MOVE HAEMOPHILIA 2023

December 2023

MOVE HAEMOPHILIA 2023

29TH & 30TH SEPTEMBER 2023
BRUSSELS, BELGIUM

PART 1

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MOVE HAEMOPHILIA 2023 – EDUCATIONAL CONTENT

Part 1

1. Factor replacement therapy
2. Non-factor therapy
3. Inhibitors in haemophilia - tolerance towards the deficient factor?

FACTOR REPLACEMENT THERAPY

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DISCLOSURES

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions.

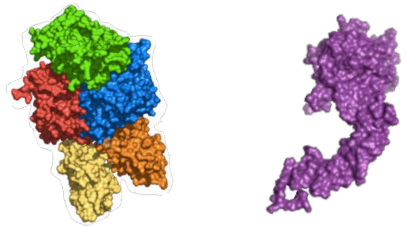
Expert Disclosures:

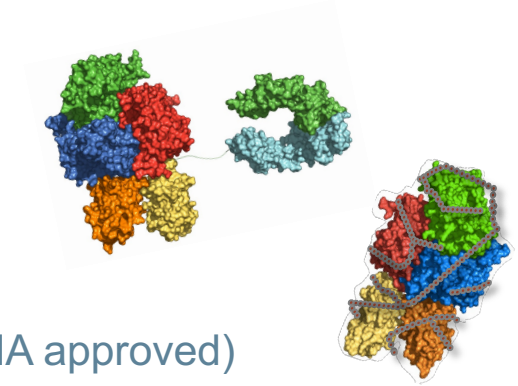
Christoph Königs's Institution has received financial support/sponsorship for research support or clinical trials (incl. GEPHARD Study) from the following companies: Bayer, Biotest, CSL Behring, Intersero, Janssen, Novo Nordisk, Pfizer, Roche/Chugai, Takeda/Shire, Sobi/Sanofi, EU H2020

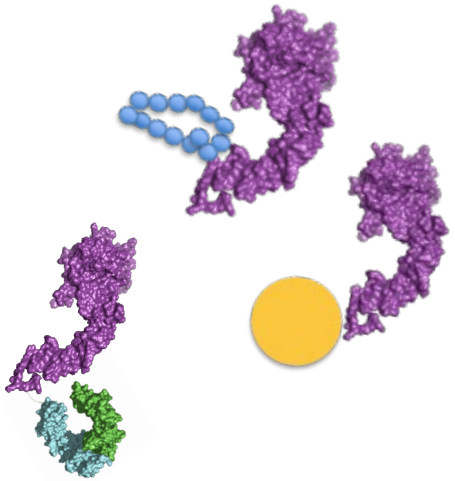
Christoph Königs has received financial support/sponsorship for consultation, or speaker fees from the following companies: BFSG, Bayer, CSL Behring, Florio, MSD, Novo Nordisk, Roche/Chugai, Sobi/Sanofi, Shire/Takeda

FACTOR REPLACEMENT THERAPY

- Many Factor VIII (FVIII) and Factor IX (FIX) concentrates available
  - Standard half-life
    - Plasma-derived
    - Recombinant
      - B-Domain deleted
      - Full length
  - Extended half-life
    - Fc-fusion
    - PEGylation
    - Albumin-fusion (FIX only)
    - vWF-XTEN-Fc-fusion (FVIII only; FDA approved, not EMA approved)



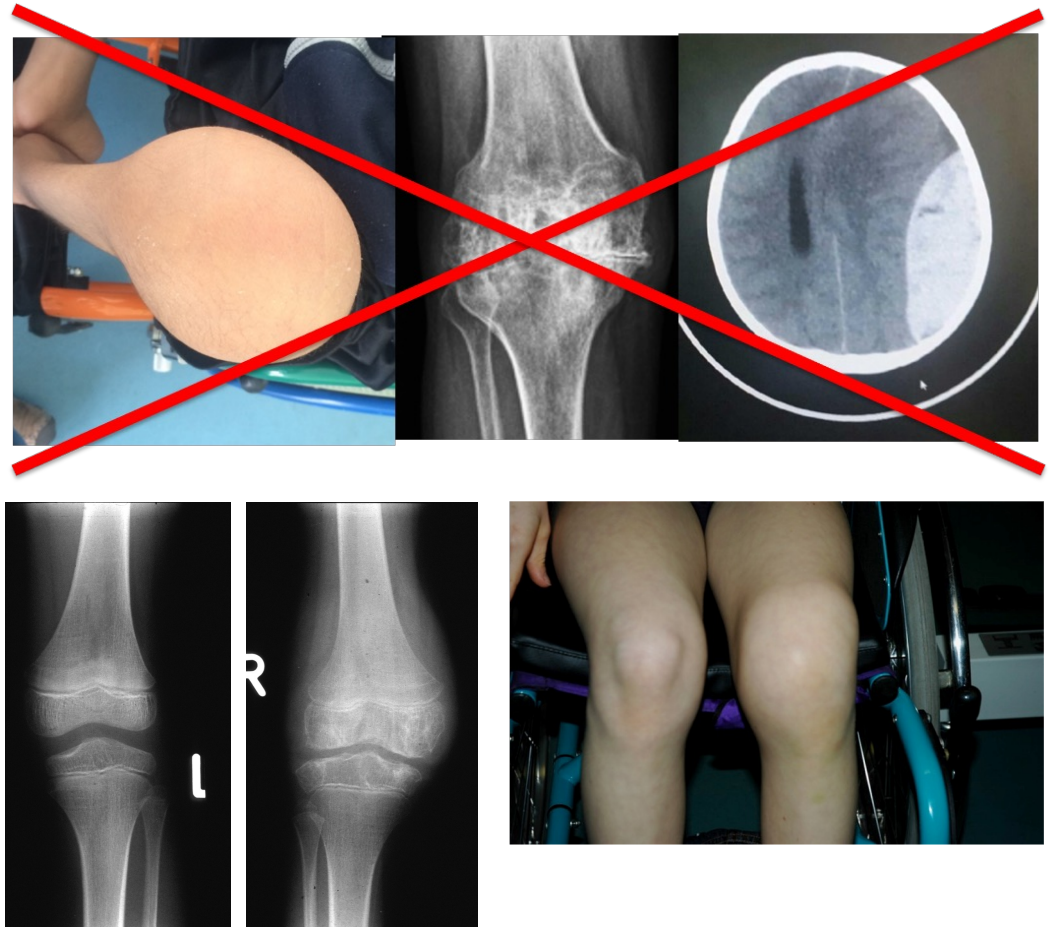




EMA, European Medicines Agency; Fc, fragment crystallisable region; FDA, (United States) Food and Drug Administration; PEG, polyethylene glycol; vWF, von Willebrand factor

AIMS OF TREATMENT

- Avoid or treat bleeds[1]
  - life-threatening bleeds
  - joint bleeds
- (Primary) Prophylaxis[2]
  - Target trough levels of 3-5%
- Avoid inhibitors[3-7]
  - approx. 30% in severe haemophilia A
  - approx. 10% in severe haemophilia B



1. Carcao MD, et al. Semin Thromb Hemost. 2012;38(7):727-34; 2. Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1-158; 3. Königs C, et al. Blood. 2022;139(26):3699-3707; 4. Gouw SC, et al. Blood. 2007;109(11):4648-54; 5. Gouw SC, et al. N Engl J Med. 2013;368(3):231-9; 6. Marcucci M, et al. Thromb Haemost. 2015;113(5):958-67; 7. Male C, et al. Haematologica 2021;106(1):123-9

HOW TO START THERAPY?

