Updates in Bleeding Disorder Medications

We've got mabs, now, just like you!

OHSU The HEMOSTASIS & THROMBOSIS Center

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Disclosures

- I am a member of the Regence Pharmacy & Therapeutics Committee.
- I provide consultation for the Hemophilia Federation of America.
- I am a member of the Foundation for Women & Girls with Blood Disorders Learning Action Committee and Medical Advisory Committee.

First, an announcement!

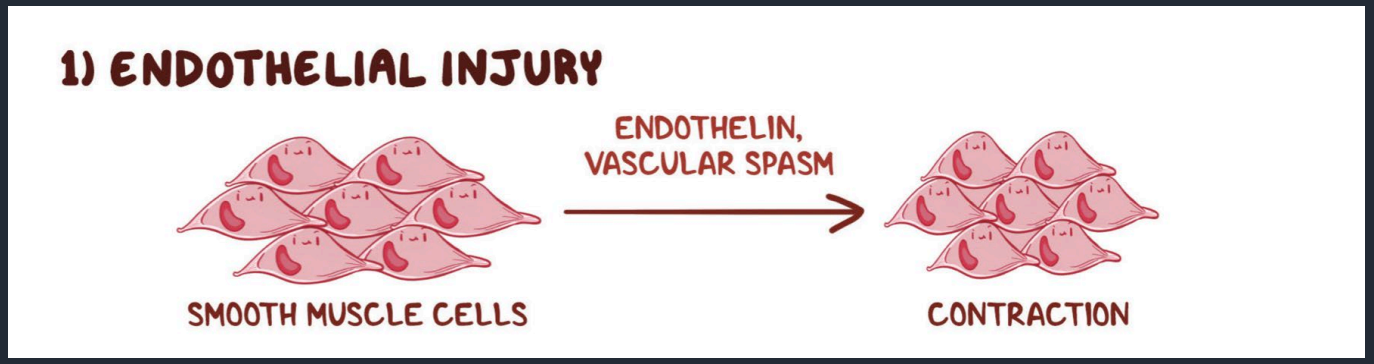
- Name Change & Center Designation:
- The Hemophilia Center is now

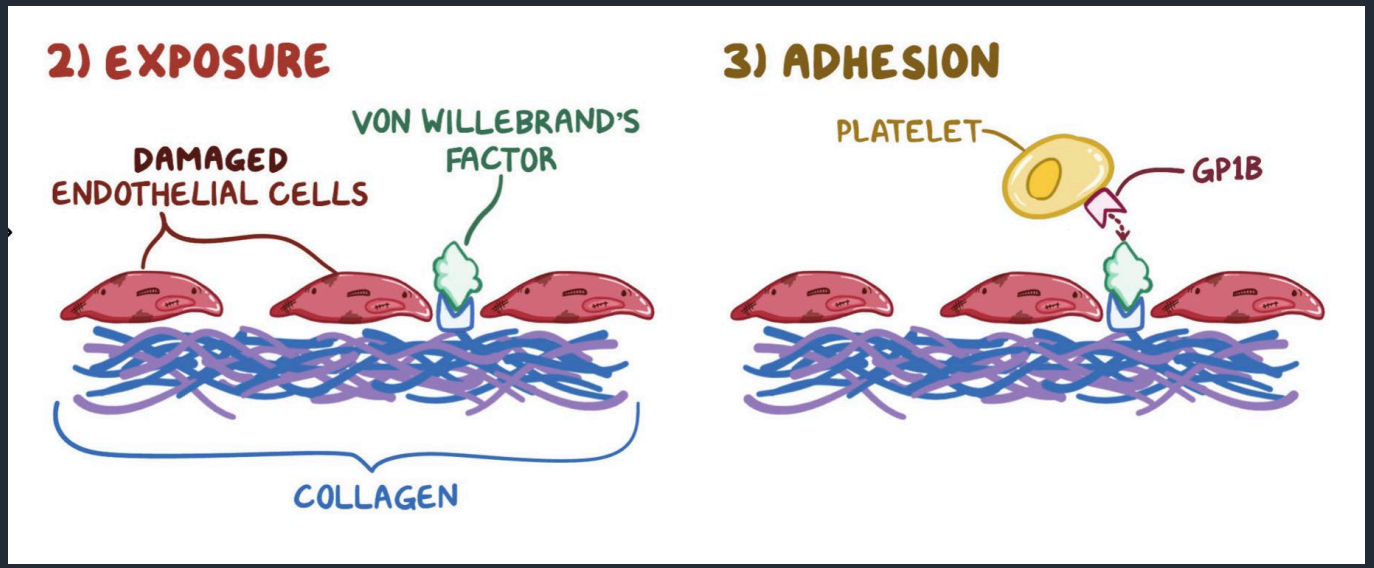
OHSU The HEMOSTASIS & THROMBOSIS Center

- We are also, officially, an OHSU designated Center

Objectives

- Recall the natural pro- and anti-coagulants.
- Review current bleeding disorder treatments.
- List the mechanism of actions of 2 novel bleeding disorder treatments.
- Describe applications of 2 novel bleeding disorder treatments.
- Assess how novel medications affect the treatment landscape for bleeding disorders.





www.osmosis.org/notes/Blood_Components_and_Function accessed 1/15/2024.

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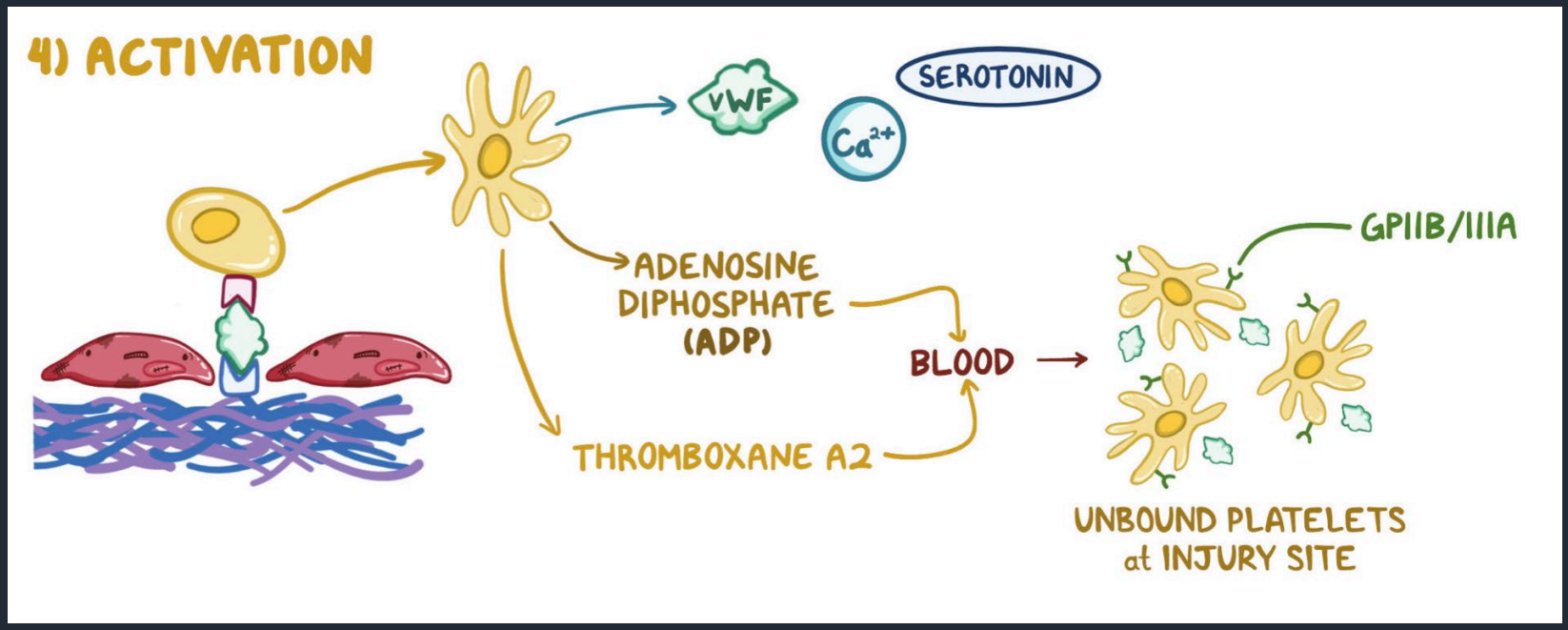

