Seattle Cancer Care Alliance

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

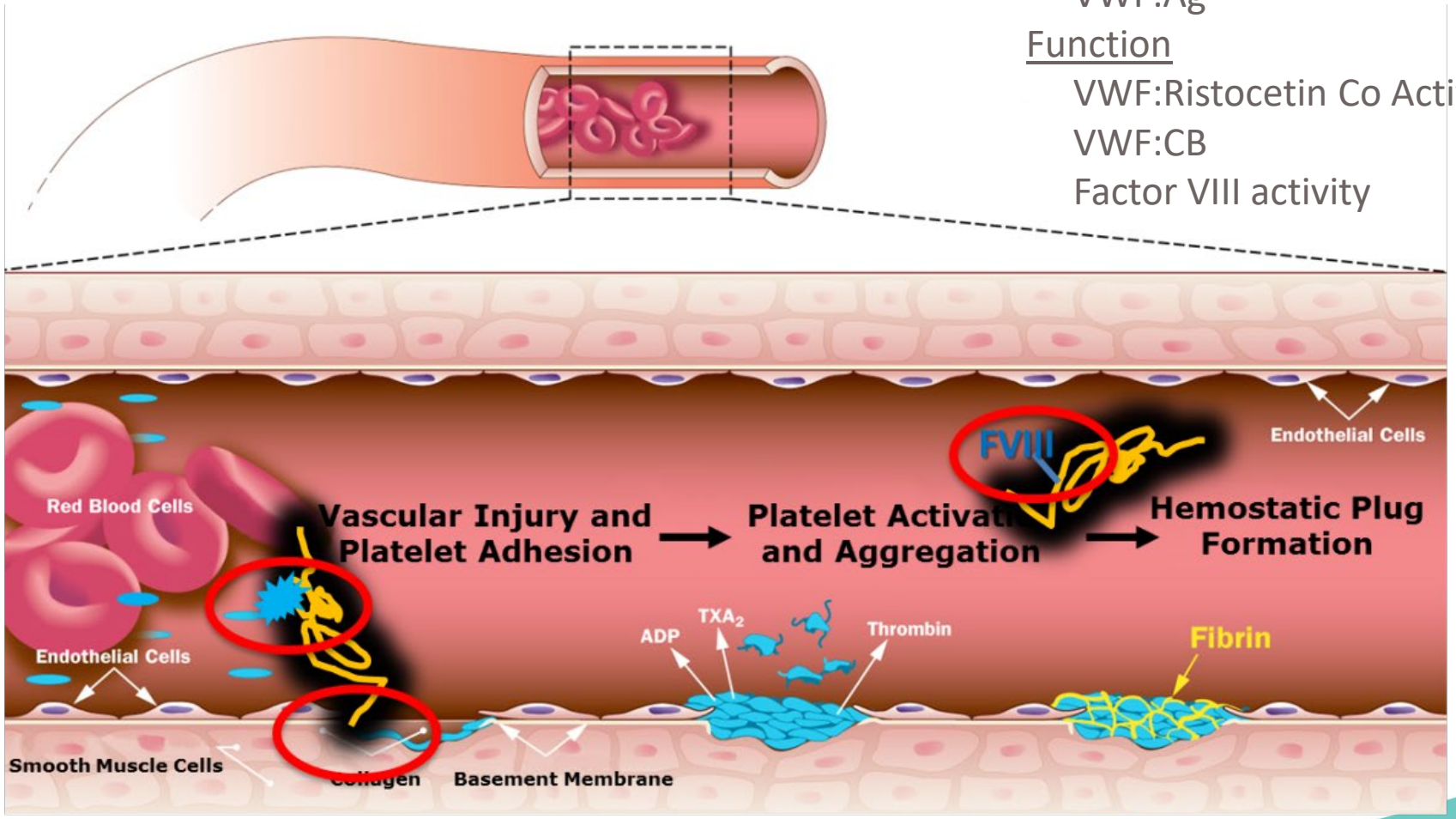
- To discuss **von Willebrand disease**
  - Treatment option
  - Acquired von Willebrand syndrome
- To describe new treatment options for **congenital hemophilia**
- To recognize **acquired hemophilia** and describe potential 1st line treatment options
- To describe some **rarer factor deficiencies**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

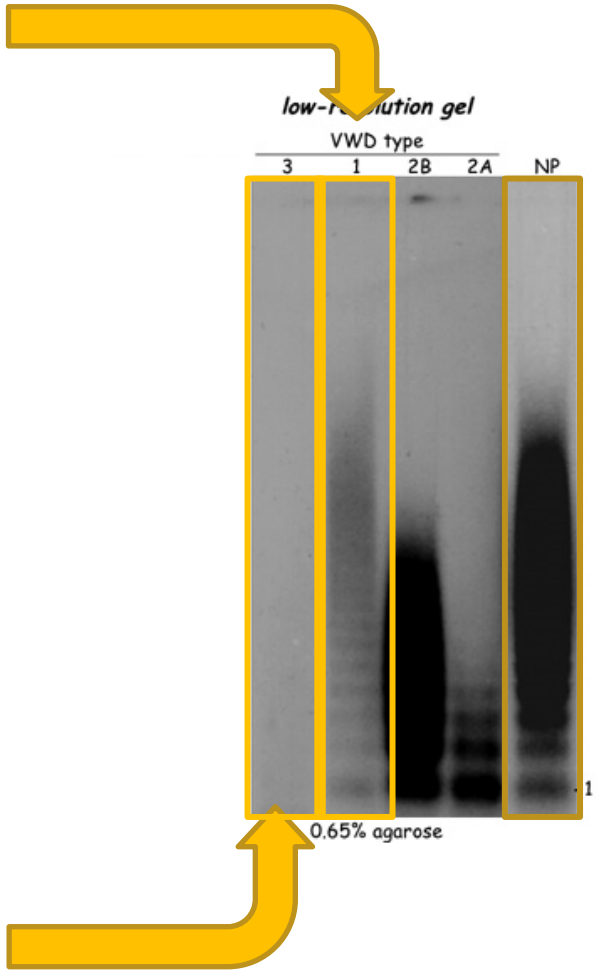
Platelet binding

Factor VIII binding

Image adjusted from Victor S. Blanchette

Quantitative defects

- Type 1
- Type 2
  - 2A
  - 2B
  - 2M
  - 2N
- Type 3



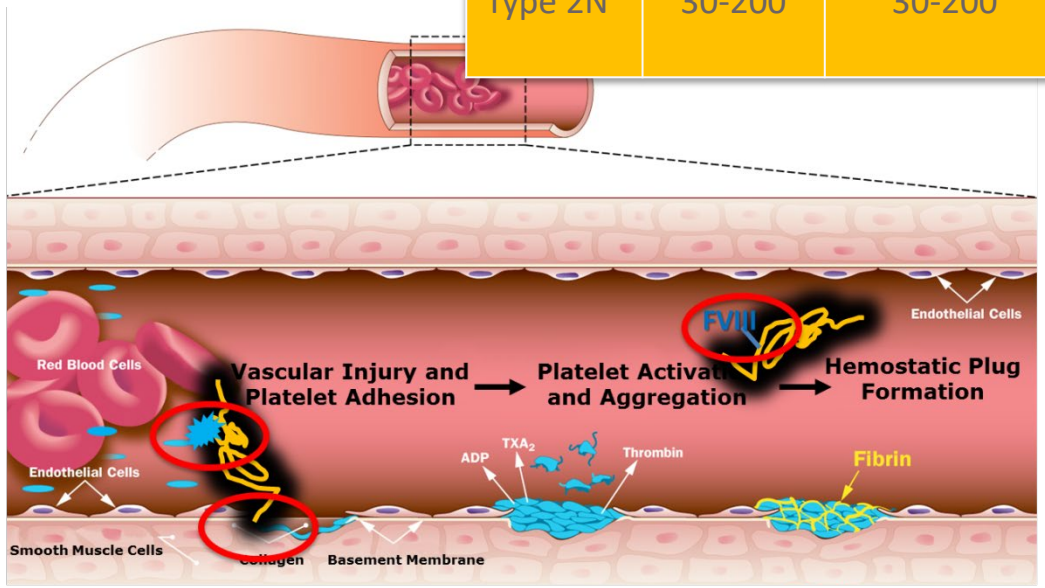
- Decreased VWF production
- Most common (75%)
- Mild bleeding symptoms

- 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 multmers Abnormal Ag/RCo ratio
Type 2B	<30*	<30-200*?	↓ or Normal	Usually <0.5-0.7	Abnormal multmers 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



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Factor VIII binding

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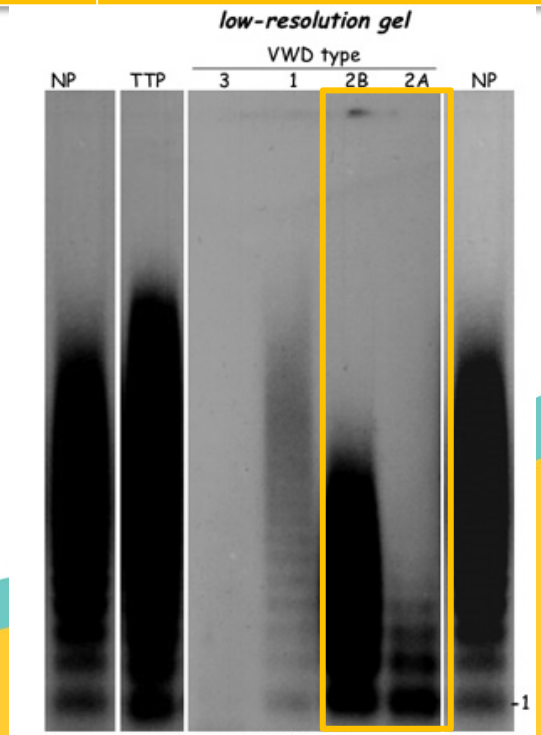
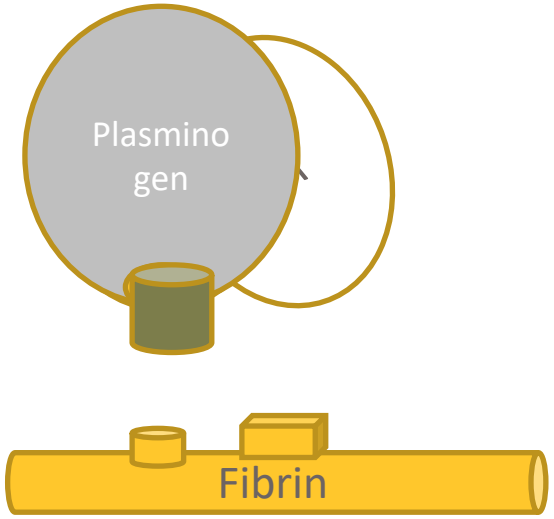