Shared decision making

Efficacy considerations:

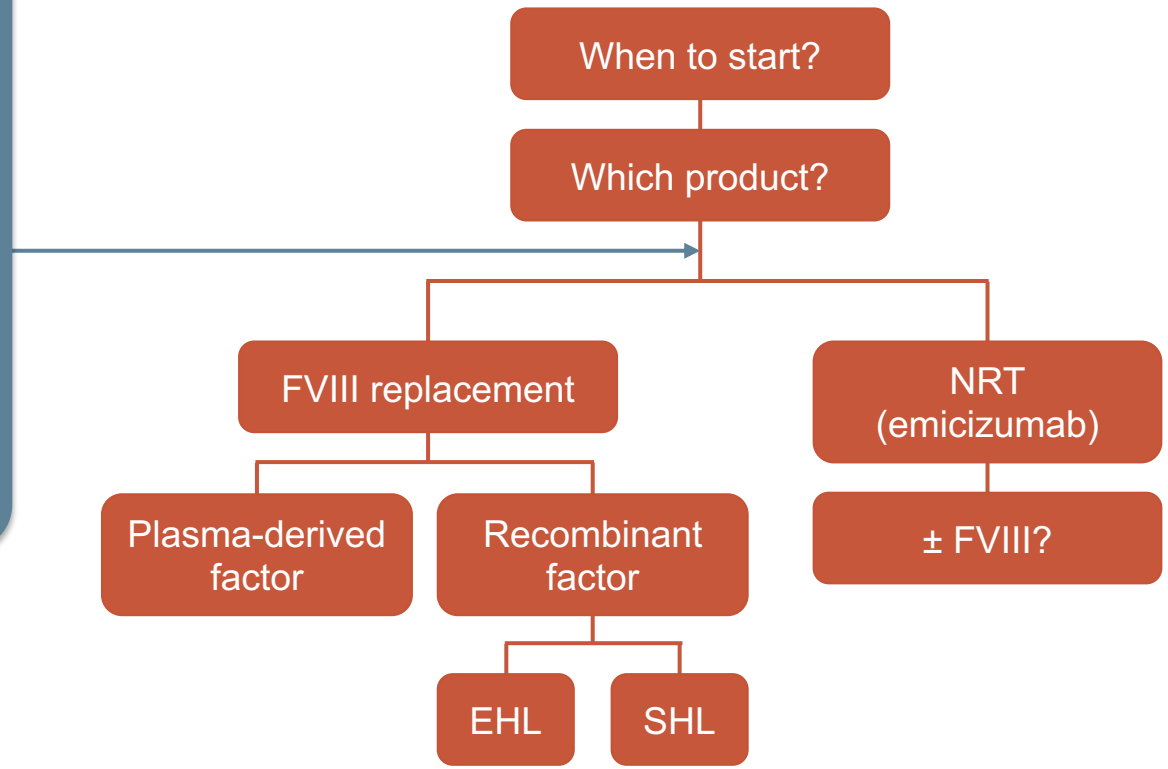
- How best to provide early protection against ICH?
- How best to achieve life-long joint protection?
- Achieving tolerance to FVIII

Safety considerations:

- Less experience with NRT than with FVIII products
- Risk of inhibitor development: FVIII product vs NRT
- Lack of a natural antagonist of NRT (FVIII is inhibited by activated protein C)

Practical considerations:

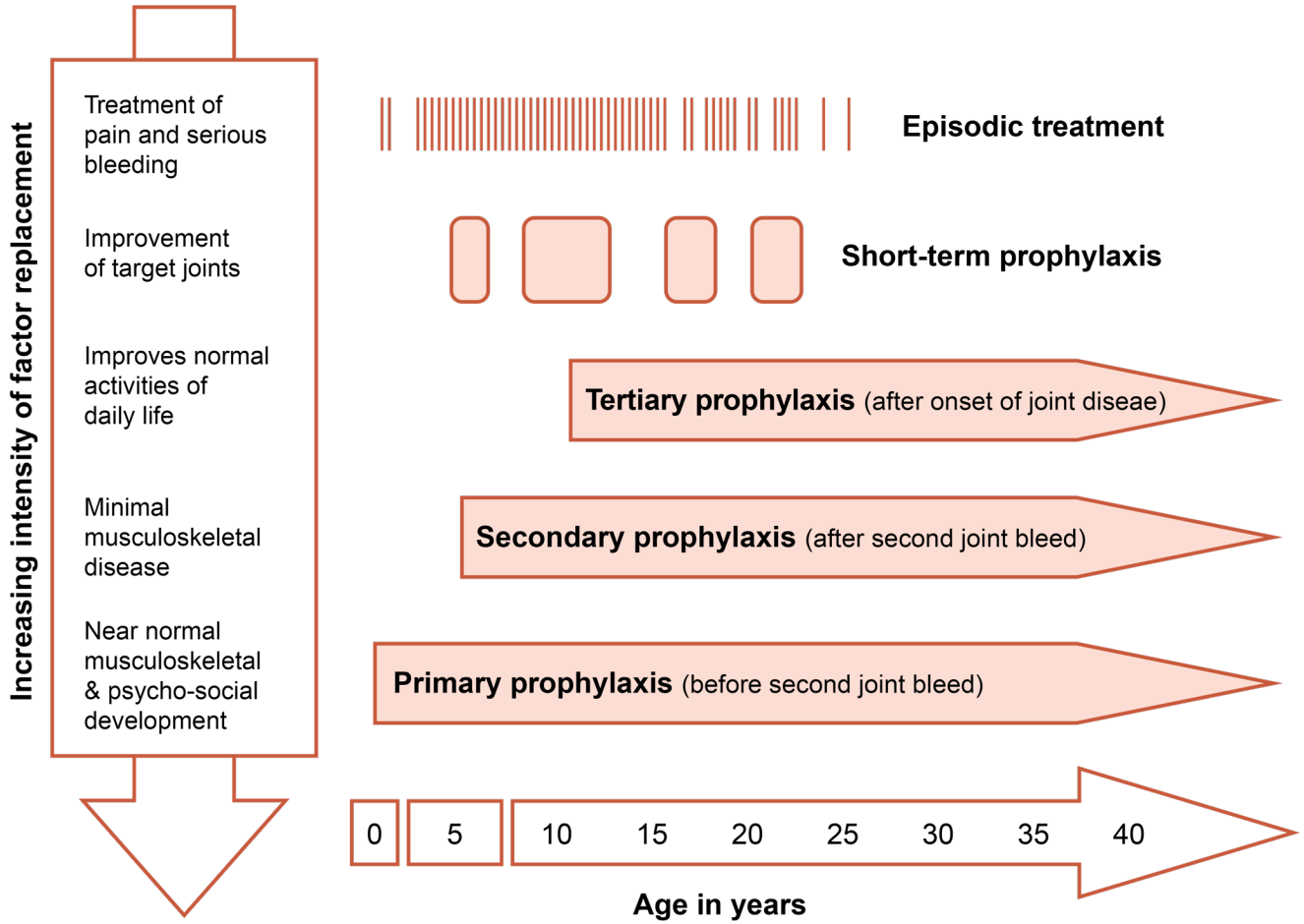
- Venous access



EHL, extended half-life; FVIII, factor VIII; ICH, intracranial haemorrhage; NRT, non-replacement therapy; SHL, standard half-life

Mancuso ME, et al. Lancet. 2021;397(10274):630-640

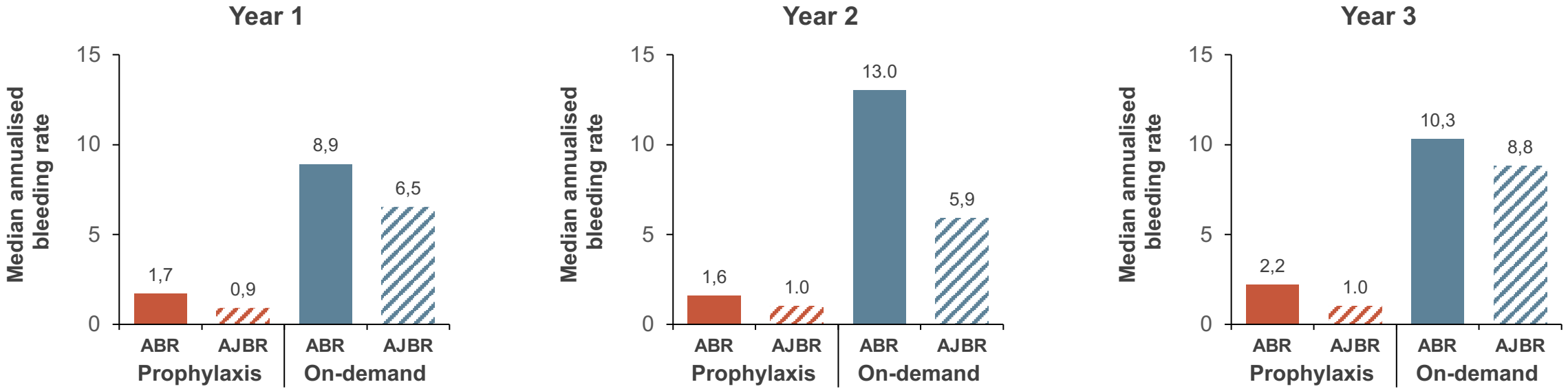
TYPES OF PROPHYLAXIS



Srivastava A, et al. Haemophilia. 2013;19(1):e1-47

PROPHYLAXIS REDUCES BLEEDING FREQUENCY COMPARED TO ON DEMAND

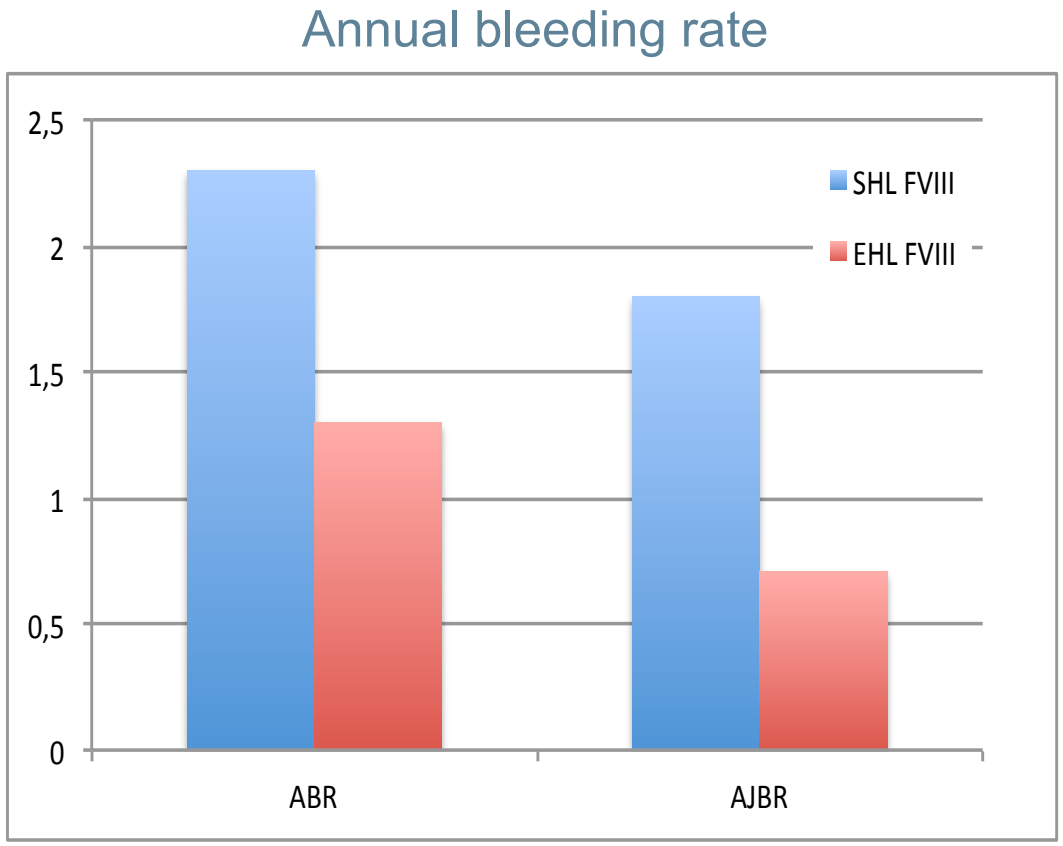
- 522 patients (811 patient years)
- 3/4 received prophylaxis
- 42% had zero bleeds