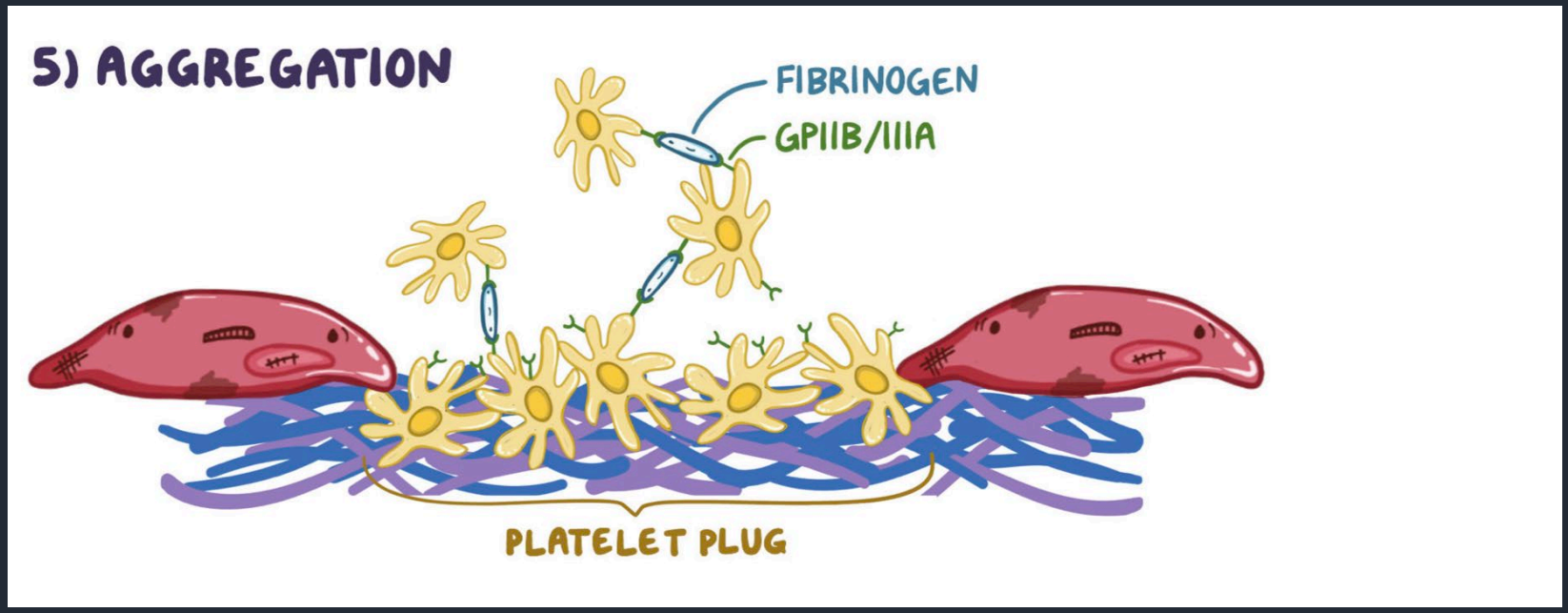

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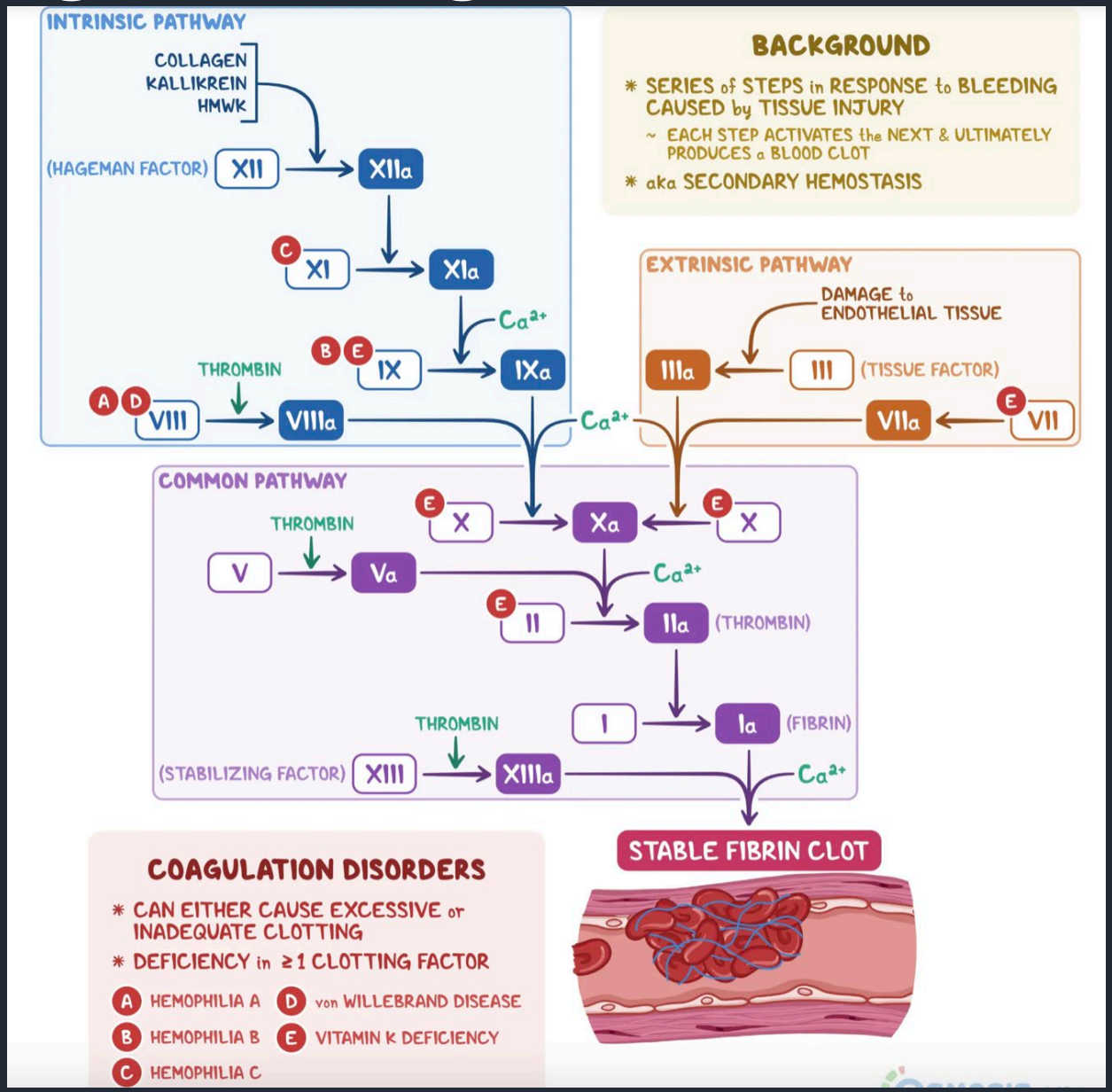
Don’t go chasing waterfalls…