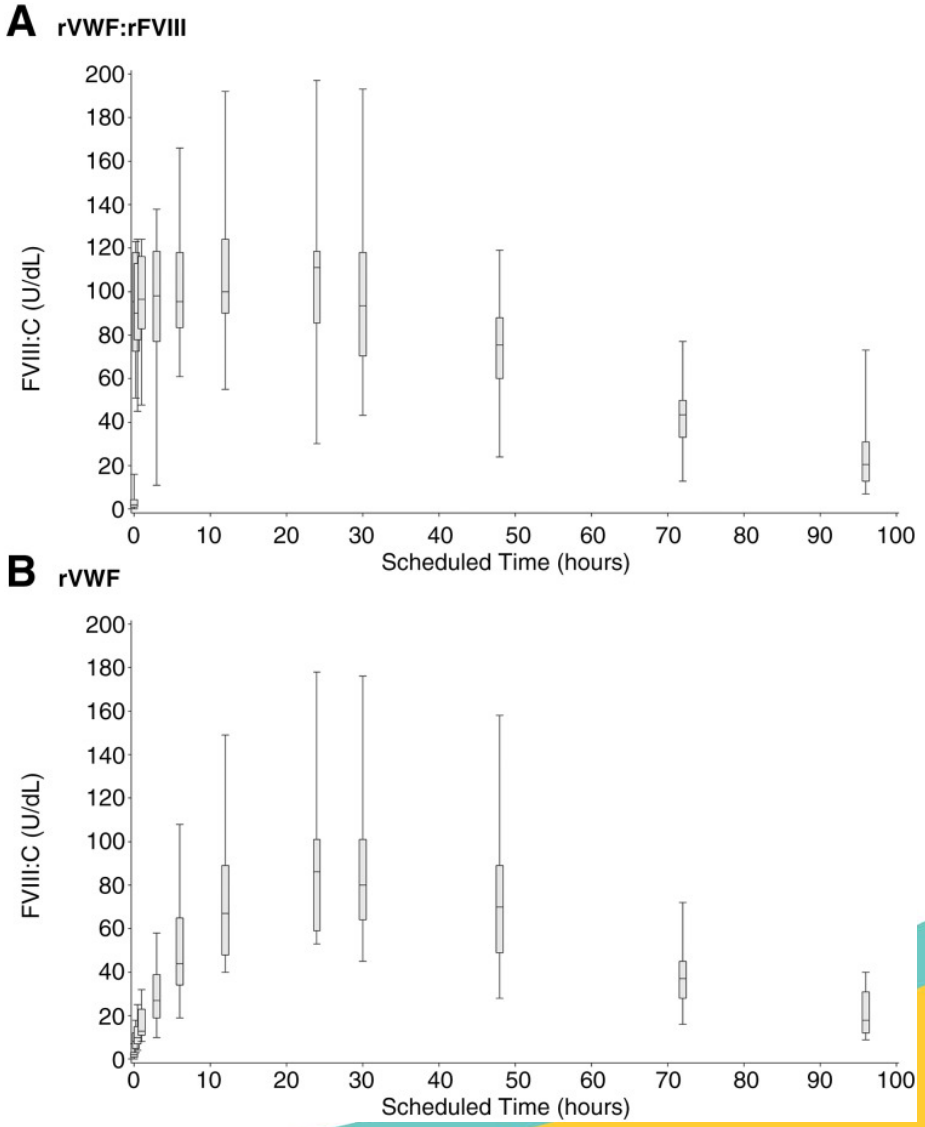
Treatment of VWD

- 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



Gill et al. Blood. 2015 Oct 22;126(17):2038-46

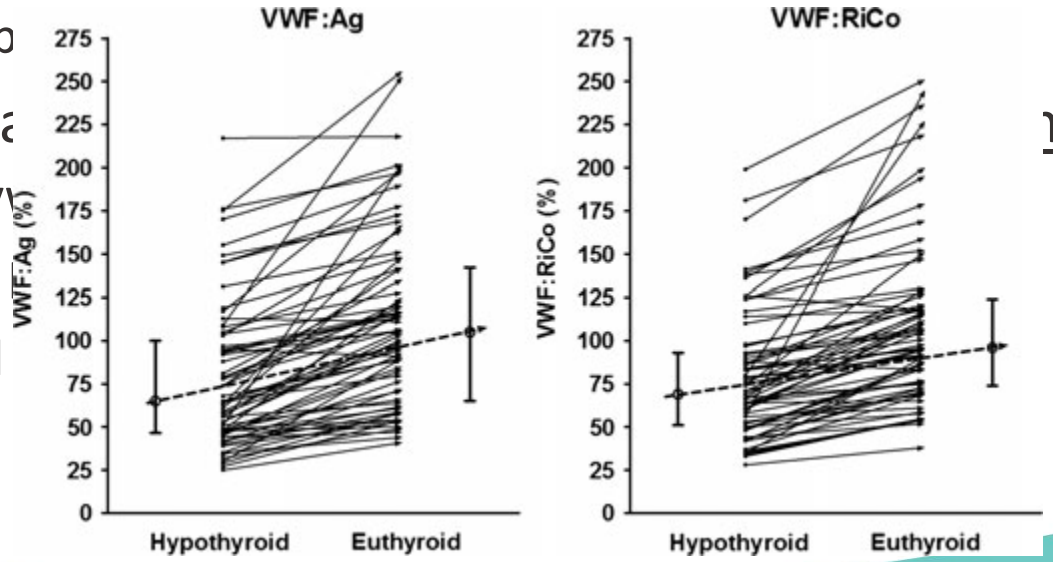
Acquired von Willebrand syndrome (AVWS)

- 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

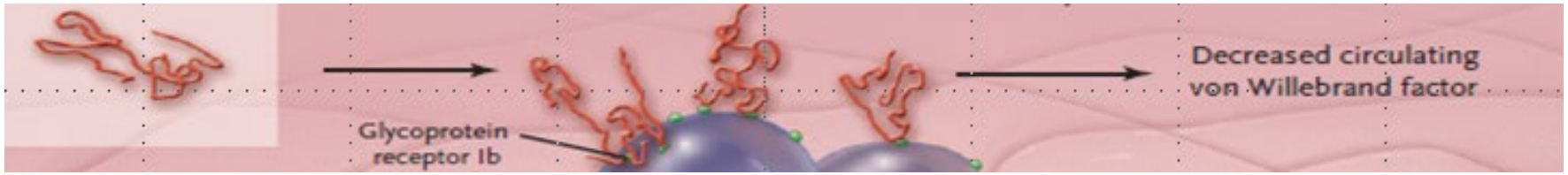
Decreased production of thyroid hormone → Decreased synthesis of von Willebrand factor

- Looks like a type 1 VWD (quantitative)
  - Low VWF:Ag and VWF:Activity
  - Normal multimers
  - Low VWF p
- Study of 90 a n
  - **33%** had V
  - Most with
  - Correlated



Stuijver et al. Haemophilia 2014

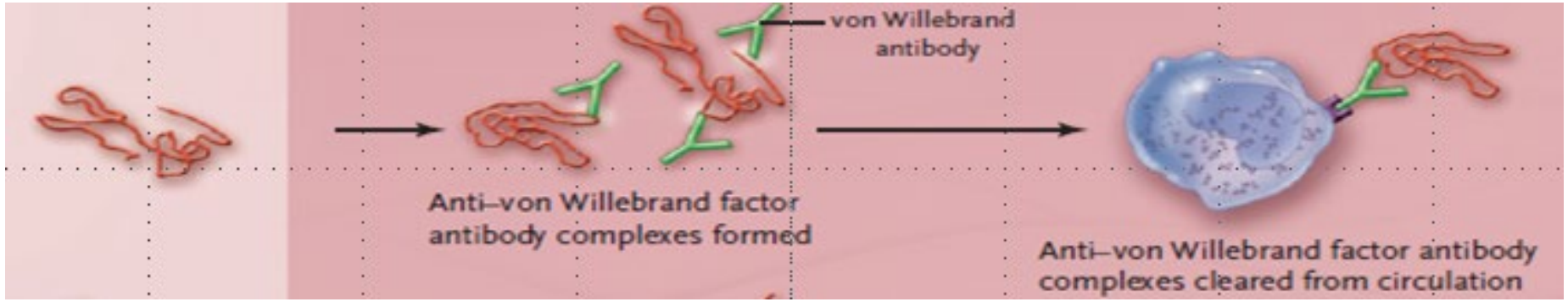
AVWS due to adsorption



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

Cuker et al, N Eng J Med 2009

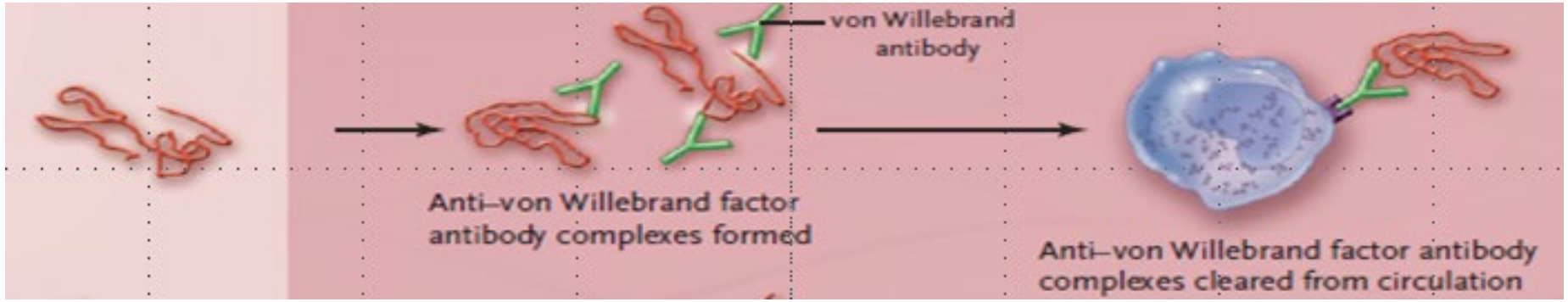
AVWS due to antibodies



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

Cuker et al, N Eng J Med 2009

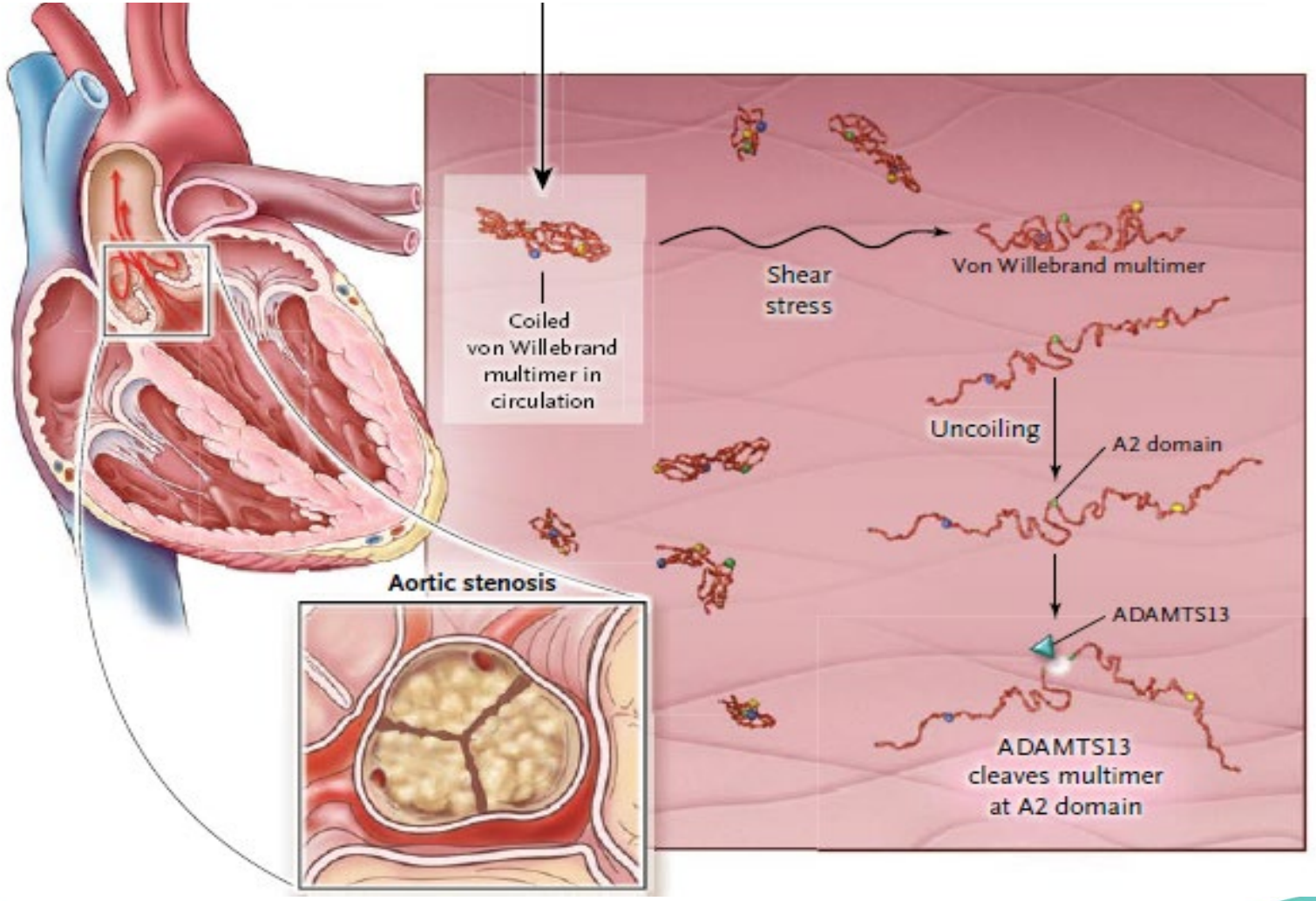
AVWS due to antibodies



- Immunosuppression
  - Intravenous immunoglobulin[1]
    - 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