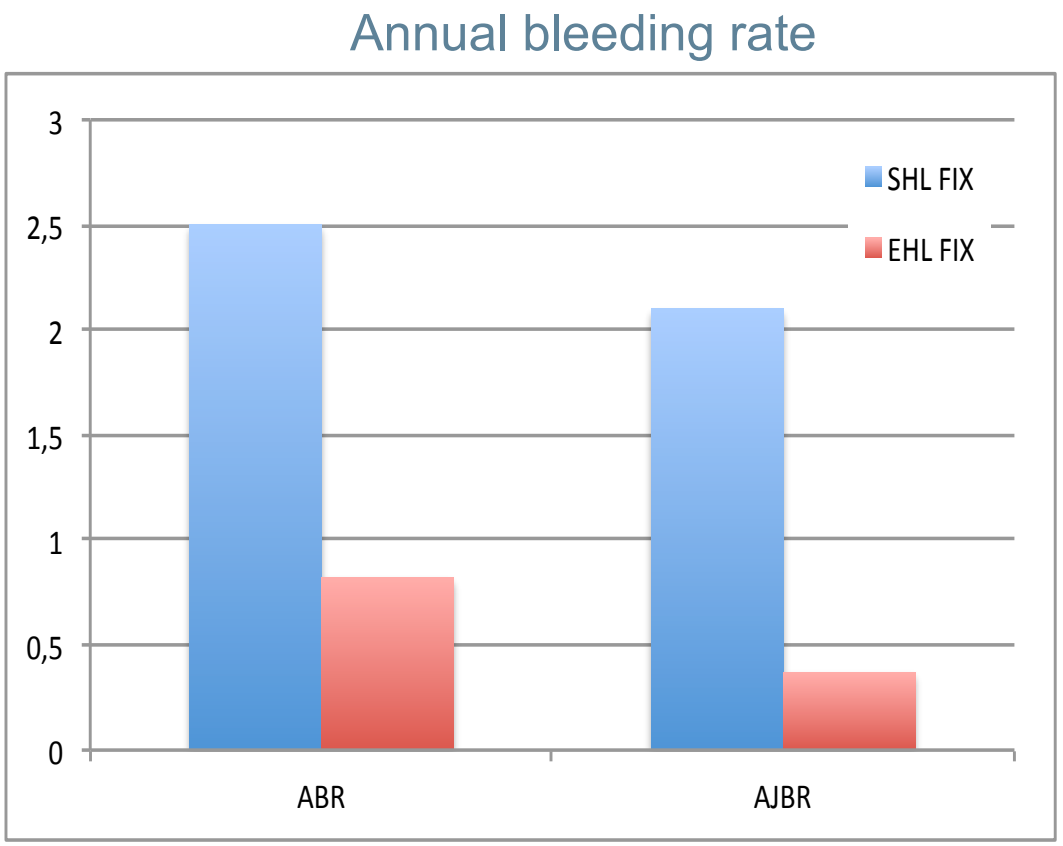


ABR, annual bleeding rate; AJBR, annual joint bleeding rate

Khair K, et al. Haemophilia. 2018;24:85-96

PROPHYLAXIS WITH EHL FVIII AND FIX MIGHT REDUCE BLEEDING FREQUENCY EVEN FURTHER

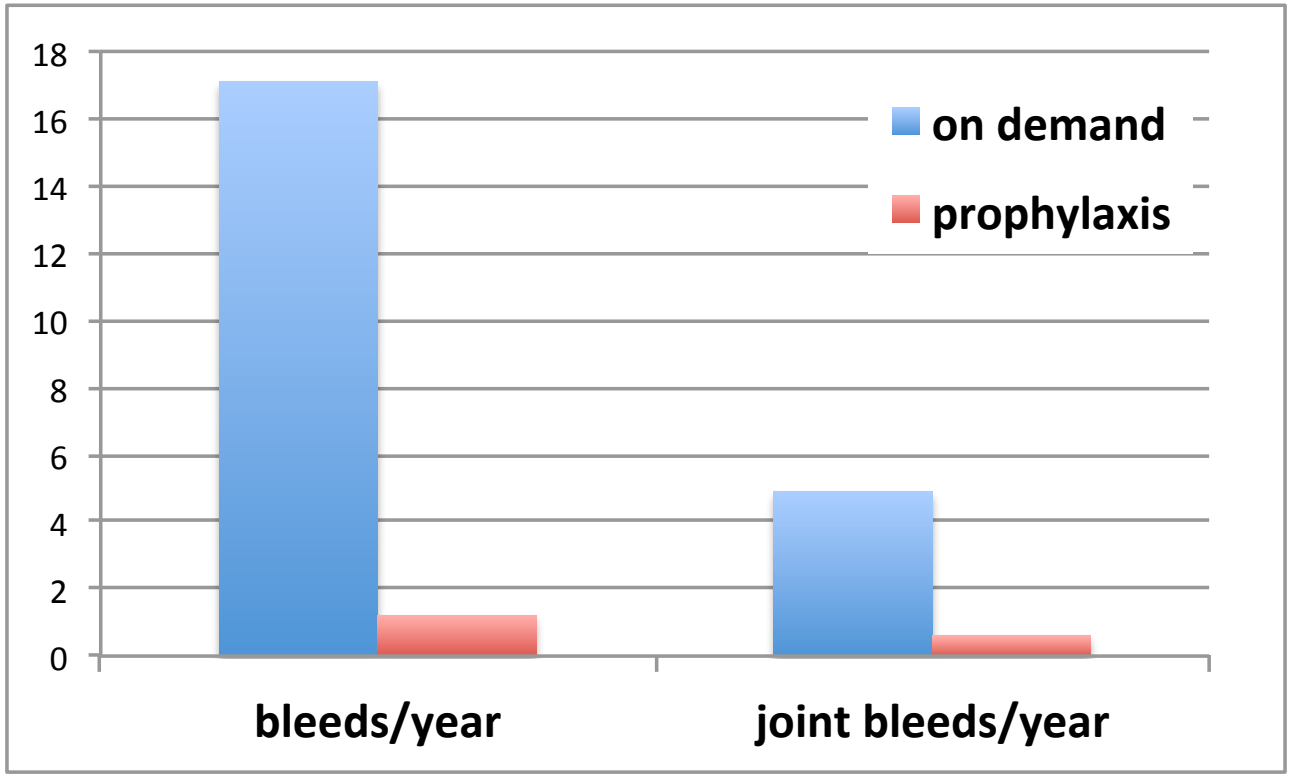




ABR, annual bleed rate; AJBR, annual joint bleed rate; EHL, extended half-life; FIX, factor IX; FVIII, factor VIII; SHL, standard half-life

Wang C and Young G. Haemophilia. 2018;24:414-9

PROPHYLAXIS REDUCES BLEEDING FREQUENCY – JOINT OUTCOME STUDY – USA



- 65 boys <30 months (completion of study when participant reached age 6 years)
- Three life-threatening bleeds in the on-demand group