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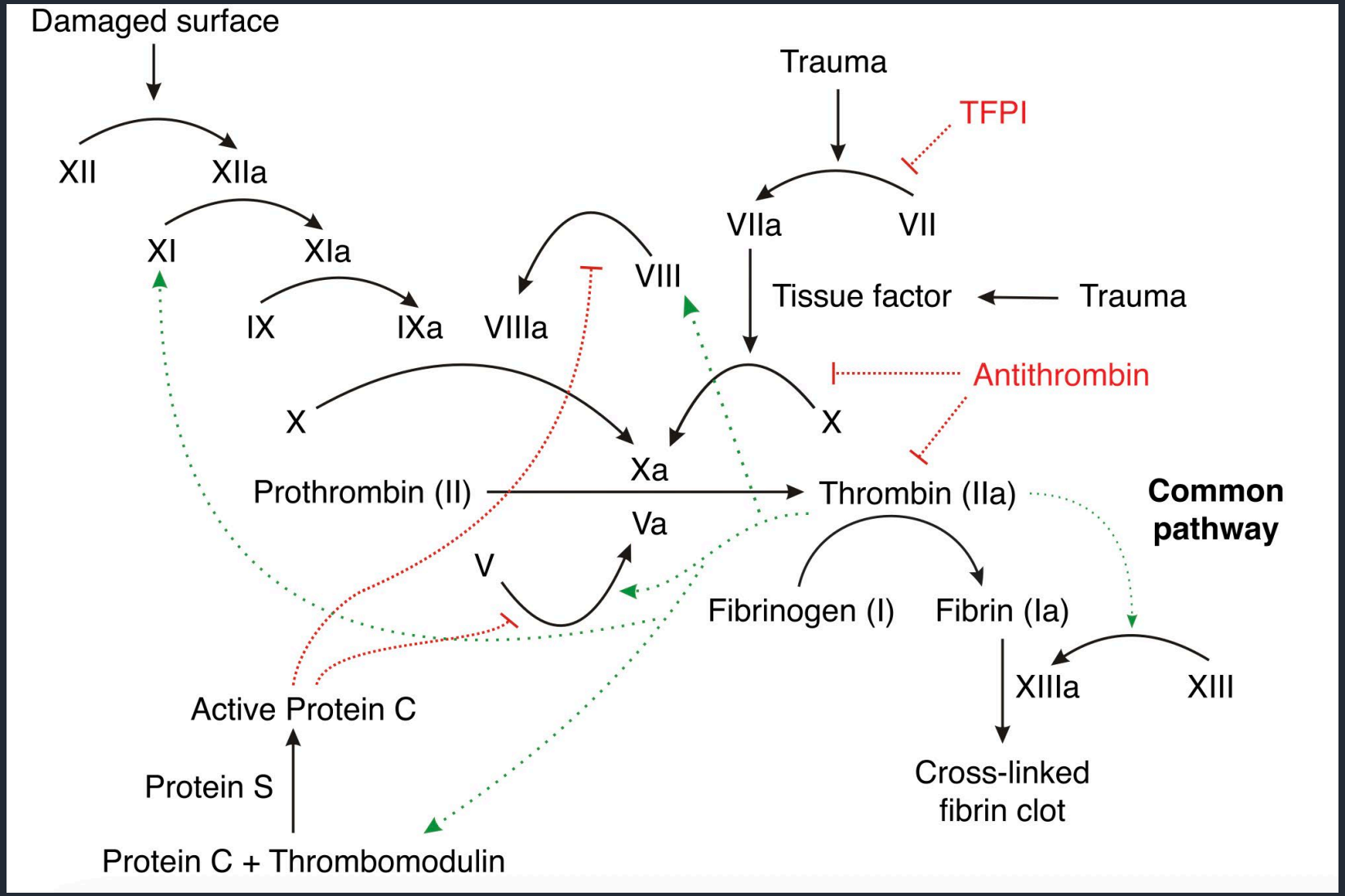


https://upload.wikimedia.org/wikipedia/commons/b/b6/Coagulation%5Ffull.svg Accessed 1/15/2024.

Bleeding Disorder Treatment Review

Before Bleeding Happens	While Bleeding is happening
Stay active – keep muscles and joints strong	First Aid measures – pressure, RICE
Dental hygiene and preventive care	Hemophilia: factor med +/- Antifibrinolytic
Wear a helmet and a seat belt (when appropriate)	VWD: DDAVP or VWF concentrate +/- Antifibrinolytic
Avoid contact sports/activities	Platelet Disorder: DDAVP or rFVII or platelet transfusion +/- antifibrinolytic
Take prophylactic medicine as prescribed (factor, hormones, anti-fibrinolytic, etc)	Other meds used: other factor products (VII, XIII)
HMB: CHCs, implants, IUD	HMB: estrogen + progesterone or progesterone only

Bleeding Disorder Treatment Review

Von Willebrand Disease Treatments:

- Release what's missing:
  - DDAVP releases stored VWF
  - Usually works in type 1 VWD and some mild type 2M
  - Contraindicated in type 2B
  - Intranasal form (Stimate) has been on recall since 2020 – but a compounded intranasal DDAVP is now available!
- Replace what's missing:
  - VWF Factor concentrate
  - Plasma derived (contain VWF & FVIII): Humate-P, Wilate, Alphanate
  - Recombinant (contains only VWF): VonVendi

Bleeding Disorder Treatment Review

Hemophilia A Treatments:

- Plasma-derived
  - Pooled human plasma
  - Contains VWF in addition to FVIII
- Recombinant
  - 3 cell lines: CHO, BHK, and HEK
  - Full length vs B-domain deleted
  - Standard half-life (SHL): Recombinate, Kovaltry, Advate, Xyntha, NovoEight, Nuwiq, Afstyla
  - Extended half-life (EHL) (Fc, PEG): Eloctate, Adynovate, Esperoct, Altuviiio, Jivi
- Typically ½ life is ~12 hours for SHL or ~18 hours for most EHL

Bleeding Disorder Treatment Review

Hemophilia B Treatments:

- Plasma-derived
  - Pooled human plasma
  - AlphaNine, Profilnine
- Recombinant
  - 1 cell lines: CHO
  - SHL: Benefix, Rixubis, Ixinity
  - EHL (Fc, PEG, Albumin): Alprolix, Idelvion, Rebinyn
- Typically ½ life is ~ 24 hours for SHL and up to ~100 hours for EHL

Bleeding Disorder Treatment Review

Factor Inhibitor Treatment:

- Bleeding:
  - Bypassing agents:
    - Recombinant factor VIIa: NovoSeven, SevenFact
    - Plasma derived: FEIBA (activated and inactivated clotting factors)
- Prophylaxis:
  - Bypassing agent
  - Emicizumab (for Hem A)
- Eradication:
  - Immune Tolerance Induction: exposure to factor product regularly and for a long time
- Prevention:
  - Consideration of factor mutation, exposure to product

Bleeding Disorder Treatment Review

Platelet Disorders

- Glanzmann Thrombasthenia:
  - Recombinant Factor VIIa: NovoSeven
  - Platelets reserved for severe, life-threatening bleeding due to risk of alloimmunization
  - Bone marrow transplant
- Bernard Soulier Syndrome:
  - Recombinant Factor VIIa: NovoSeven
  - Platelets reserved for severe, life-threatening bleeding due to risk of alloimmunization
  - Bone marrow transplant
- Other platelet disorders (eg: Dense Granule Deficiency):
  - DDAVP
  - Platelet Transfusions

Shifting Paradigms #1

People with bleeding disorders other than severe hemophilia bleed, too.

- Database study of patients with nearly 20,000 patients with VWD (median age 47 years) over a 4 year period showed: 15% experienced one or more major bleed event.
- US Hemophilia Treatment Center Network data for 105 children < 2 years of age with VWD (63% with type 1): 70% had bleeding events (oral mucosa most common); 5% had intracranial hemorrhage.
- In a study of 34 females who carried the Hemophilia A gene and had normal factor levels: over 70% had abnormal bruising, nearly 50% had post-surgical bleeding, and 20% had hemarthroses.