Cuker et al, N Eng J Med 2009

AVWS associated with cardiovascular abnormalities



Loscalzo. N Eng J Med 2012

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

Waldow et al. 2014

AVWS associated with cardiovascular abnormalities

- Mitral valve regurgitation:

Variable	Mild (N = 13)	Moderate (N = 14)	Severe (N = 26)	P-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

Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

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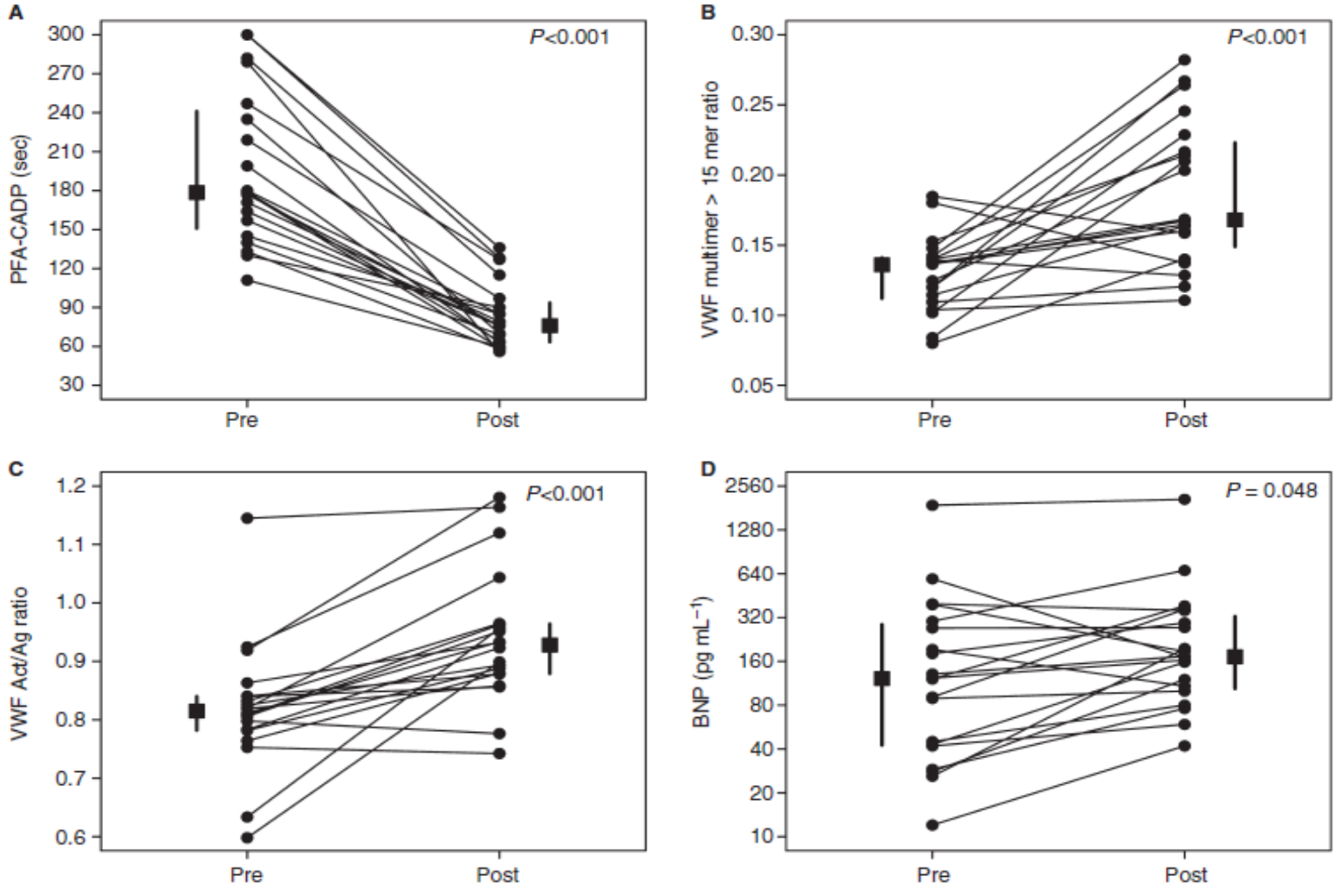
AVWS associated with cardiovascular abnormalities

Effect of mitral valve repair



Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

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

Loscalzo. N Eng J Med 2012

Congenital Hemophilia

1803 First Blood Transfusion for Hemophilia

1823 First Plasma Transfusion

1840 Cryoprecipitate discovered by Dr. Judith Pool

1936 First Factor Concentrates

1964 First Monoclonal Factor Concentrates

1960/70's First Recombinant Factor Concentrates

1987 Prophylaxis In U.S.

1993

2007

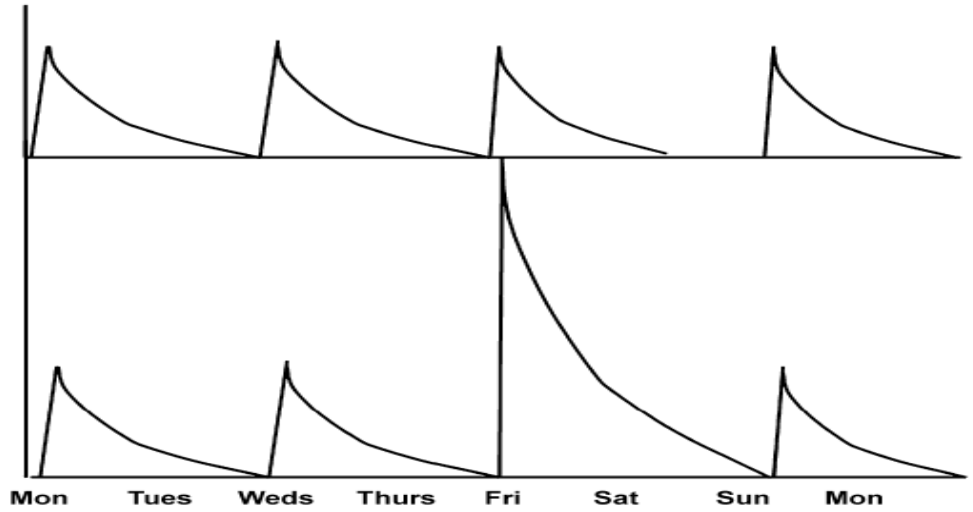
2014

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



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1987 Prophylaxis In U.S.

