²

Subcutaneous bleeding	57%
Delayed umbilical cord bleeding	56%
Muscle hematoma	49%
Postoperative bleeding	40%
Hemarthrosis	36%
Intracerebral bleeding	34%
Gastrointestinal bleeding	6%

Summary

- Reviewed von Willebrand disease
 - New treatment option – recombinant VWF
 - Acquired von Willebrand syndrome – always an underlying etiology
- New treatment options for congenital hemophilia
 - Extended half-life factor: FXI more than FVIII
 - Bispecific antibody
- Treatment options for Acquired hemophilia A
 - Bypassing agents (rFVIIa, aPCC, porcine FVIII)
- Some rarer factor deficiencies and their treatment approaches

An aerial photograph of a city skyline, likely Seattle, emerging from a thick layer of fog or low clouds. In the background, a large, snow-capped mountain (Mount Rainier) is visible against a sky with soft, orange and yellow hues, suggesting a sunrise or sunset. The text "Thank you for attention!" is overlaid in a bold, yellow font across the upper portion of the image.

Thank you for attention!