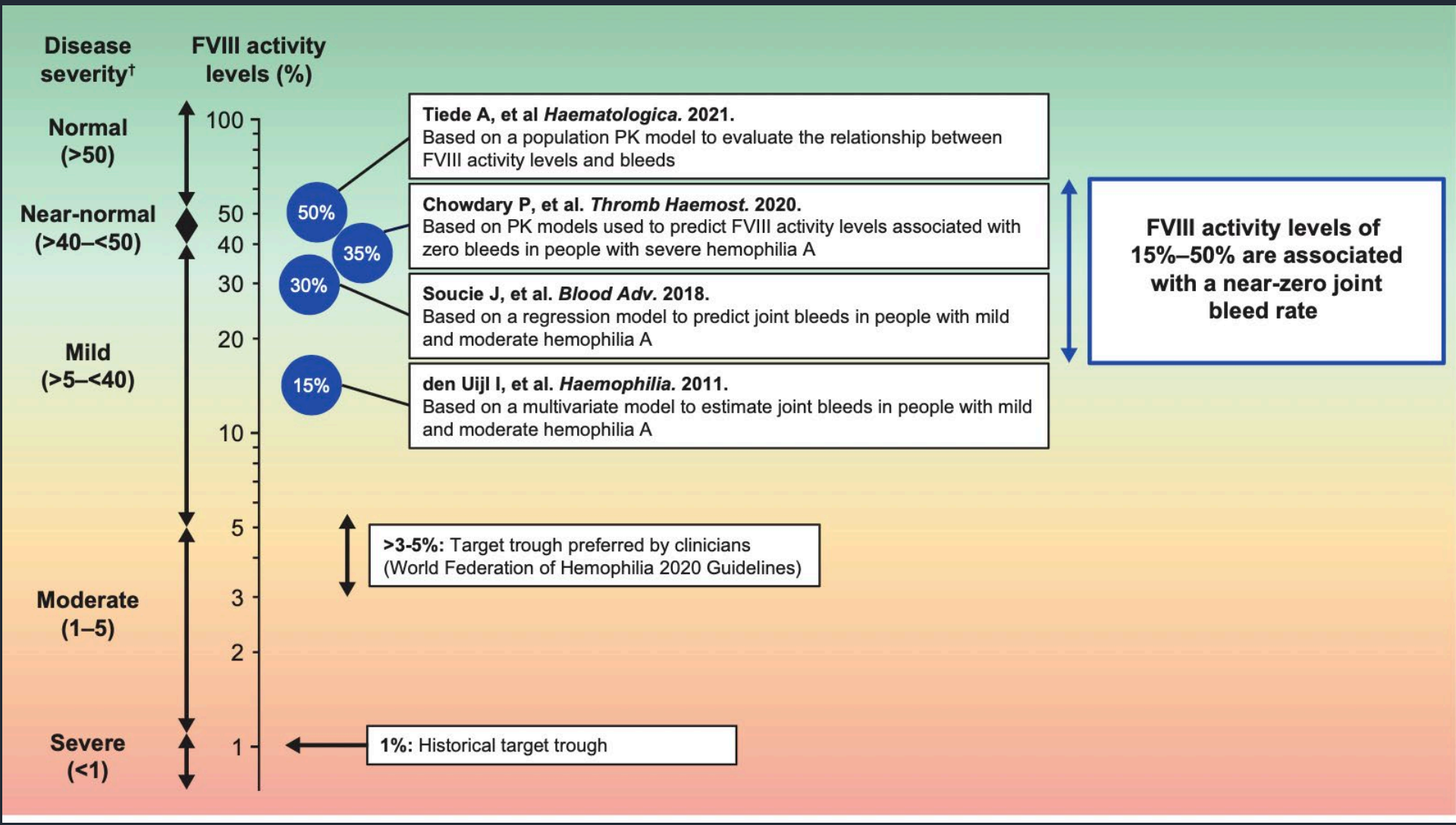
Paroskie A, et al. BJH 2015.
Dupervil B, et al. Blood Advances. 2021.
Lu M, et al. J Managed Care Spec Pharm. 2021.

Shifting Paradigms #2

A factor level of 1% is inadequate to prevent bleeding in hemophilia.

- Joint outcomes study: prophylactic factor infusions resulted in less joint damage than episodic infusions.
- The goal has historically been to keep trough levels in the moderate hemophilia range (1-5%).
- PK-guided study of EHL factor VIII: 42% of those whose factor level was 1-3% had no bleeding events and 62% of those whose factor level was 8-12% had no bleeding events.
- Retrospective study evaluating joint bleeding and factor levels: an 18% reduction in joint bleed frequency was identified for every 1% increase in factor activity
- Retrospective study of nearly 5000 patients evaluating joint bleeding and factor levels: predicted number of joint bleeds approached zero when factor levels were >30%

Manco-Johnson M, et al. NEJM 2007.
Soucie JM, et al. Blood Advances. 2018.
Klamroth R, et al. Blood. 2021.
Den Uijl I, et al. Haemophilia. 2011.
Malec L, et al. Haemophilia. 2023.



Malec L, et al. Haemophilia. 2023.

Shifting Paradigms #3

There is a risk of ICH in the first year of life of children with hemophilia: we are starting prophylaxis too late.

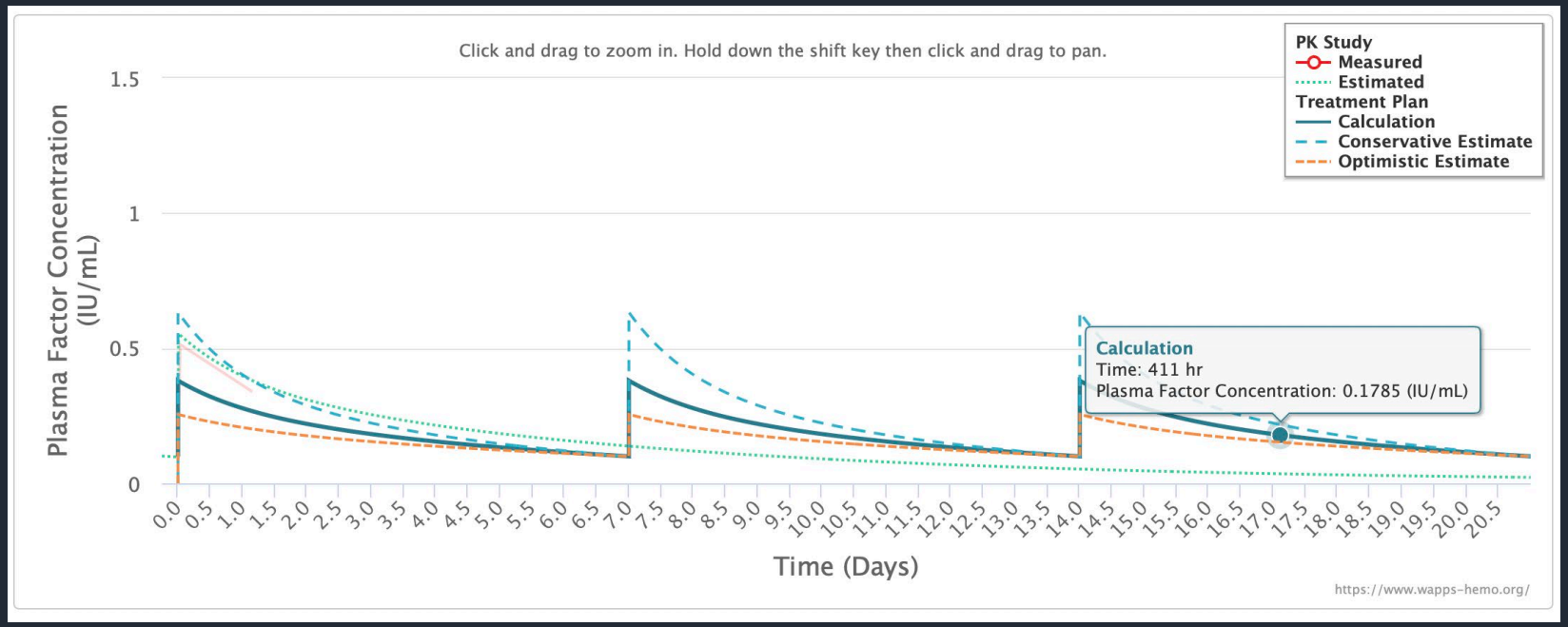
- Historically, factor prophylaxis for patients with severe hemophilia has started at around 9-12 months of age.
- ICH in neonates with hemophilia is 40-80 times higher than in neonates without bleeding disorders: 3-4% of neonates with hemophilia will have an ICH at birth.
- UK study cumulative rate of ICH:
  - All Hemophilia: 6.4 per 1000 patient years
  - Median age at presentation: 4 month and 58% presented between one month of age and 2 years of age
  - In the 44 children who had ICH after neonatal period, trauma was noted in 11
  - 94% of the children were not on prophylaxis prior to ICH presentation

Chalmers EA, et al. Haemophilia. 2018.
Zanon E and Pasca S. Blood Transfus. 2019.

Shifting Paradigms #4

Pharmacokinetic studies can improve outcomes.

- Individualized dosing and frequency of dosing utilizing population PK measurements is now available.



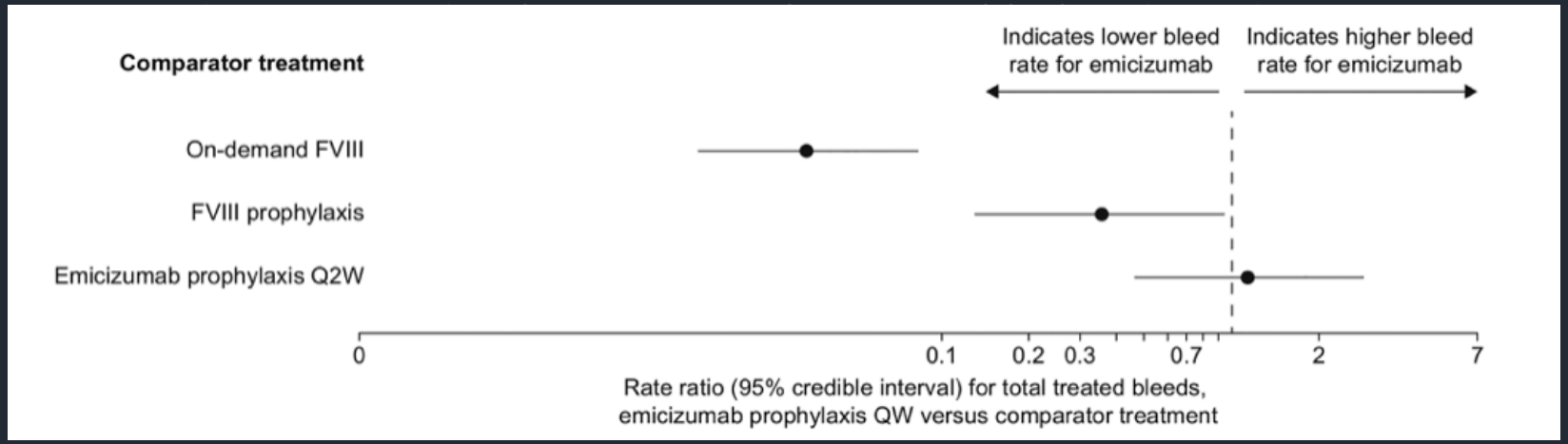
Iorio A. Hematology Am Soc hjematol Educ Program. 2017.