1993 Extended half-life factors (EHL)

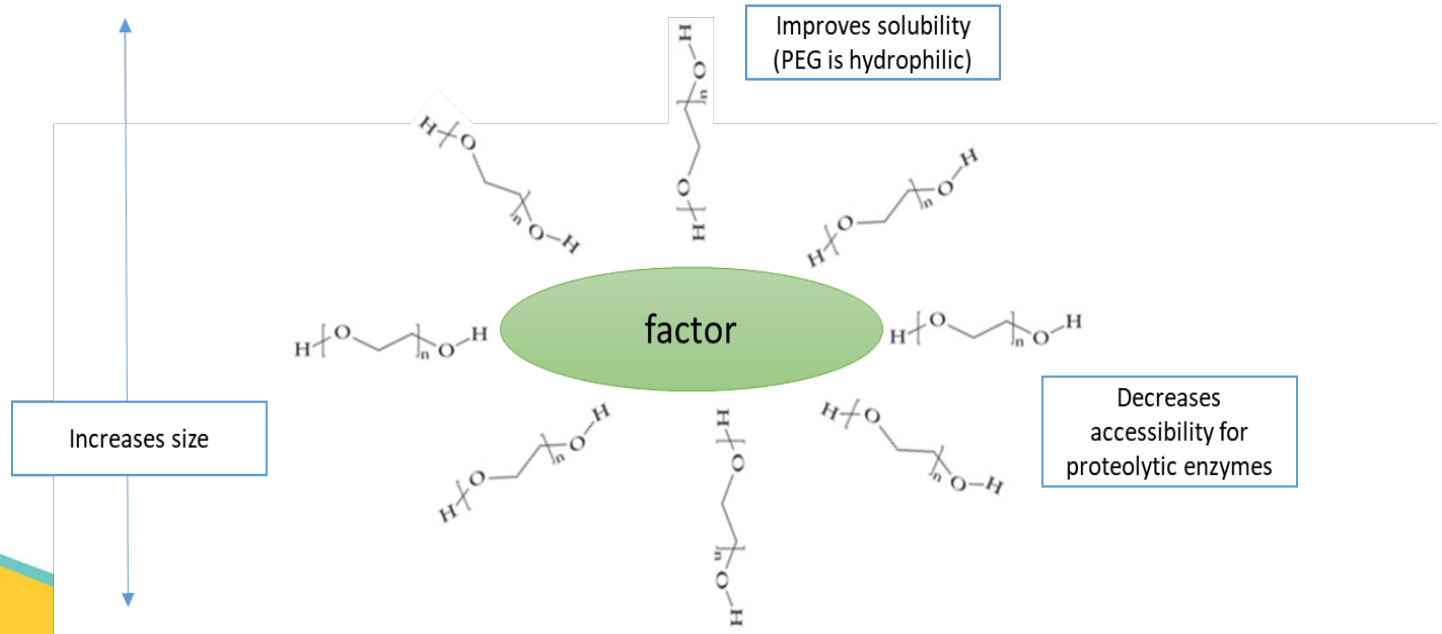
2007 Bi-specific Ab

2014 Gene therapy

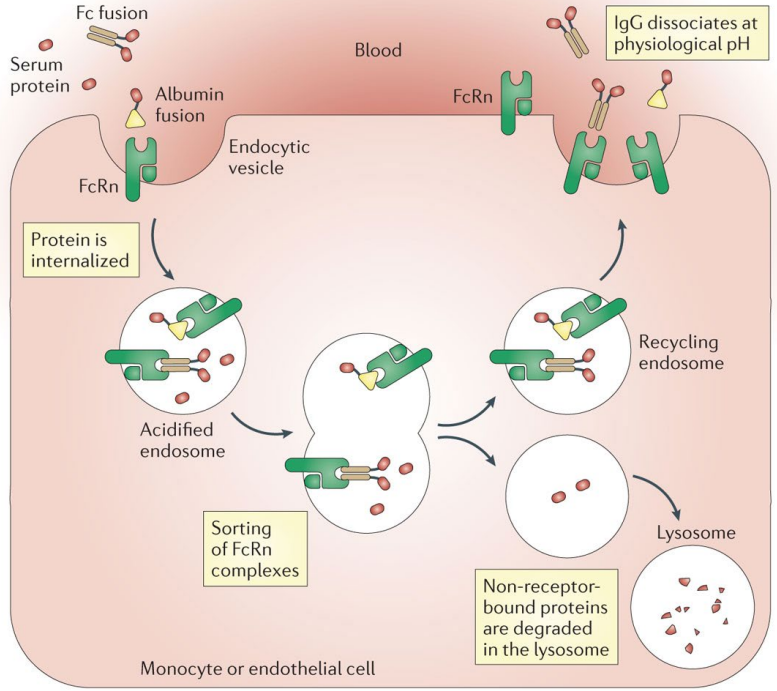
2017

Mechanism of extended half-life factors

Pegylation



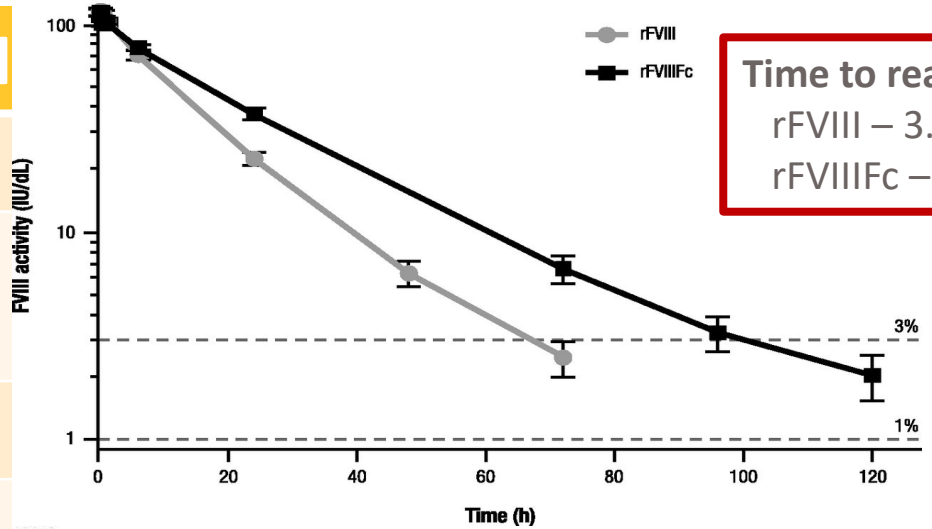
Fc or albumin fusion



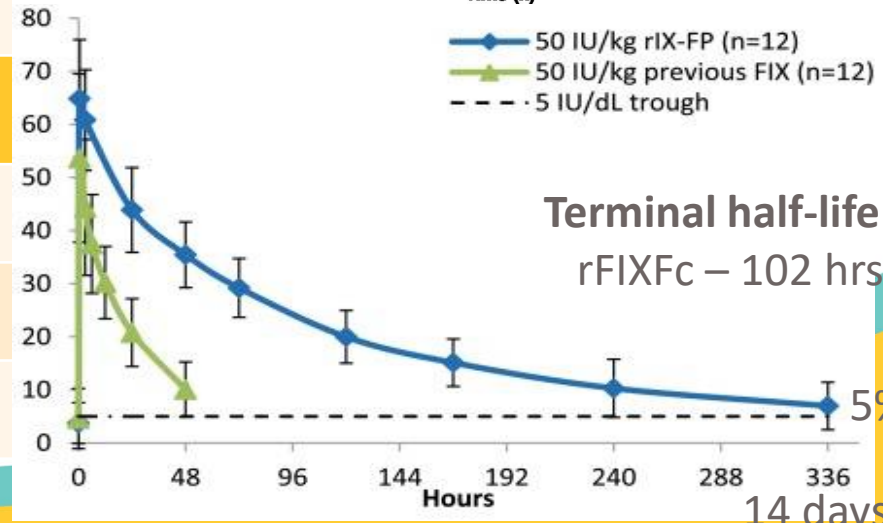
Nature Reviews | Drug Discovery

Products with phase III data in the U.S.

	Factor VIII
rFVIIIFc (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
rIXFc (Alprolix)	2.4 fold
rIX-FP (Idelvion)	> 5 fold
N9-GP (Rebinyn)	> 5 fold



Time to reach 1%:
rFVIII – 3.3 days
rFVIIIFc – 4.9 days



Terminal half-life:
rFIXFc – 102 hrs
14 days

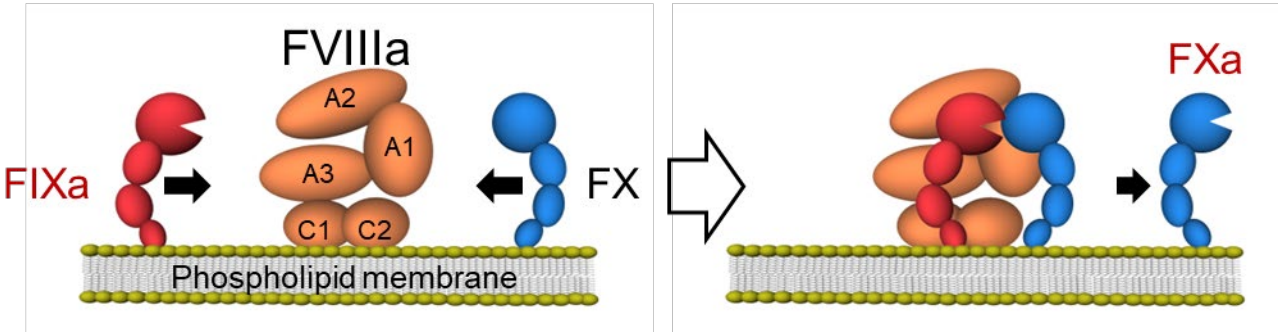
Santagostino et al. Blood 2016

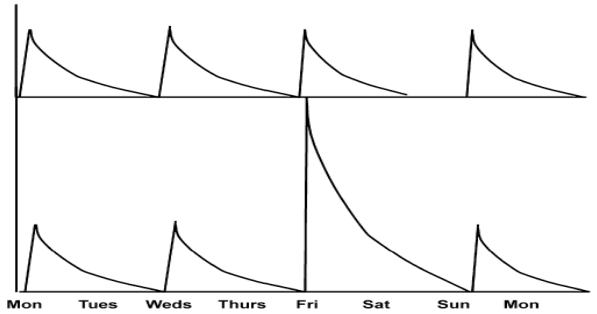
The biggest challenges for hemophilia #2

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

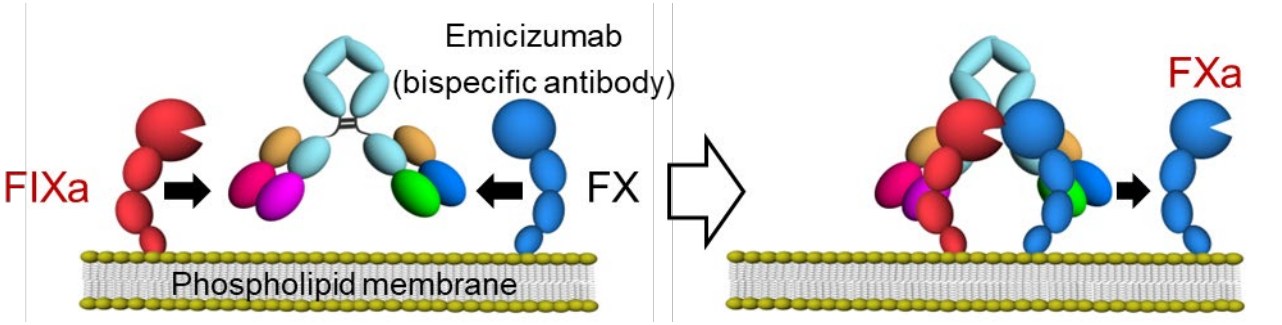
- 30% of people with severe hemophilia A develop antibodies
- High titer inhibitors do not respond to FVIII replacement
  - Need to treat bleeding with **bypassing agents**
    - recombinant factor VII activated (rFVIIa)
    - activated prothrombin complex concentrate (aPCC, contains factor II, VII,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

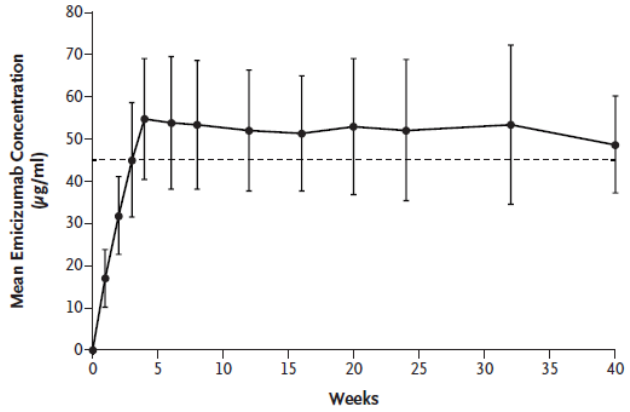
Concept of FVIIIa-Mimetic Bispecific Antibody





IV
$T_{1/2}$ ~ 8 hours





SQ
$T_{1/2}$ ~ 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.

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 November 16, 2017

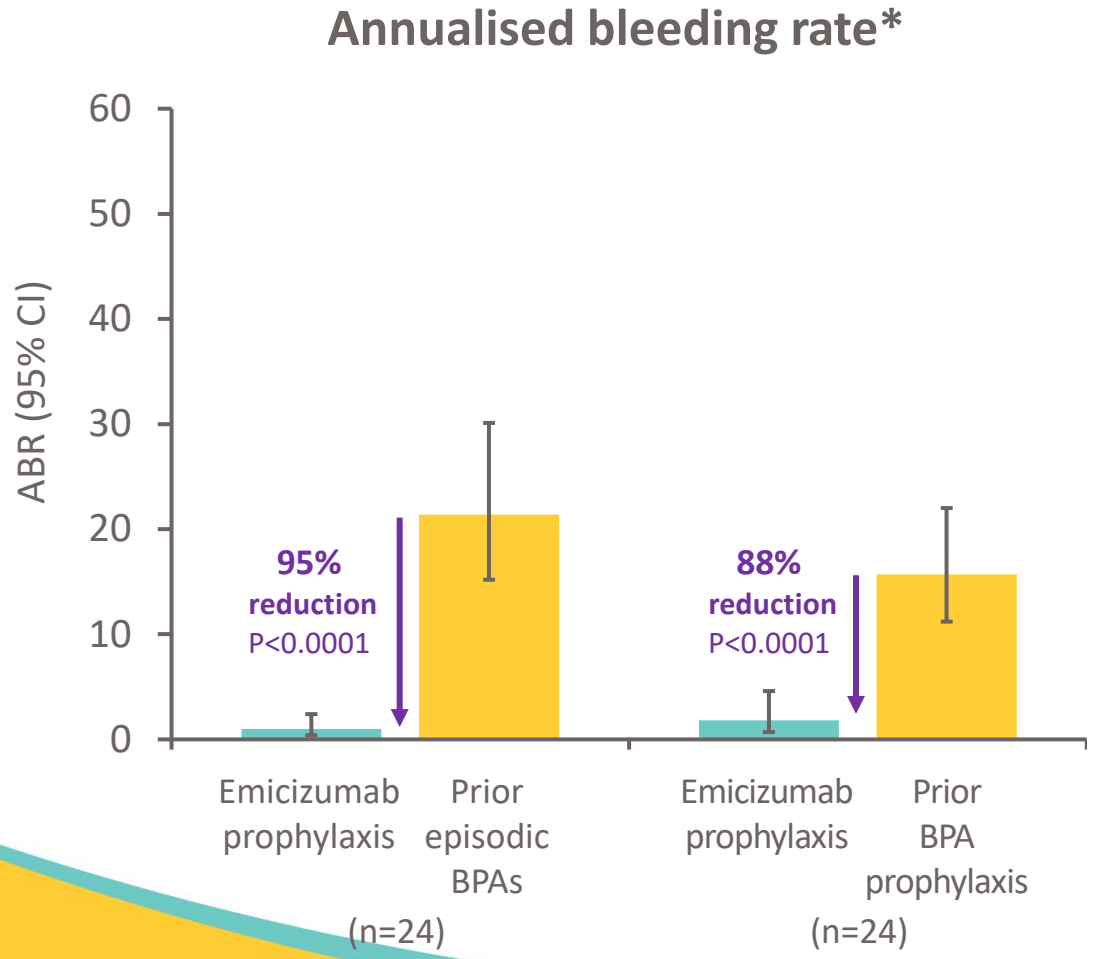
to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies called Factor VIII (FVIII) inhibitors