Manco-Johnson MJ, et al. N Engl J Med 2007;357:535-44

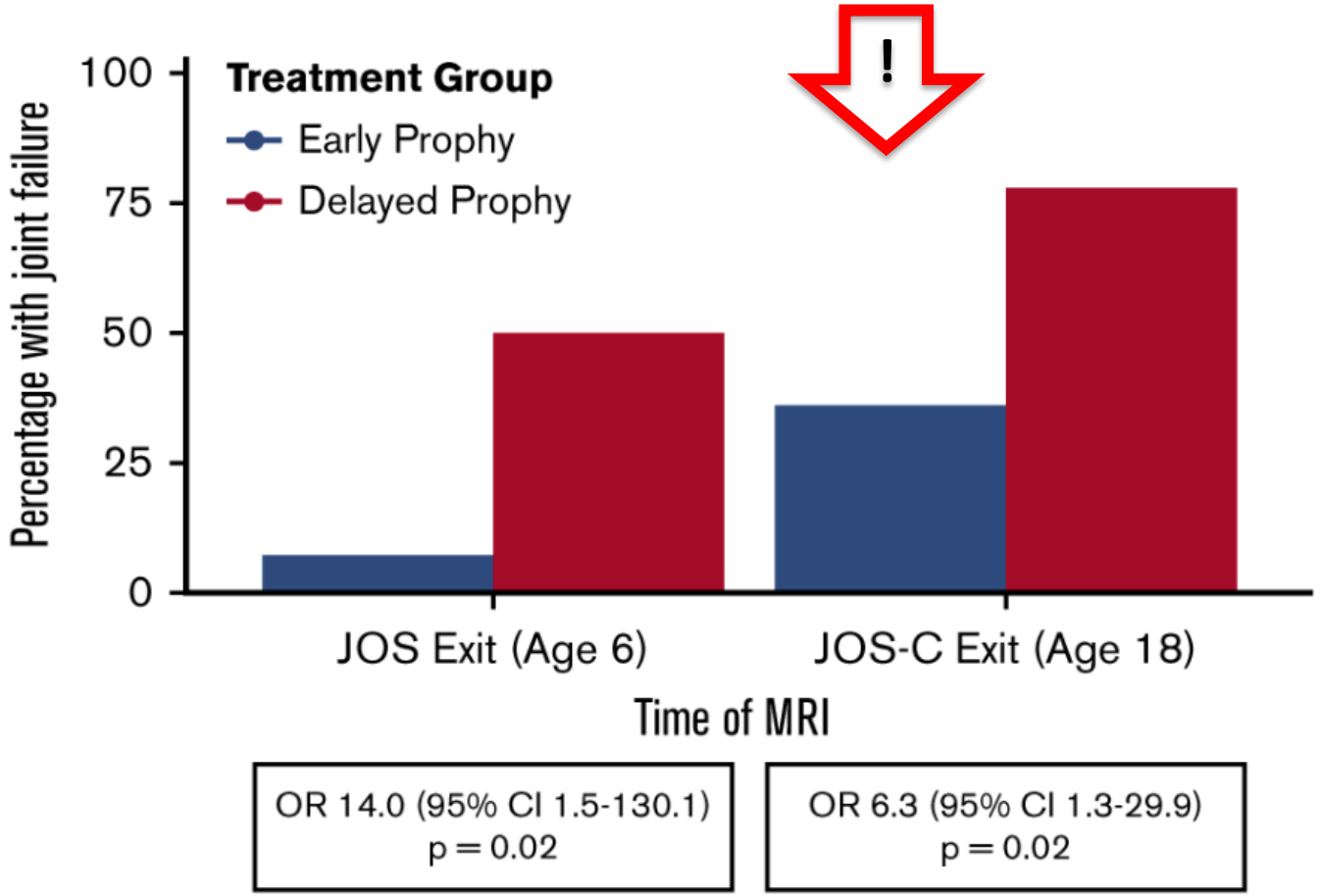
REDUCED BLEEDS WITH HIGHER TROUGH LEVELS

	FAS (N=115)		PPAS (N=95)	
	FVIII trough level 1% to 3% (n=57)	FVIII trough level 8% to 12% (n=53)	FVIII trough level 1% to 3% (n=52)	FVIII trough level 8% to 12% (n=43)
Total ABR				
Mean (SD)	3.6 (7.5)	1.6 (3.4)	2.8 (3.0)	1.2 (2.4)
Median (Q1 to Q3)	2.0 (0.0-4.0)	0.0 (0.0-2.0)	2.0 (0.0-4.0)	0.0 (0.0-2.0)
Spontaneous ABR				
Mean (SD)	2.5 (6.6)	0.7 (1.7)	1.7 (2.5)	0.6 (1.5)
Median (Q1 to Q3)	0.0 (0.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-4.0)	0.0 (0.0-0.0)
Spontaneous joint ABR				
Mean (SD)	2.0 (6.4)	0.5 (1.7)	1.2 (2.0)	0.4 (1.4)
Median (Q1 to Q3)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)
Joint ABR				
Mean (SD)	2.6 (7.4)	1.1 (2.6)	1.8 (2.2)	0.8 (2.3)
Median (Q1 to Q3)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	1.0 (0.0-3.0)	0.0 (0.0-0.0)
ABR of joints ≥4 spontaneous bleeds in 6 consecutive months				
Mean (SD)	1.0 (6.8)	0.4 (1.5)	0.1 (0.6)	0.2 (1.3)
Median (Q1 to Q3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.0 (0.0-0.0)	0.0 (0.0-0.0)
Injury-related ABR				
Mean (SD)	1.1 (2.0)	0.9 (2.6)	1.1 (1.9)	0.7 (1.7)
Median (Q1 to Q3)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)

ABR, annualised bleeding rate; FAS, full analysis set; FVIII, factor VIII; PPAS, per-protocol analysis set; Q, quarter; SD, standard deviation

Klamroth R, et al. Blood. 2021;137(13):1818-1827

PROPHYLAXIS – ARE WE GOOD ENOUGH?