Ongoing gaps/challenges

- IV access – most of the available treatments are still intravenous medications
- Limited options for prophylaxis for non-hemophilia bleeding disorders
- Limited options for bleeding treatment for non-hemophilia/non-VWD bleeding disorders
- Increasing activities and adventures – more and different bleeding
- Costs for treatment remain sky high
- New/different medications make the simple “when in doubt, just infuse” a little more complicated

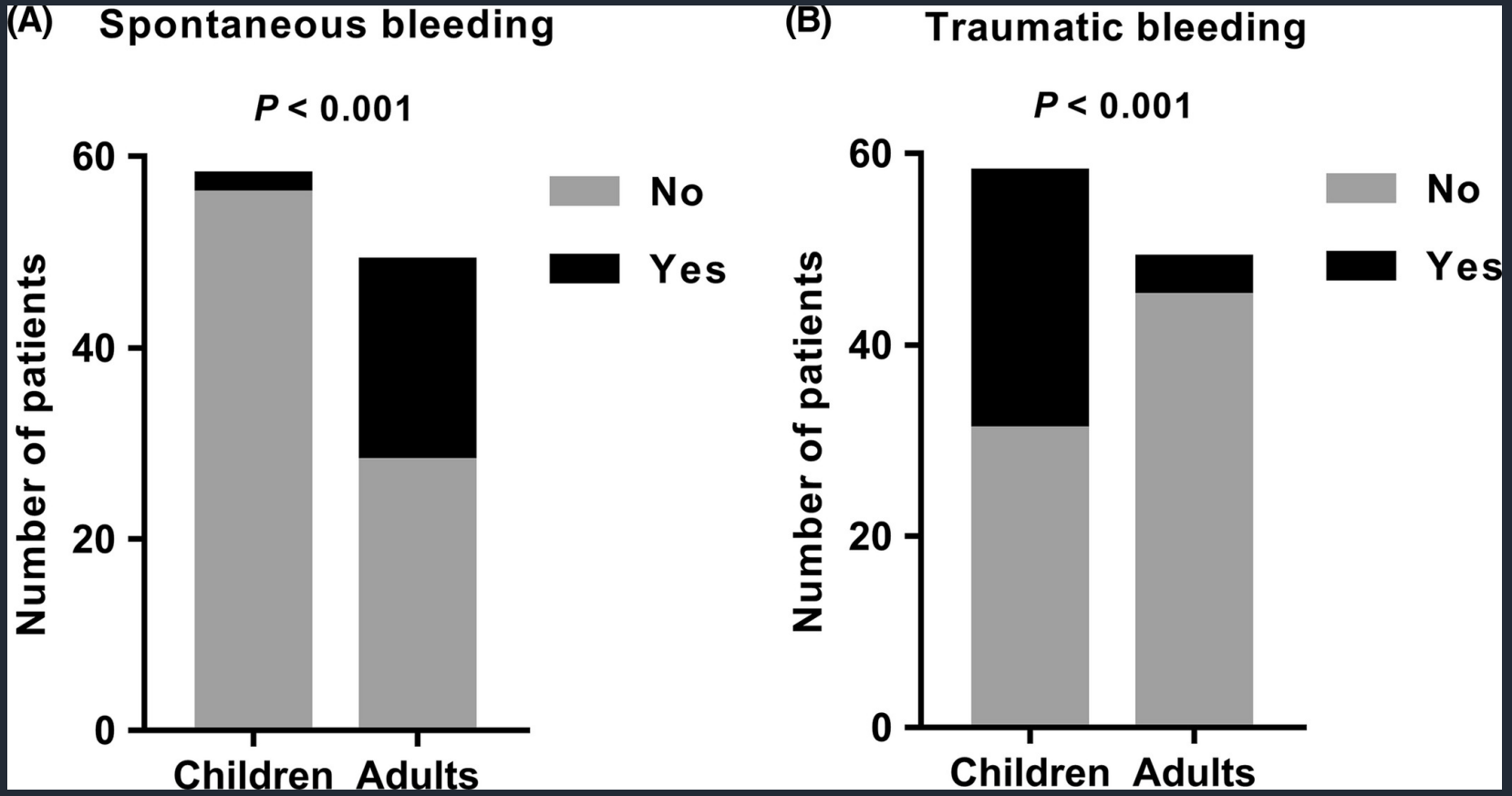
The start of subcutaneous options

- Emicizumab – brand name Hemlibra
  - Humanized monoclonal modified IgG4 bispecific antibody that binds factor IXa and factor X – mimicking the action of FVIII
  - FDA approved 2017 for adults and children with Hem A and inhibitors; FDA approved 2018 for adults and children with Hem A and without inhibitors



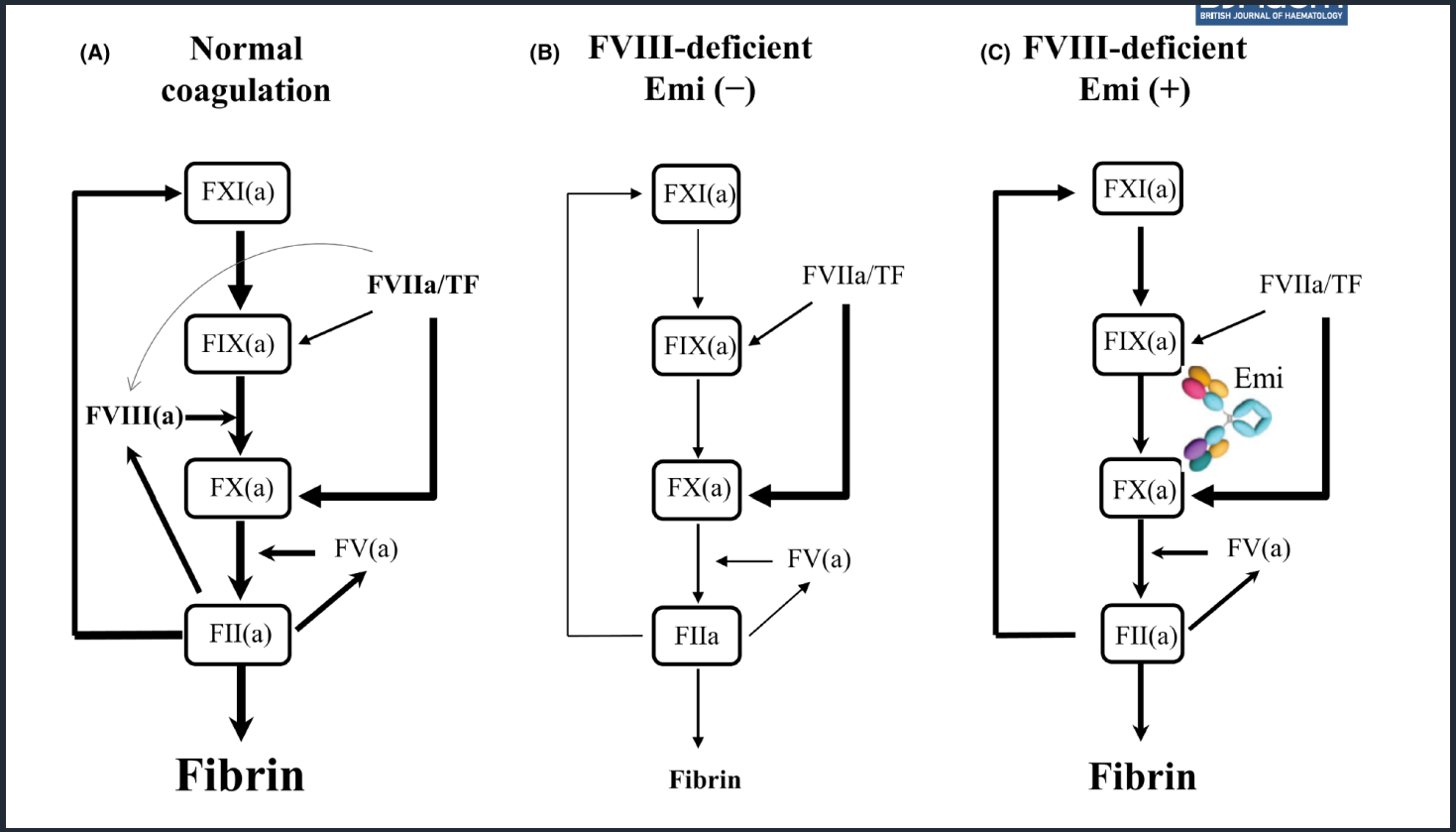
Reyes A, et al. Current Medical Research and Opinion. 2019.