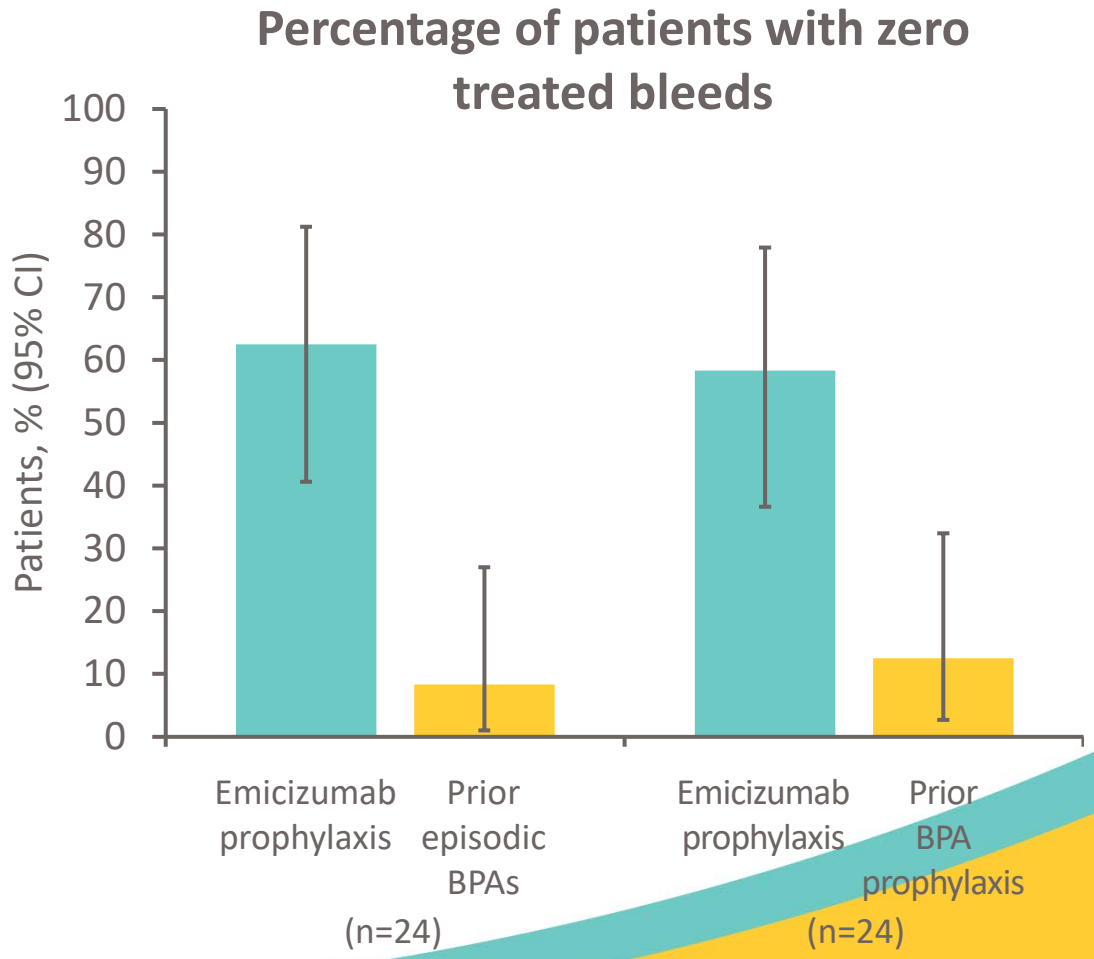
FDA Approval in USA for on October 4, 2018

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



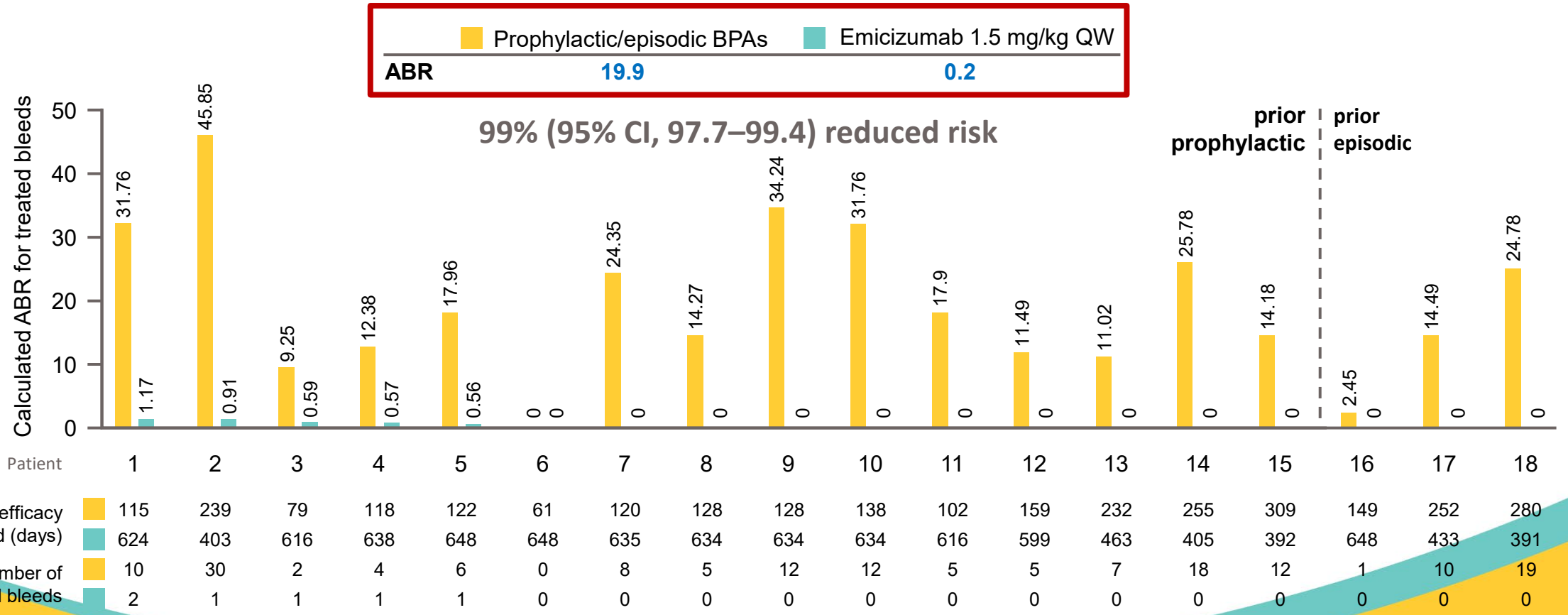


*Negative binomial regression model.
ABR, annualised bleeding rate; BPA, bypassing agent.

Mancuso et al. 2nd International Conference on Inhibitors in Coagulation Disorders 2018, Milan

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

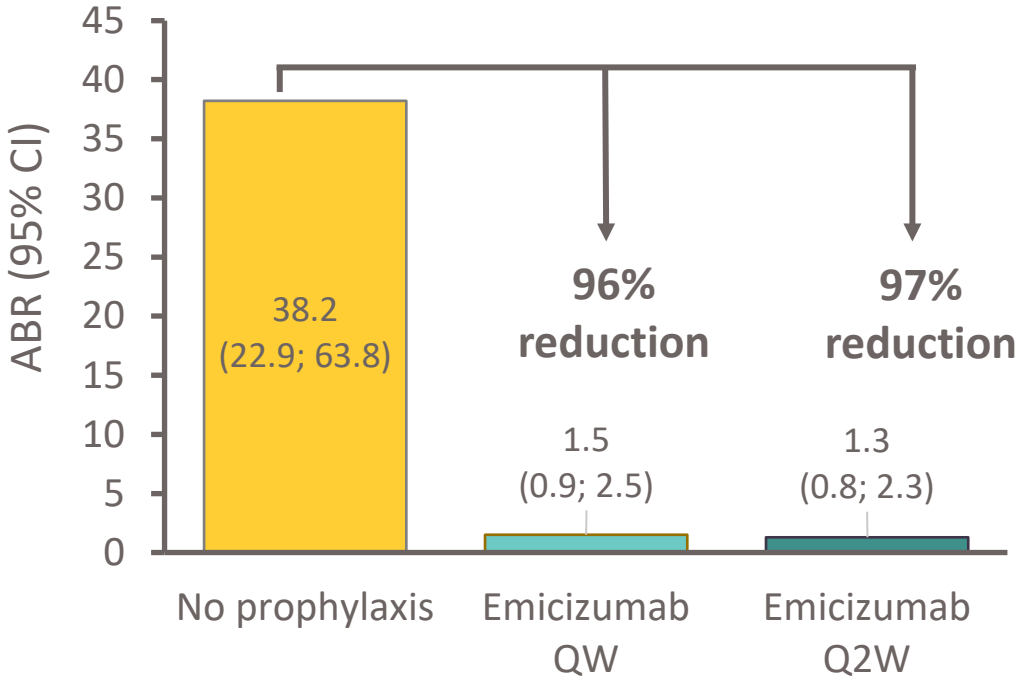
Intra-individual comparison



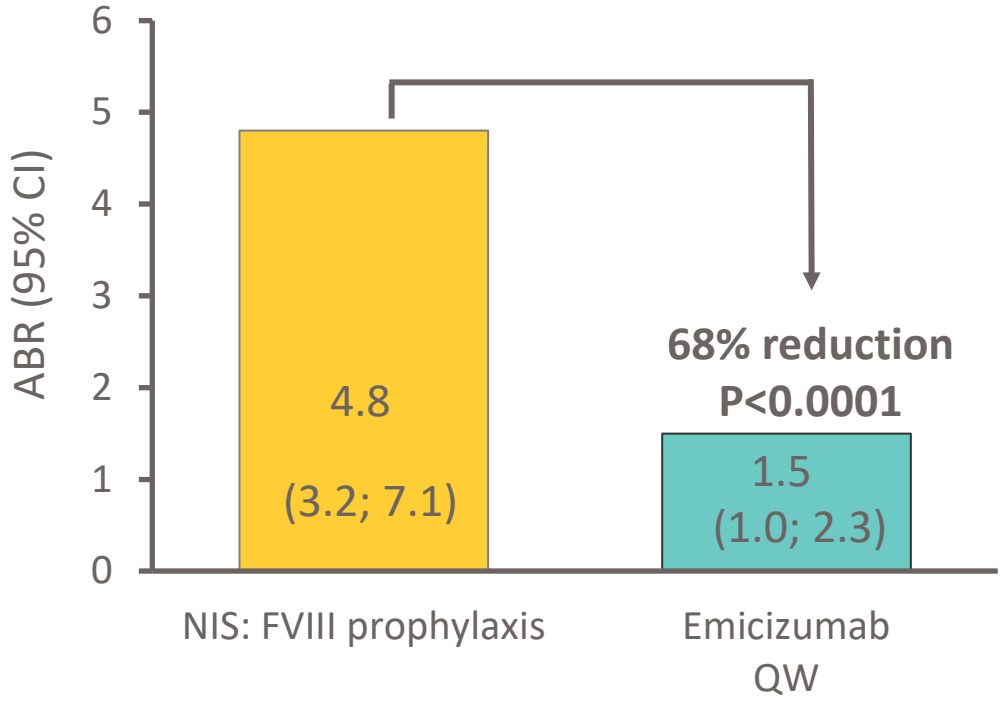
Young G, et al. ASH 2018 – oral presentation

Efficacy of emicizumab – Non-Inhibitor (HAVEN 3)

On demand FVIII



Prophylactic FVIII



Mahlangu et al. *NEJM*. 2018.