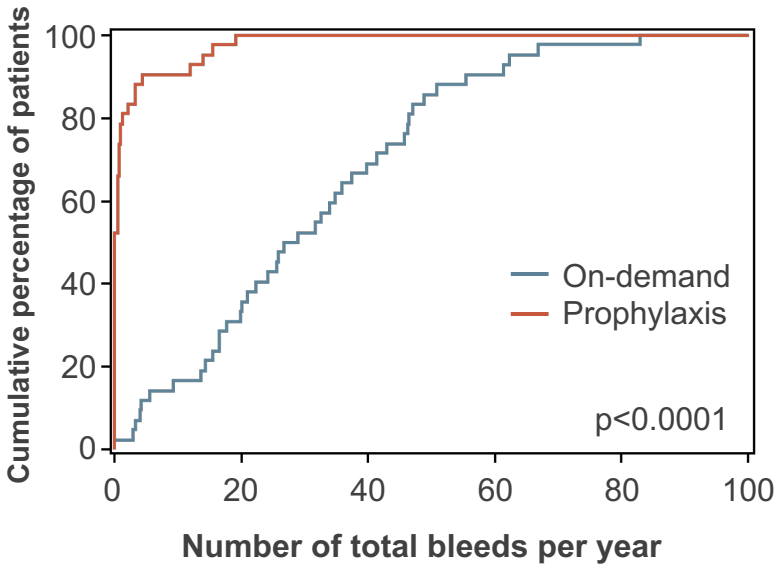


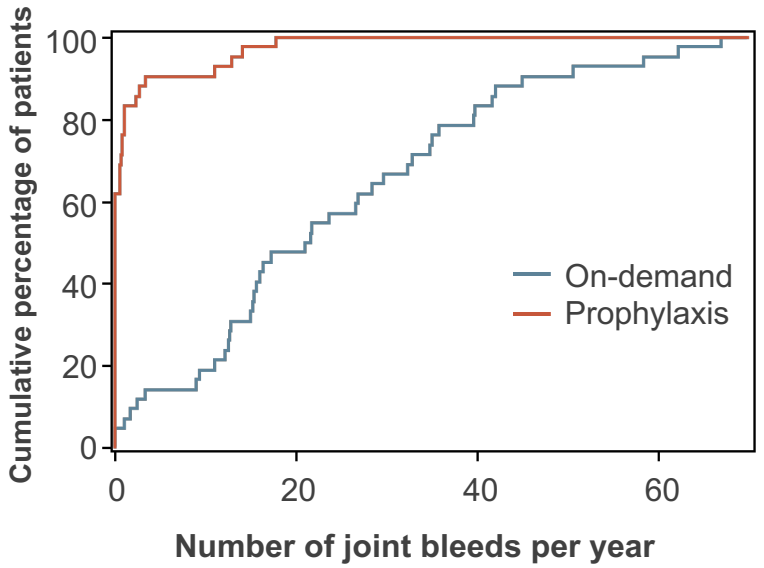
CI, confidence interval; JOS, Joint Outcome Study; JOS-C, Joint Outcome Continuation Study; MRI, magnetic resonance imaging; OR, odds ratio

Warren BB, et al. Blood Adv. 2020;4(11):2451-2459

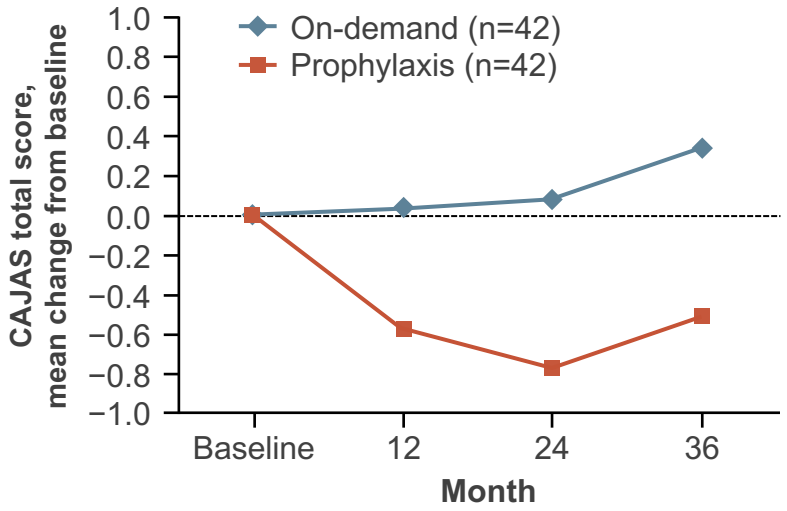
TERTIARY PROPHYLAXIS IN ADULTS

Cumulative distributions of number of total bleeds/joint bleeds per year[1]





Changes over time in CAJAS joint health scores[2]



CAJAS, Colorado Adult Joint Assessment Scale

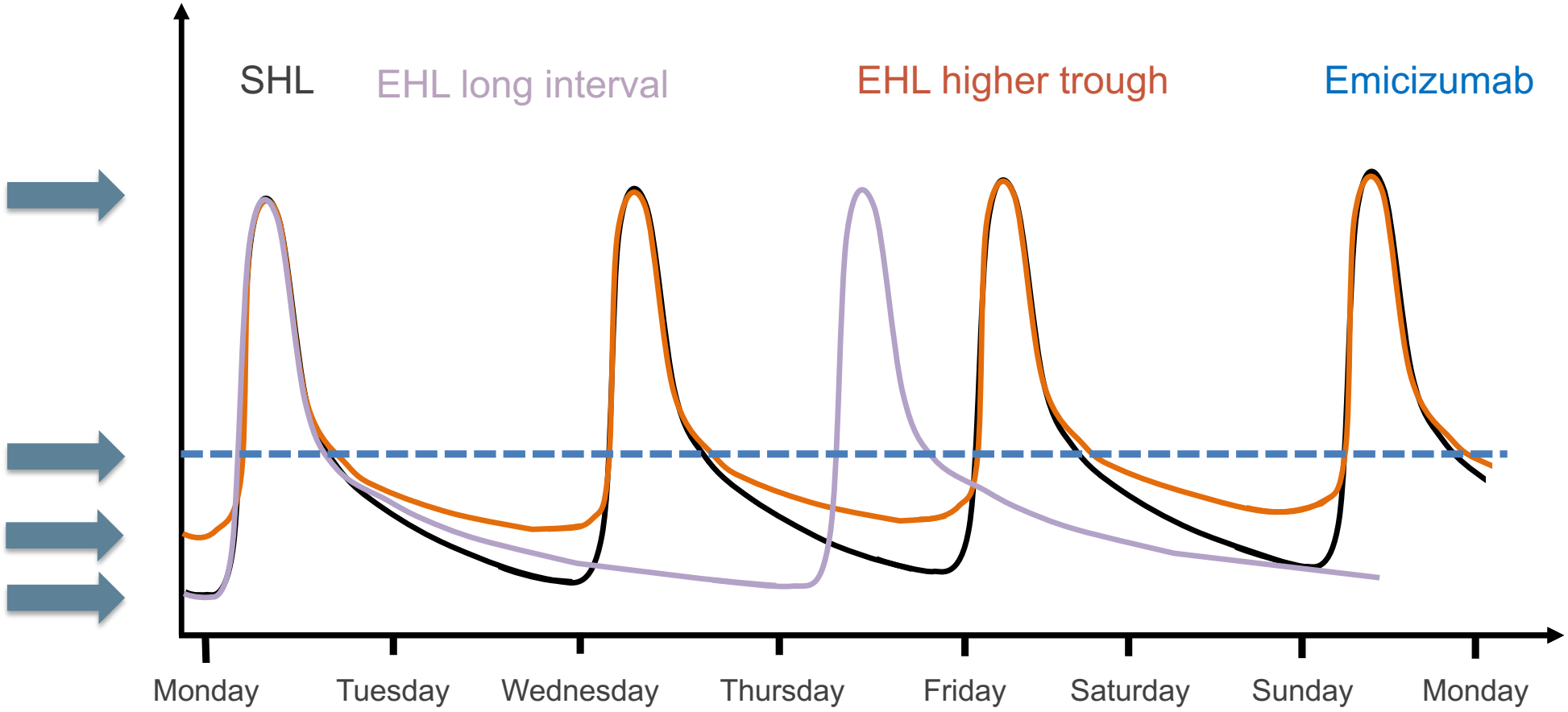
1. Manco Johnson MJ, et al. J Thromb Haemost. 2013;11(6):1119-27; 2. Manco Johnson MJ, et al. J Thromb Haemost. 2017;15(11):2115-2124