Emicizumab



Barg AA, et al. Haemophilia. 2021.

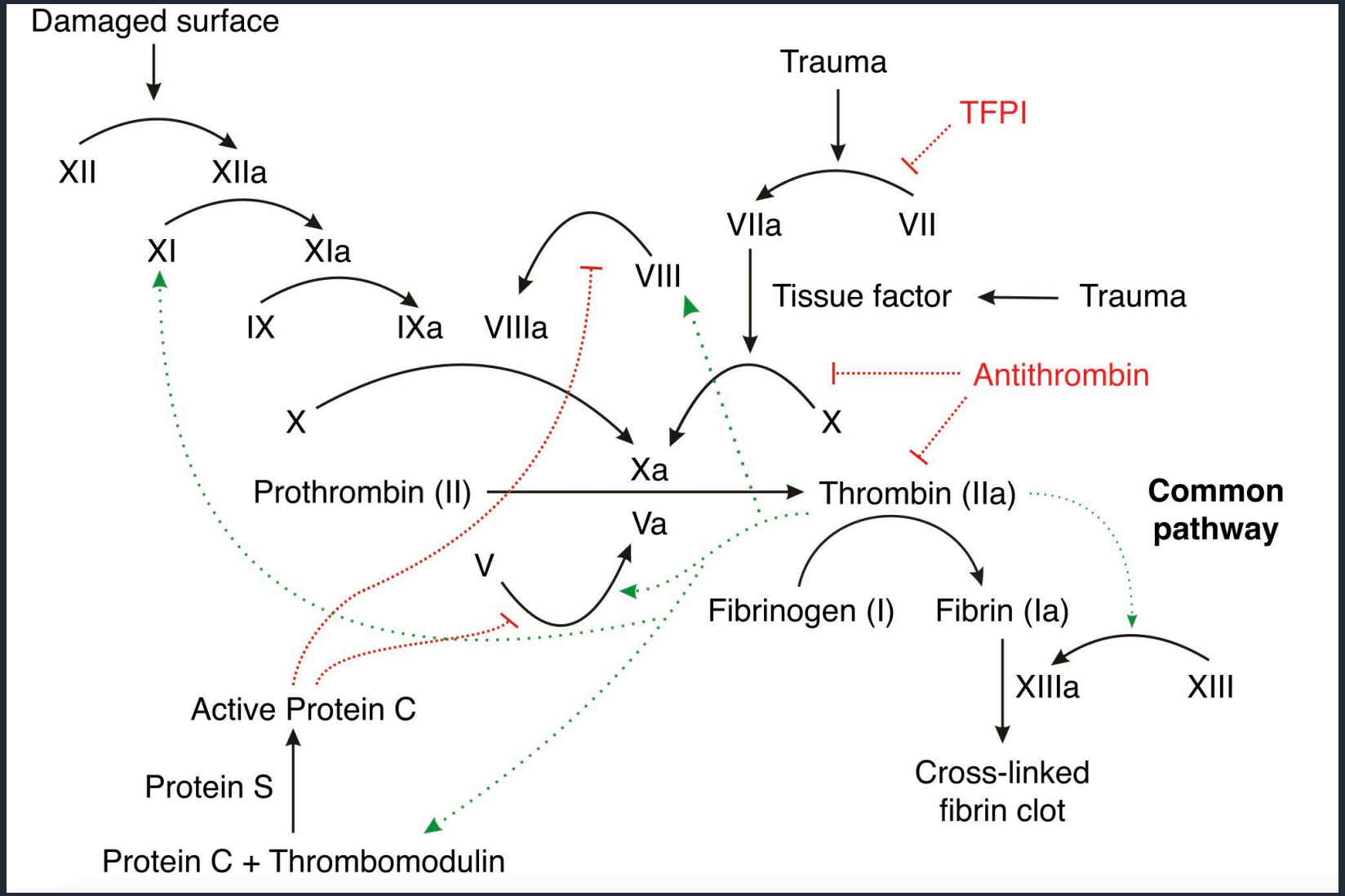
Emicizumab



Coagulation process and fibrin induced potential in different scenarios. “The thickness of characters and lines represents the degree of promotion.” The catalytic efficiency of Emi is 1/11 fold of FVIIIA. FVIII still wins?

Nogami K, t al. British Journal of Haematology. 2023.

Targeting Natural Anticoagulants



https://upload.wikimedia.org/wikipedia/commons/b/b6/Coagulation%5Ffull.svg Accessed 1/15/2024.

Targeting Natural Anticoagulants

- Antithrombin inactivates FXa and Thrombin – thus acting as a natural anticoagulant
- An antithrombin siRNA was developed to reduce hepatic expression of antithrombin mRNA = Fitusiran
  - (siRNA – small interfering RNA, interferes with the expression of specific genes - in this case, antithrombin)
- Fitusiran is given as a subcutaneous injection

Nogami K, t al. British Journal of Haematology. 2023.

Fitusiran

- Phase I trial: 4 healthy adults + 25 adults with Hem A or Hem B, given Fitusiran at varying doses/intervals
  - Constantly low antithrombin levels
  - Monthly dosing resulted in 70-90% lower levels of antithrombin than normal
- Phase II trial: adults with Hem A or Hem B, with and without inhibitors, given monthly doses
  - 80% reduction in antithrombin levels
  - Annualized bleeding rates was 1 in non-inhibitor patients and zero in inhibitor patients
  - One non-inhibitor patient developed a fatal CSVT while receiving FVIII for a bleed treatment
  - Trials were stopped – re-evaluated, changed protocols
    - Changed antithrombin target (15-35%)
    - Revised dosing regimen

Peyvandi F, et al. The Lancet. 2023.

Nogami K, t al. British Journal of Haematology. 2023.

Fitusiran

- Phase III trial: individuals with Hem A or Hem B, with and without inhibitors
- For the 57 participants with inhibitors:
  - An 88% reduction in annualized bleeding rate was observed vs on-demand bypassing agent therapy
  - One participant withdrew from the study due to “spinal vascular disorder and thrombosis”
  - Overall, 4 thromboembolic events were reported in 2 patients
- For the 120 participants without inhibitors:
  - Mean ABR was 0 for those receiving Fitusiran vs 16.1 for those receiving on-demand factor
  - No thromboses reported

Nogami K, t al. British Journal of Haematology. 2023.
Young G, et al. The Lancet. 2023.
Peyvandi F, et al. The Lancet. 2023.

Targeting Natural Anticoagulants

- Tissue Factor Pathway Inhibitor (TFPI) impairs the initiation phase of clotting by inhibiting FVIIa/TF and prothrombinase (Xa+Va)
  - K1 domain binds FVIIa
  - K2 domain binds FXa
  - K3 domains interacts with protein S
- Humanized monoclonal antibodies against TFPI have been developed to inhibit the K2 domain = Concizumab and marstacimab
  - Leads to amplified generation of FXa and thus Thrombin

Nogami K, t al. British Journal of Haematology. 2023.

Concizumab

- Phase I trial: 28 healthy adults + 24 adults with Hem A or Hem B
  - Plasma TFPI activity decreased x 14 days after 1 dose
  - Thrombin generation increased
- Phase II trial: 53 adults with Hem A or Hem B with or without an inhibitor
  - Daily subcutaneous injections
  - ABR was 3-6 for those with inhibitor, 7 without inhibitor
- Phase III trial: ongoing but was temporarily halted in 2020 due to non-fatal thromboembolic events in 3 participants (2 arterial, 3 venous)
  - Mitigation plan was created and implemented, trial restarted

Nogami K, t al. British Journal of Haematology. 2023.
Matsushita T, et al. NEJM. 2023.