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)

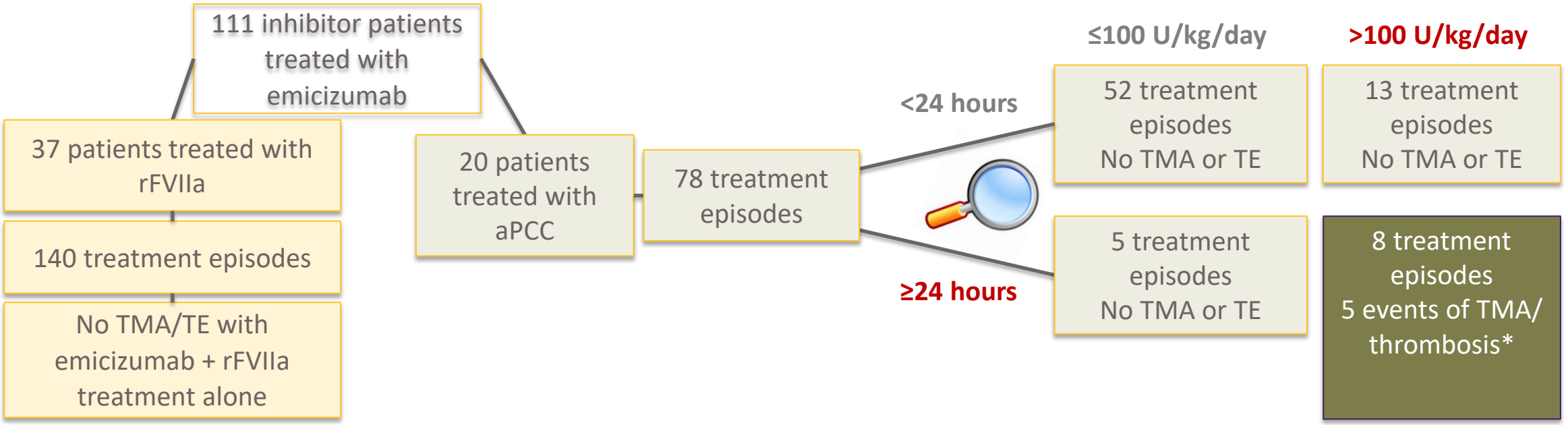
Serious adverse

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

Oldenburg J, et al. ISTH 2017

HAVEN 1: assessment of interaction between emicizumab and aPCC

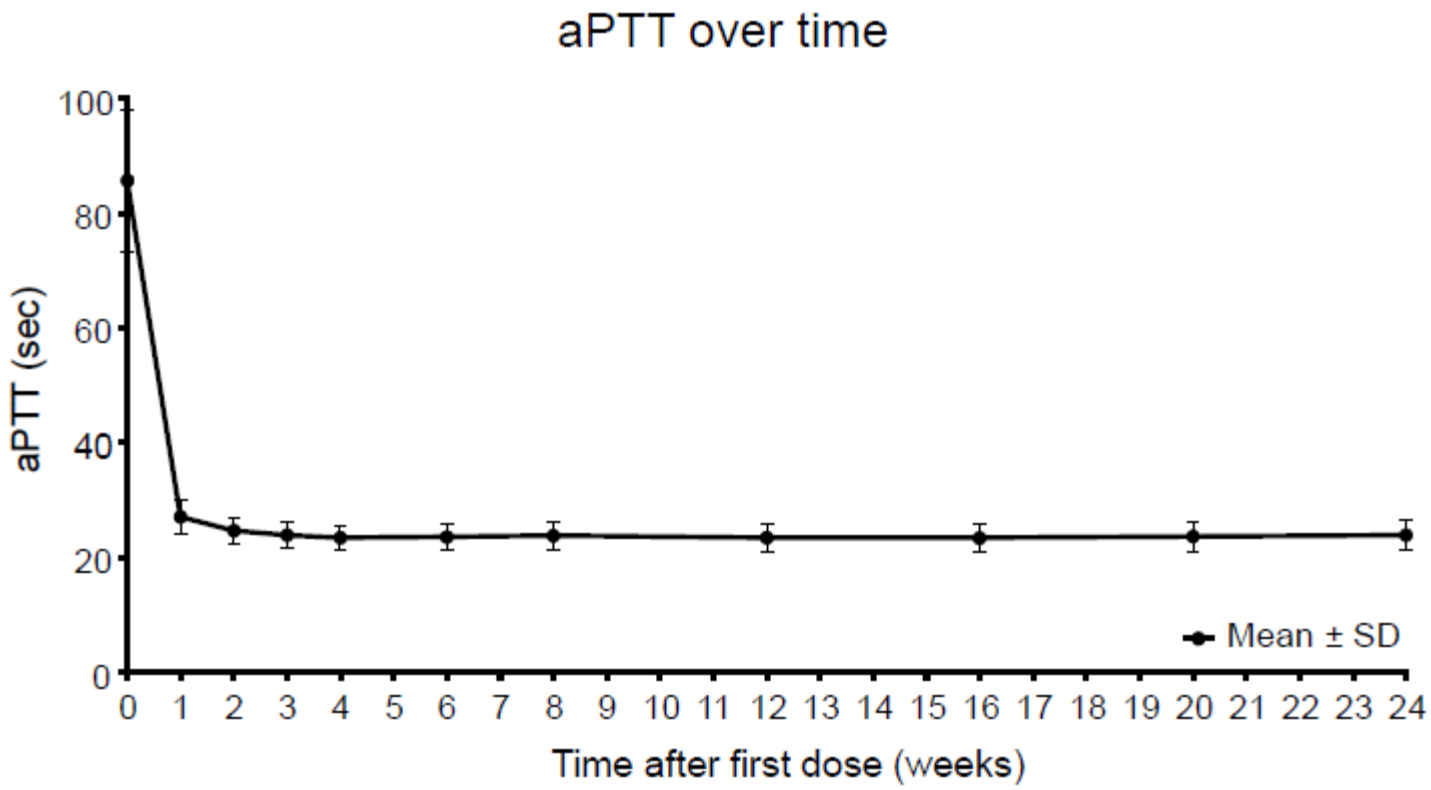


- aPCC contains activated and non-activated coagulation factors, including FII, FVII, **FIX** and **FX**, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date

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

Oldenburg J, et al. ISTH 2017

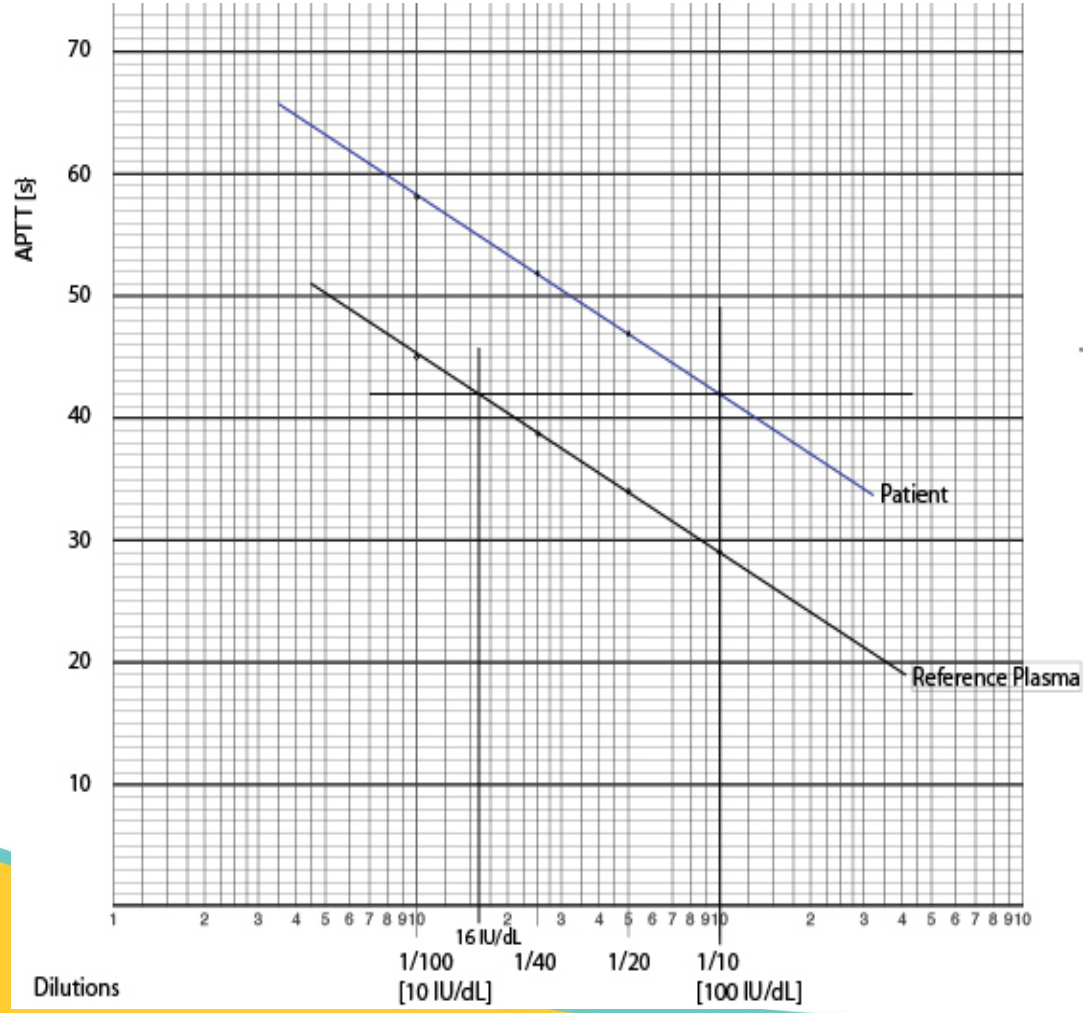
Emicizumab has a strong effect on aPTT



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

Adamkewicz et al – data from HAVEN 1 study

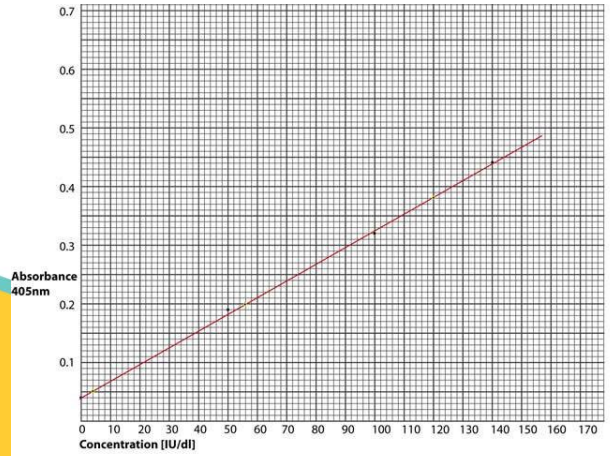
Effect on one stage assay (OSA) factor VIII assay…

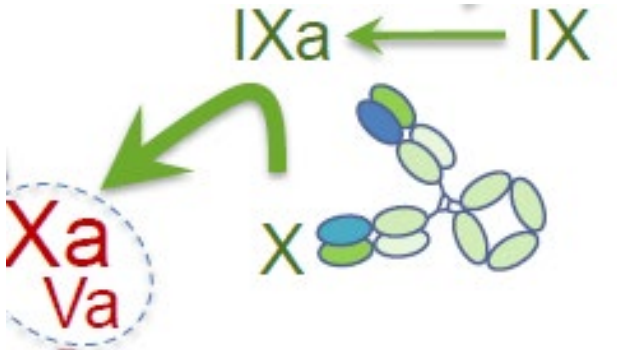


- OSA is based on aPTT
- Not a reliable assay to measure FVIII on emicizumab

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

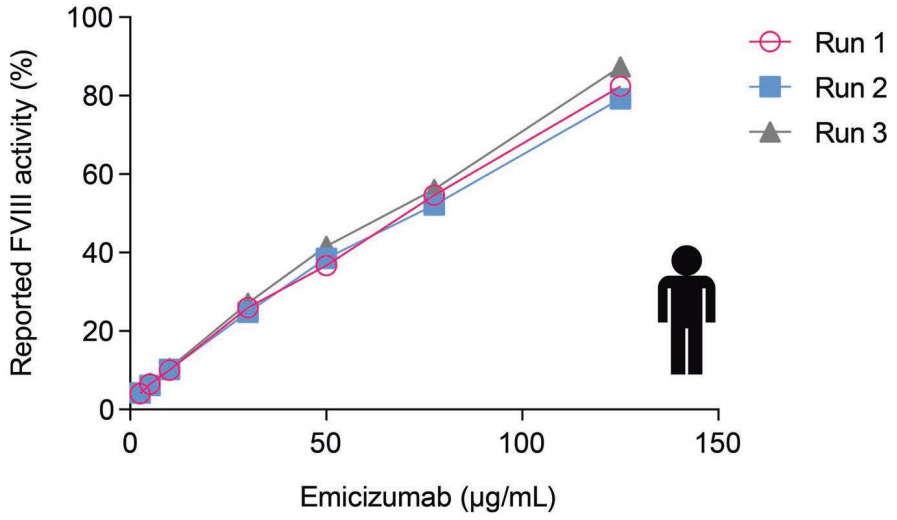




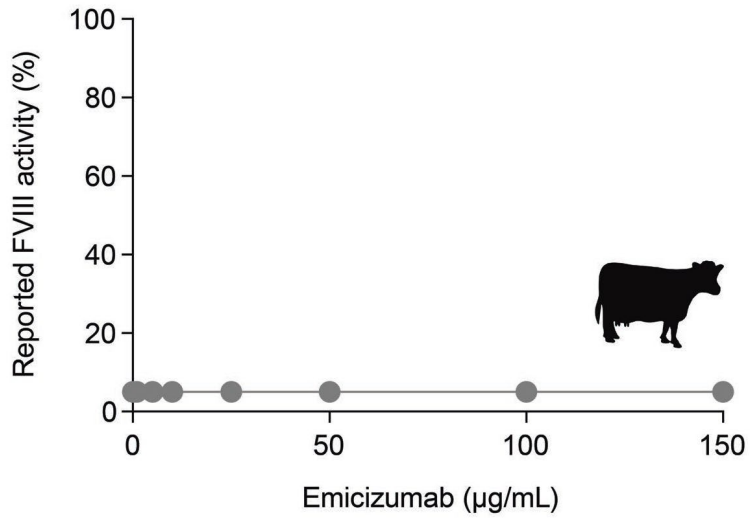
Works with **human** or **bovine** reagent