CHALLENGES OF FACTOR REPLACEMENT THERAPY

- Pharmacokinetics
- Inhibitor development
- Venous access
- Outcome
- …

- Different challenges in different Individuals
  - Age groups
  - Life circumstances

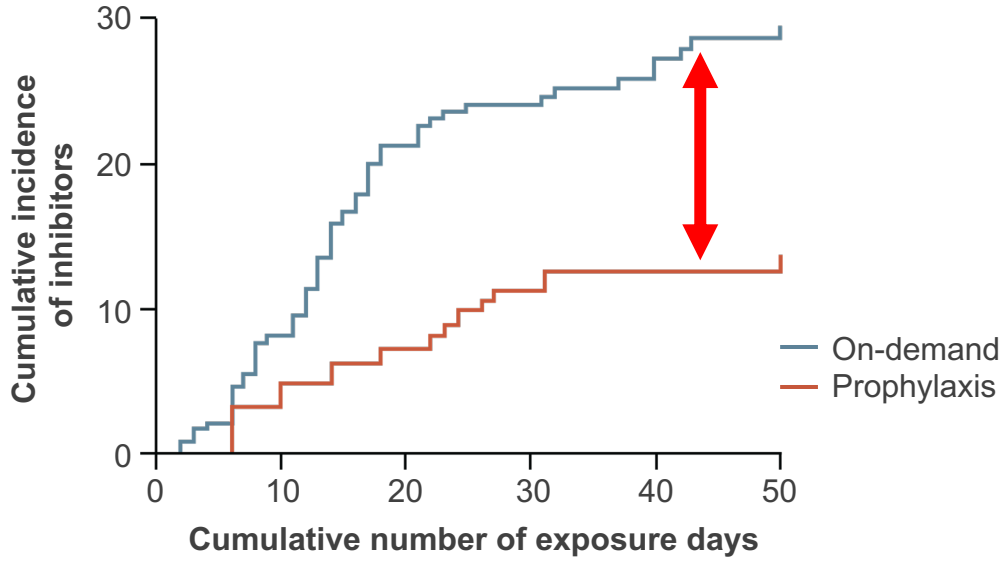
THE UPS AND DOWNS – CHALLENGES AND BENEFITS



EHL, extended half-life; SHL, standard half-life

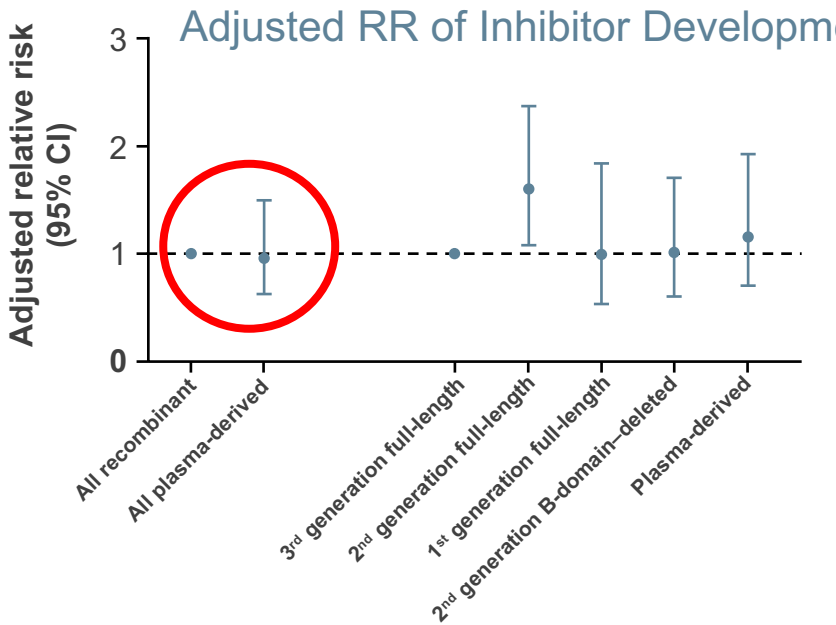
INHIBITOR DEVELOPMENT AND CHOICE OF TREATMENT

Cumulative incidence of inhibitor development[1]

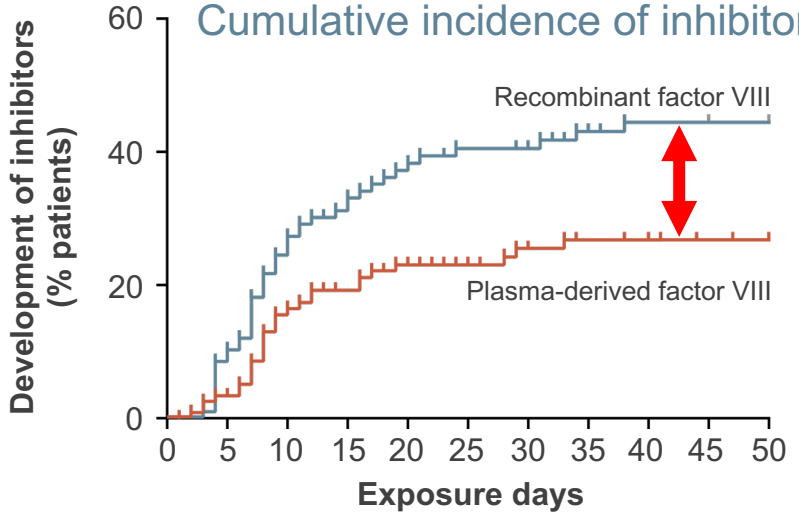


Patients at risk:						
On demand	339	263	177	136	107	89
Prophylaxis	4	54	103	133	157	168

Adjusted RR of Inhibitor Development[2]



Cumulative incidence of inhibitor development[3]



CI, confidence interval; RR, relative risk

1. Gouw SC, et al. Blood. 2007;109:4648-54; 2. Gouw SC, et al. N Eng J Med. 2013;368:231-9; 3. Peyvandi F, et al. N Eng J Med. 2016;374:2054-64

CONCLUSIONS

- Factor replacement therapy is
  - Highly effective for prophylaxis and treatment of bleeds
- Challenging and rewarding
  - Many options and strategies available
- Therapy is much more than factor replacement (or non-replacement)
- Gene therapy not covered in this presentation

NON-FACTOR THERAPIES

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DISCLOSURES

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Expert Disclosures:

- **Prof. Pratima Chowdary** has received financial support/sponsorship for consultation, or speaker fees from the following companies: Bayer, Boehringer Ingelheim, Centessa, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, Sobi and Takeda