Concizumab

- Phase III trial data for participants with inhibitors is published:
  - 4 groups:
    - Group 1: no prophylaxis → ABR 11.8 episodes
    - Group 2: Concizumab prophylaxis → ABR1.7 episodes
    - Group 3 & 4: Concizumab prophylaxis (nonrandomized)
  - No thromboembolic events reported after the trial was restarted
  - Study deaths:
    - 1 fatal case of pneumonitis in someone not on Concizumab
    - 2 patients died during the study pause who had been on Concizumab due to bleeding and then IVC thrombosis and the other due to GI bleeding
    - 1 patient died in an MVC who had been on Concizumab
    - 1 patient died due to COVID19 who had been on Concizumab

Matsushita T, et al. NEJM. 2023.

Targeting Natural Anticoagulants

- Fitusiran and Concizumab offer a subcutaneous option for patients with Hemophilia B
- Could these therapies be an option for patients with other factor deficiencies?

Extending half-life in novel ways

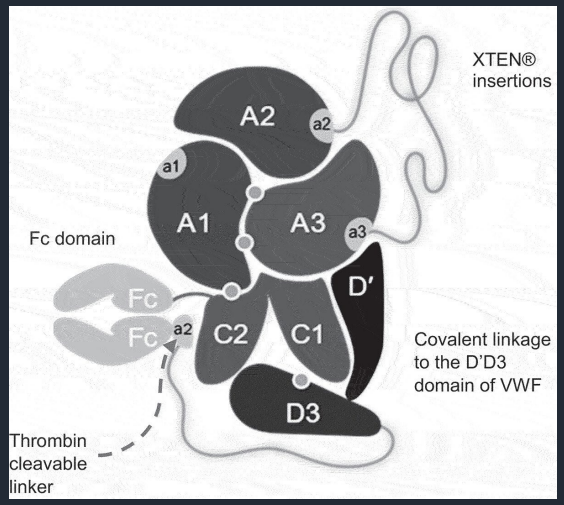
- Factor VIII and IX products have been complexed with other molecules to extend half-life
  - PEG
  - Fc
  - Albumin
- In some cases, changes the dosing (IU/kg) that the patient might have at home from the typical bleed dose of 50 IU/kg (FVIII) Or 100 IU/Kg (FIX)
- Significant success with factor IX allowing for less frequent infusions, but limited success for factor VIII due to VWF half-life

Introducing Efanesoctocog Alfa

- FDA approved in February 2023 for Hemophilia A for prophylaxis and treatment – brand name Altuviiio
- XTEN polypeptide chains —
  - unstructured hydrophilic, biodegradable protein polymers
  - alter the hydrodynamic radius of the fusion protein
  - reducing clearance and degradation rates
- VWF D'D3 domain covalently coupled to B domain deleted rFVIII that is fused to Fc
- Two XTEN polypeptides were added

to extend the half-life further

  - Inserted at the B-domain region of FVIII
  - Inserted between the D'D3 domain and Fc



Keam SJ. Drugs. 2023. Konkle B. Expert Review of Hematology. 2023. Podust VN, et al. Journal of Controlled Release. 2016.

Efanesoctocog Alfa

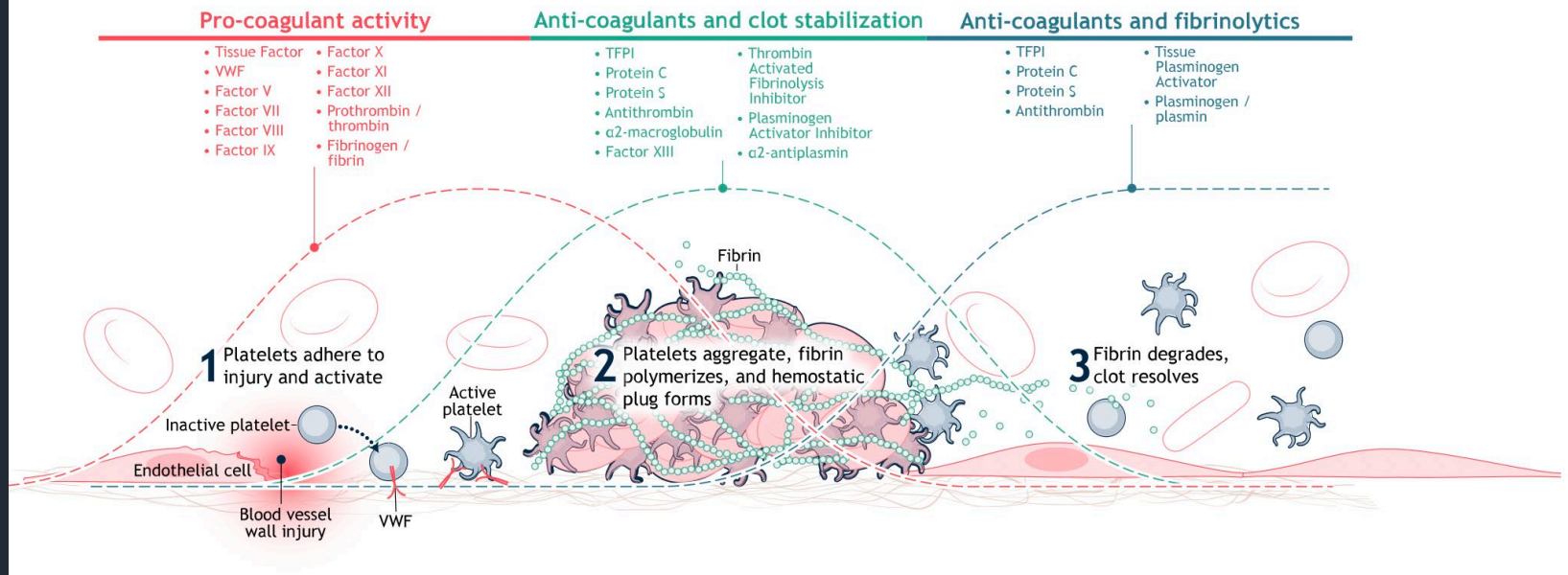
- Patient's own VWF cannot bind to Efanesoctocog Alfa
- Upon thrombin activation, the two XTEN moieties are released
- Half-life extension is ~4x a standard half life FVIII product
- Prophylaxis: 50 IU/kg once weekly
  - Peak levels of 100-130%
  - In adults, results in FVIII of ~40% at 4 days and ~15% at 7 days
  - In 1-6 year olds, results in FVIII of ~40% at 2.5 days
- Bleeding: infuse 50 IU/kg and then consider additional doses of 30-50 IU/kg every 2-3 days
- To resume prophy after a bleed: wait at least 72 hours after last 50 IU/kg dose
- Studies ongoing for type 2N and type 3 VWD

Package Insert - Efanesoctocog Alfa

Konkle B. Expert Review of Hematology. 2023.

Using the knowledge of hemostasis

Our therapeutic candidates* bind the body's native clotting factor(s) with high specificity and affinity. This binding can stabilize the native clotting factor(s), preventing breakdown and allowing accumulation to therapeutic levels. Furthermore, the binding can be neutral (preserving the activity of the native clotting factor) or inhibitory (inactivating the clotting factor), giving us the versatility to address challenges across the clotting pathway. Our state-of-the-art technology also allows us, when necessary, to recruit native clotting factors directly to the site of injury.



https://hemab.com

HEMAB pipeline

- HMB-001: Glanzmann Thrombasthenia
- HMB-VWF: prophylaxis for VWF, preclinical studies
- HMB-TAF: prophylaxis for Hereditary Hemorrhagic Telangiectasia and Disorders of hyperfibrinolysis, preclinical studies
- HMB-AT3: prophylaxis for antithrombin deficiency, preclinical studies

HEMAB pipeline – HMB-001

- Platelets store TLT-1 (triggering receptor expressed on myeloid cell–like (TREM-like) transcript-1) in alpha granules
- TLT-1 is translocated to the platelet surface upon activation
- TLT-1 binds fibrinogen and some cell adhesion molecules
- HMB-001 – bispecific antibody that “binds, stabilizes, and recruits endogenous factor VIIa to the site of vascular injury”
- Binds FVIIa and TLT-1 on activated platelets

Schmoker AM, et al. Journal of Proteomics. 2018.
Smith CW, et al. Blood Advances. 2018.