Effect of emicizumab on chromogenic factor VIII activity

Human reagent
– detects emicizumab



Bovine reagent
– does NOT detect emiczumab

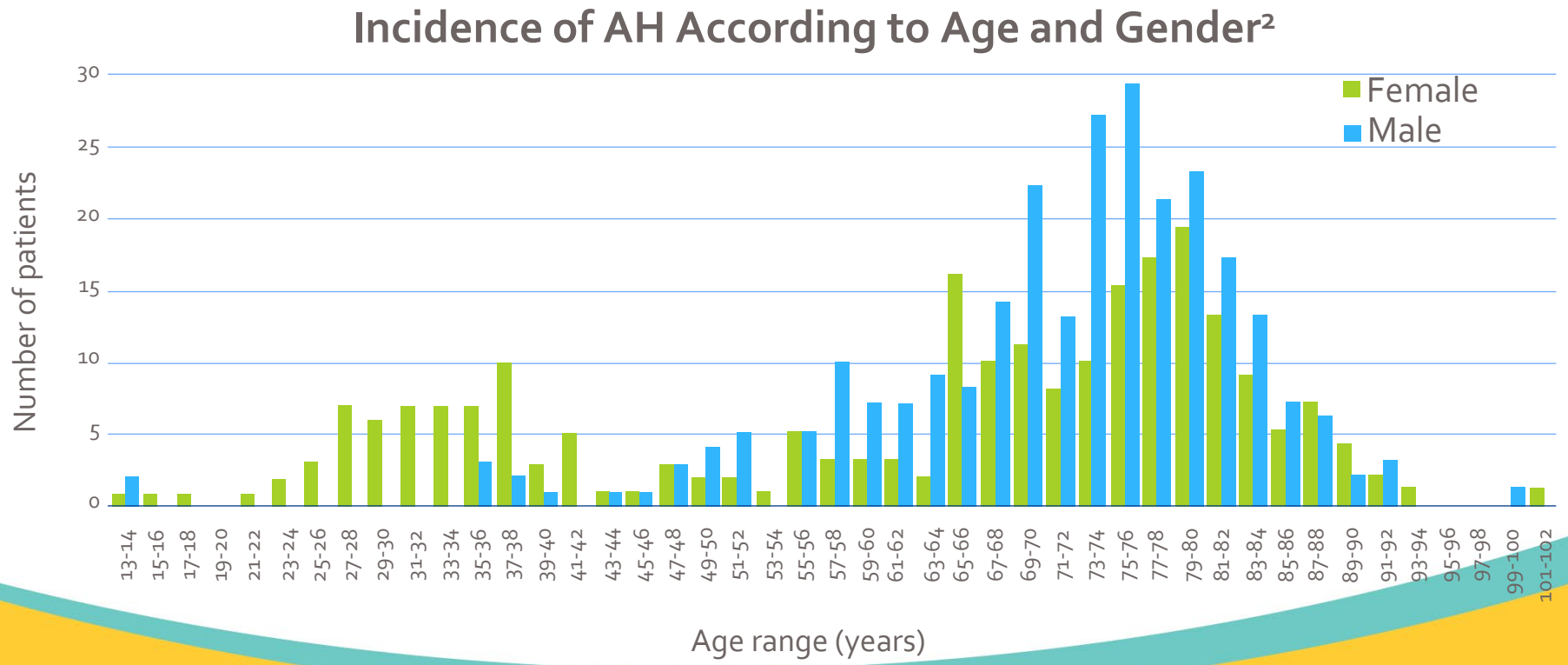


Adamkewicz et al – poster presentation – HTRS 2017

Acquired Hemophilia A

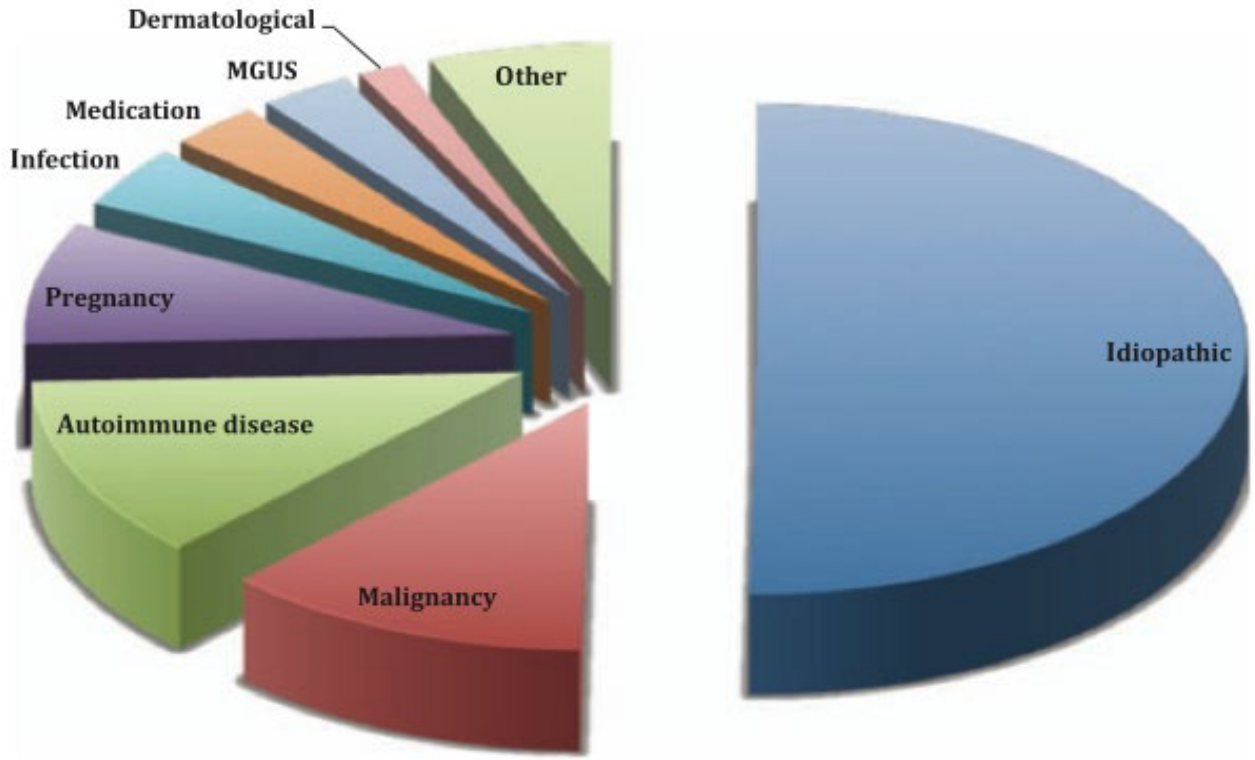
Epidemiology of Acquired Hemophilia

- Rare bleeding condition caused by an autoantibody (inhibitor) to coagulation factor VIII (FVIII)
  - Incidence: 1.5 cases per million/year[1]



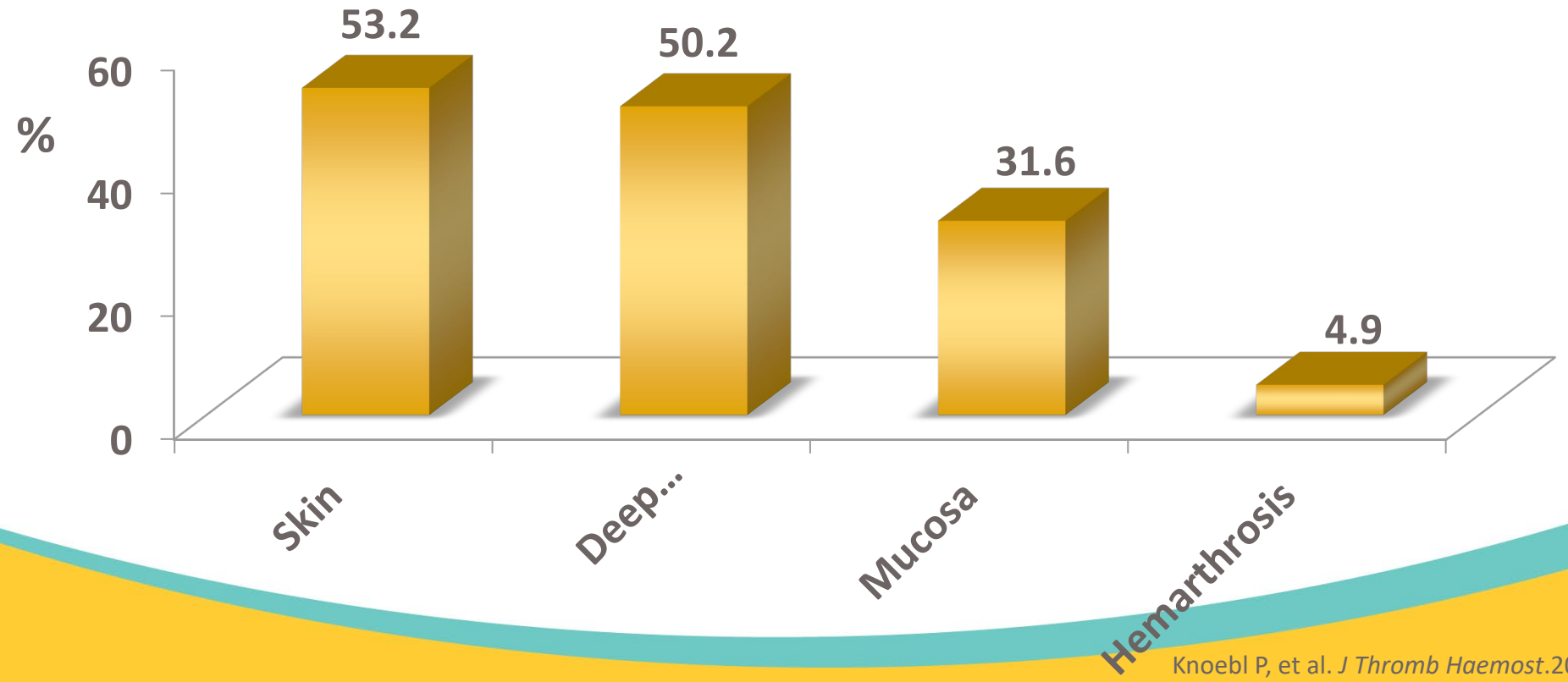
1. Collins et al Blood 2007, 2. Knoebl, et al.

Associated Conditions



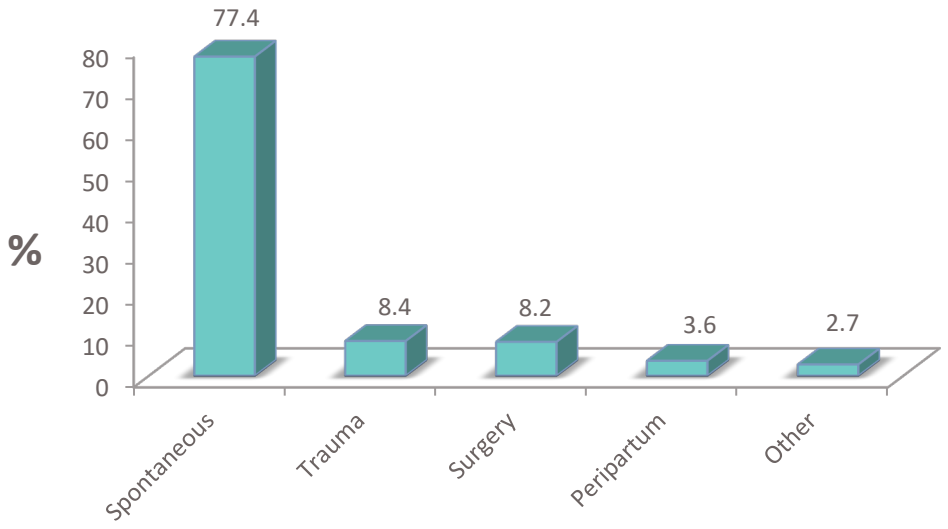
Adapted from: Knoebl P, et al. *J Thromb Haemost*. 2012;10:622-631.

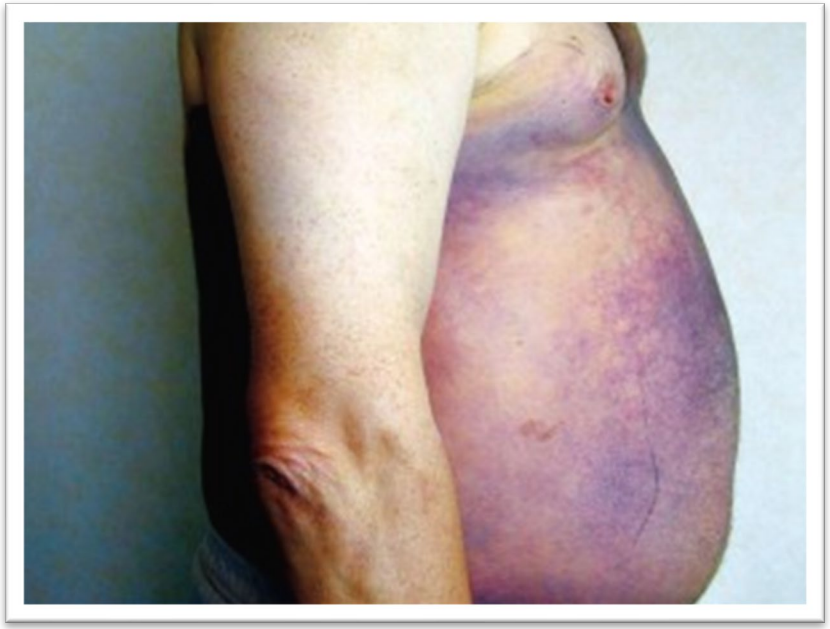
Bleeding Pattern in AHA



Knoebl P, et al. *J Thromb Haemost*.2012

Bleeding Severity in AHA



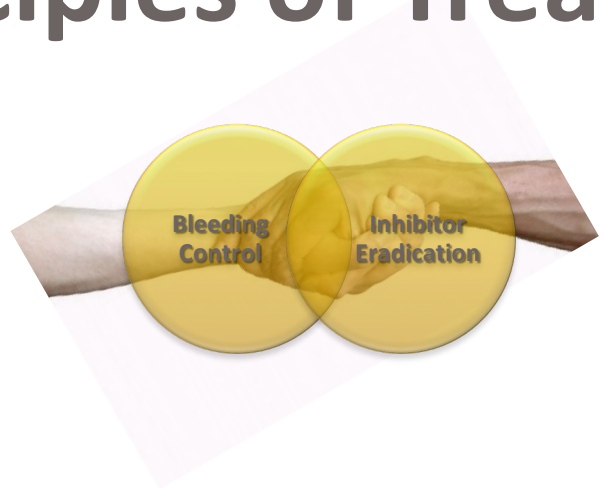


73% severe
Mortality - 8% to 22%

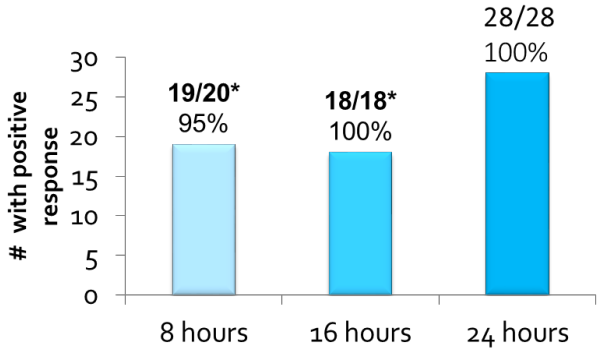
Collins P, et al. *BMC Res Notes*. 2010;3:161.

Zeitler H, et al. *Atheroscler Suppl*. 2013.

Principles of Treatment



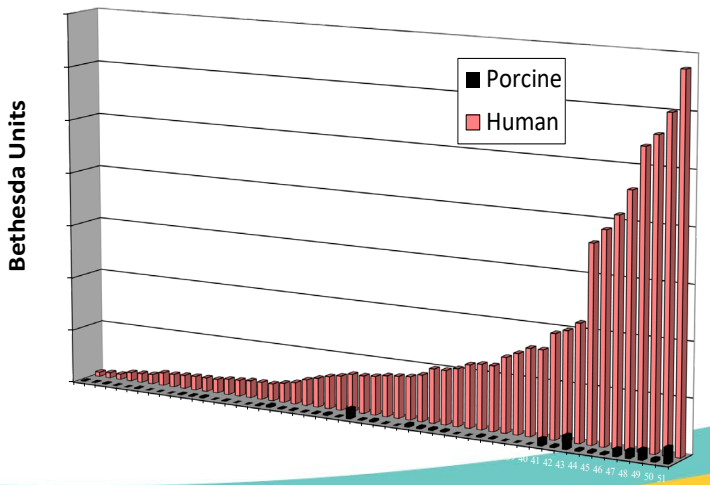
Principles of Treatment

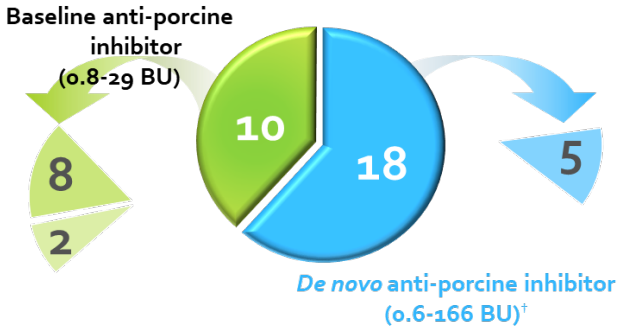


Rates of Control for First Bleeding Episodes by First-line Therapy

	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



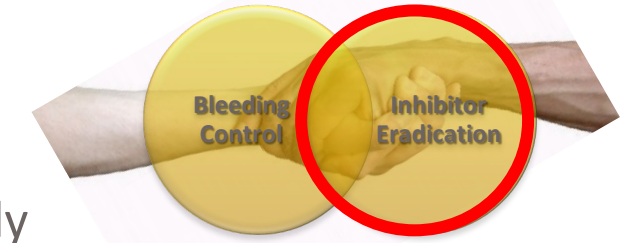


Adapted from Baudo et al - Blood 2012.

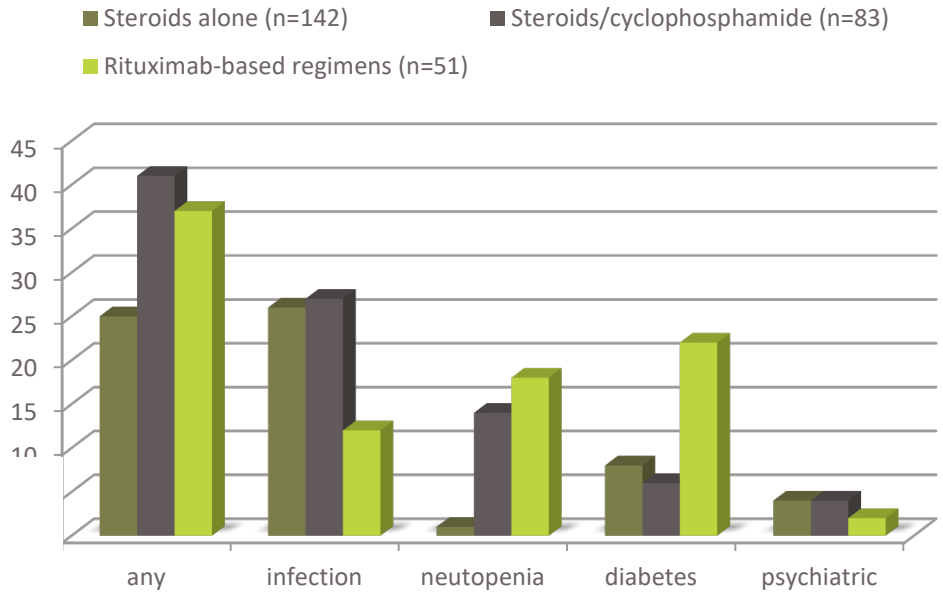
Adapted from Morrison et al. Blood 1993; 81: 1513

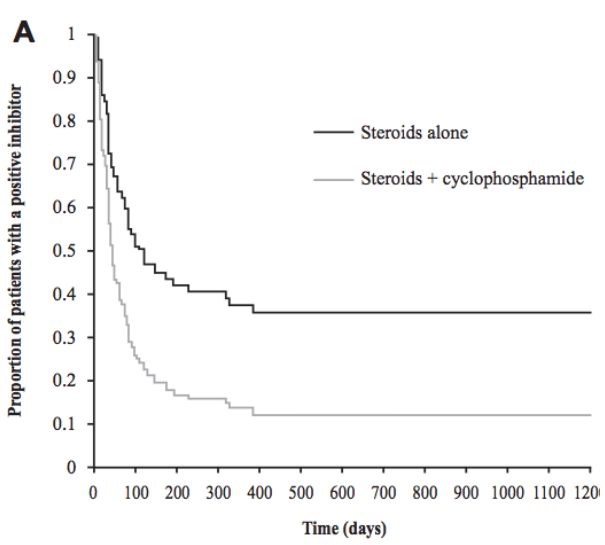
Kruse-Jarres et al. Haemophilia 2015

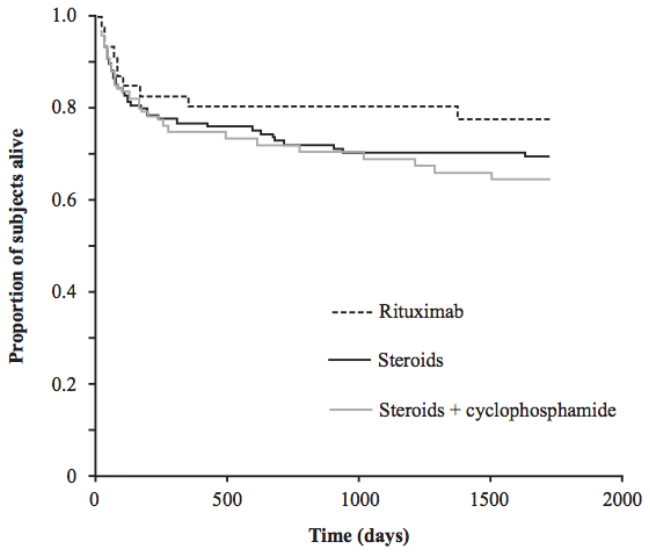
Immunosuppressive therapy (IST)



- 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%

Collins et al. Blood. 2012 .

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

Lippi et al. Blood Coagul Fibrinolysis 2011;22:160-6
Bouchard et al. Blood 2015;125:3647-51
Franchini et al. J Thromb Thrombolysis 2011;31:449-57

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%

Austin et al. Haemophilia. 2016 May;22(3):419-25

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

International registry of 104 patients with factor XIII deficiency[2]	
Subcutaneous bleeding	57%
Delayed umbilical cord bleeding	56%
Muscle hematoma	49%
Postoperative bleeding	40%
Hemarthrosis	36%
Intracerebral bleeding	34%
Gastrointestinal bleeding	6%

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)

1. Austin et al. Haemophilia. 2016 May;22(3):419-25
2. Ivaskevicius et al. Thromb Haemost. 2007;97(6):914.

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


Thank you for attention!