HMB-001

- Pre-clinical studies in either models of Glanzmann Thrombasthenia and Hemophilia A demonstrated potentiation of endogenous factor VIIa by 6-14 fold
- Phase I trial of HMB-001 in patients with Glanzmann Thrombasthenia was completed in UK.
- Phase I/II trial currently recruiting in the US
- Fast track designation by the FDA
- Promising option for both treatment and prophylaxis in patients with Glanzmann Thrombasthenia

Gene therapy for Hemophilia

- Hemophilia A: FDA approved 6/29/2023, valoctocogene roxaparvovec-rvox, Roctavian
- Hemophilia B: FDA approved 11/22/2022, ertanacogene dezaparvovec-drib, Hemegenix
- Hemophilia Gene Therapy Basics:
  - Virus gets created in the lab → factor VIII or IX gene gets inserted into the virus (AAV) → virus with its new gene gets infused into the blood → virus goes to the liver → virus goes into some of the cells in the liver and puts the gene into those cells → the cells use the gene as instructions to make factor VIII or IX → only the cells with the gene make factor

Gene therapy for Hemophilia

Criteria	Roctavian – Hemophilia A	Hemegenix – Hemophilia B
age	• 18 years or older • One patient over 65 years was infused on study	• 18 years or older • Oldest patient on studies was 75 years
gender	Males only	Males only
phenotype	• Severe Hemophilia A only (FVIII <1%)	• Any severity • Currently using prophylaxis • Have current or historical life-threatening bleeding • Have repeated serious bleeding
antibodies	• Cannot have antibodies to the virus (AAV5 antibodies) • Cannot have active FVIII inhibitor	• Cannot have active FIX inhibitor

Gene therapy pre-infusion evaluations

- Current status
  - Hemophilia treatment
  - Joint health and function
  - Other bleeding symptoms
- Patient readiness
  - Understanding of the process
  - Patient identify
  - Commitment to follow up
- Liver health
  - h/o Hep C
  - Non-alcoholic steatosis
  - Hepatotoxic medications
  - Alcohol exposure
- Other co-morbidities
  - Hypertension
  - Diabetes
  - Etc
- And then what?
  - Follow up plans
  - Where will follow up occur

Anticipate at least a 3 month lead in to infusion to evaluate the patient – from labs to joint evaluation to QOL assessments to informed consent to readiness assessments.

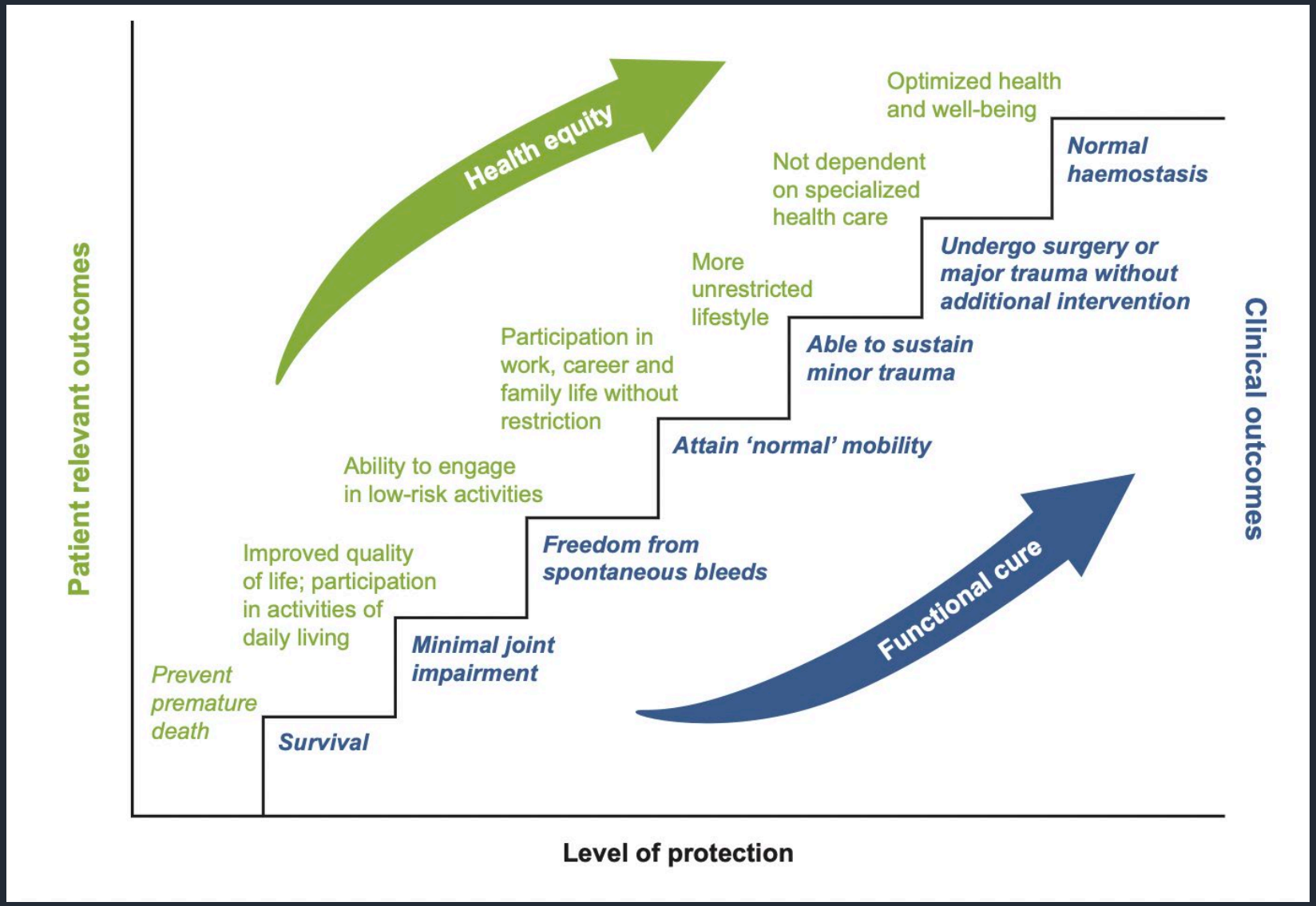
	Roctavian	Hemegenix
# of participants evaluated	134, phase 3 data includes 112	54, but one was excluded d/t reaction
Factor level changes	• Levels increased at 5-8 weeks • @52 weeks, median factor level 32.9% (11.9-62.3%) • 50% had a level between 5-40% at 1 year • 12.1% had a level of <5% • Estimate that at 5 years, the median factor VIII would be 5.7%	• Levels increased starting around 3 weeks • @ 6 months, mean level 39% +/- 18.7% • @18 months, increase from baseline of 34.3% (29.5-39.1%) • @ 3 years, mean factor level 38.6%
Factor use changes	98.6% reduction in factor VIII infusions	• 96% discontinued prophylaxis • Infuses decreased from 72.5 infusions to 2.5 infusions
Joint health/bleeding	• ABR for treated joint bleeds decreased by 84.2% • 90.3% had no treated bleeds in 1st year	• ABR decreased from 4.19 to 1.51 • Pre-infusion, 44% had had spontaneous bleeding and post-infusion, 17% had spontaneous bleeding
Adverse events	• 85.8% had an elevation in ALT • 79.1% received steroids (median duration 230 days)	• 13% had infusion related AE's • 17% received steroids (mean 79 days • One episode of hepatocellular CA

Gene therapy in hemophilia

- Provides a functional cure for some patients – but hard to know who that will be
- May significantly alleviate the burden of therapy for some patients
- Important to have upfront discussion regarding expectations and efficacy – and these discussions rely heavily on established relationships

Bleeding Disorder treatment evolution and impacts

- Continuing to promote prophylaxis for patients with severe bleeding disorders – trying to broaden the focus from severe Hemophilia A and B
- Recognizing the burden of intravenous treatment
- Bleeding phenotypes are changing – in some ways, making treatment even more complicated
- Improving awareness regarding bleeding in non-severe Hem A/B
- Costs remain sky high
- Despite the complicated treatment landscape, prevention and treatment of bleeding is better for most bleeding disorders than it has ever been – allowing other concerns to come to the forefront of clinical care
  - Access
  - Food
  - Housing
  - Education



Malec L, et al. Haemophilia. 2023.

- Thank you for your time and attention – happy to discuss and take any questions/comments.