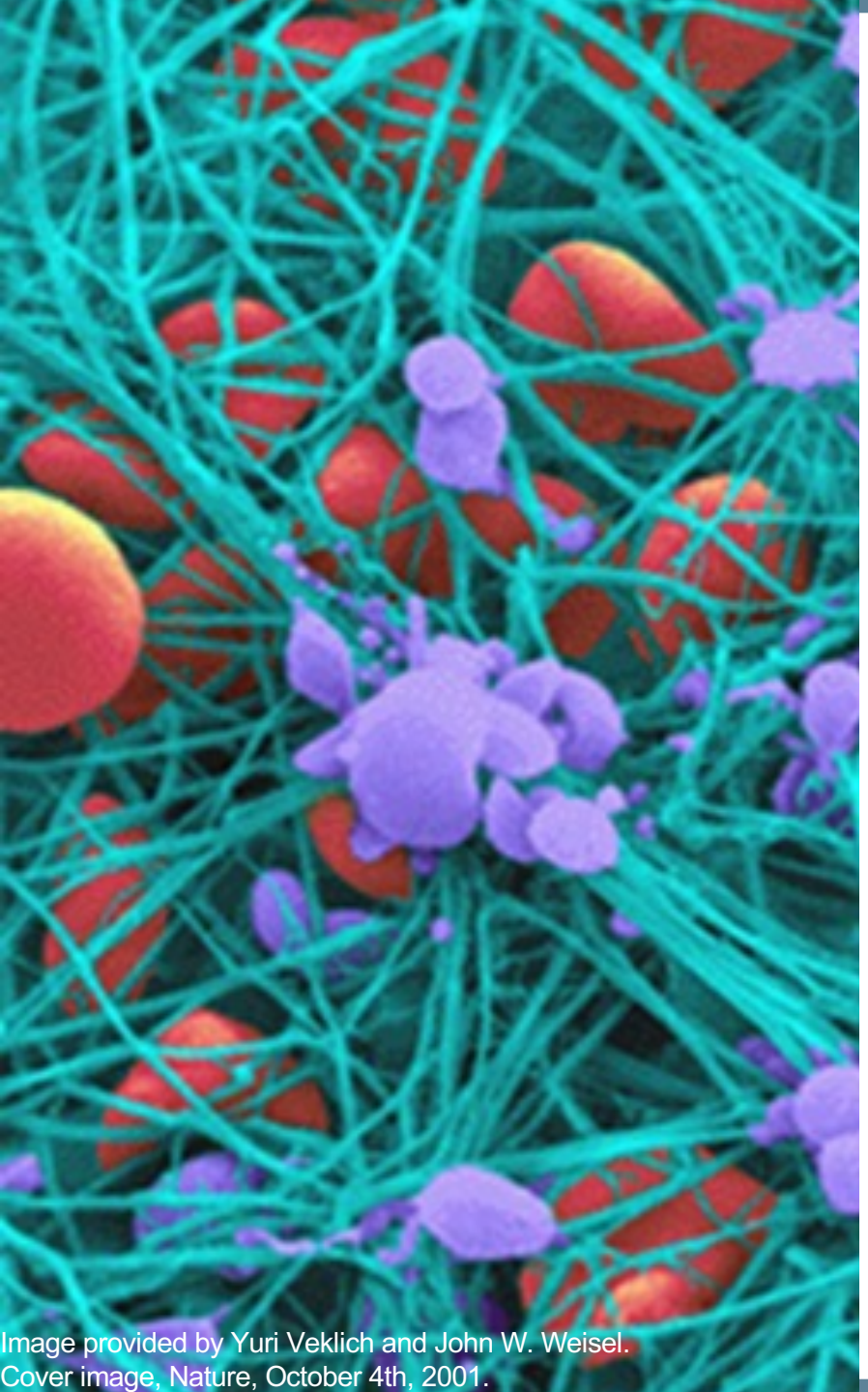


Image provided by Yuri Veklich and John W. Weisel. Cover image, Nature, October 4th, 2001.

NON-FACTOR THERAPIES

Non-factor therapies for haemophilia A

- ***Bispecific antibodies***
  - Emicizumab
  - Mim8

Pan-haemophilia therapies (inhibitors of natural anticoagulants)

- ***Inhibitors of the tissue factor inhibitor pathway (TFPI)***
  - Concizumab
  - Marstacimab
  - Befovacimab (development discontinued)
- ***Antithrombin (inhibitor of serine proteases) knockdown***
  - Fitusiran
- ***Inhibitors of activated protein C***
  - SerpinPC

Swan D, et al. EJHaem. 2022;3(3):584-595.

REPLACEMENT THERAPY WITH FVIII OR FIX CORRECTS THE BLEEDING PHENOTYPE

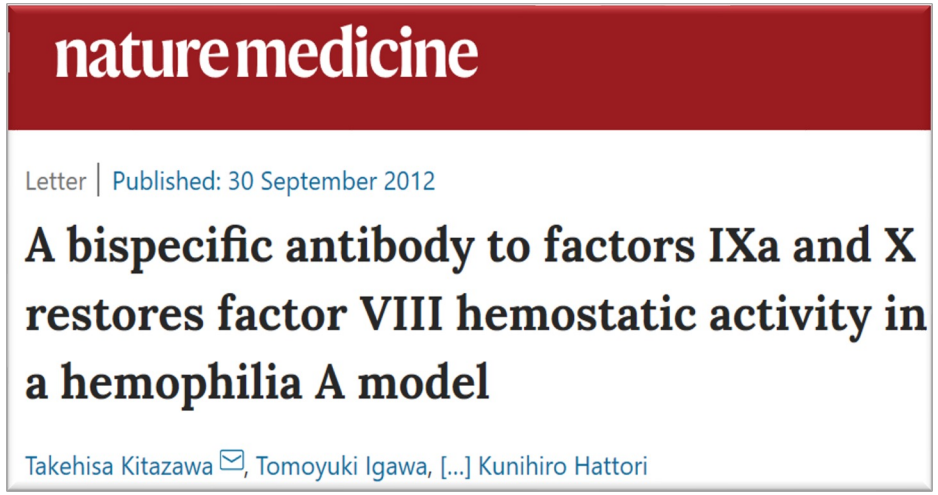
Aim of treatment	GOAL of replacement therapy	Prophylaxis with FVIII or FIX to prevent spontaneous bleeding has been standard of care until 2020
• Decrease **mortality** • Decrease **morbidity** • Improve **quality of life** • Improve participation and **activity**	• Arrest bleeding • **Prevent bleeding** i.e. spontaneous, trauma, activity or surgical • Arrest progression of **joint damage**	• **Prevents** fatal bleeding • **Reduces** joint bleeds and joint damage • **Reduces** spontaneous bleeds • **Decreases** hospital admissions • **Improves** patient outcomes and quality of life

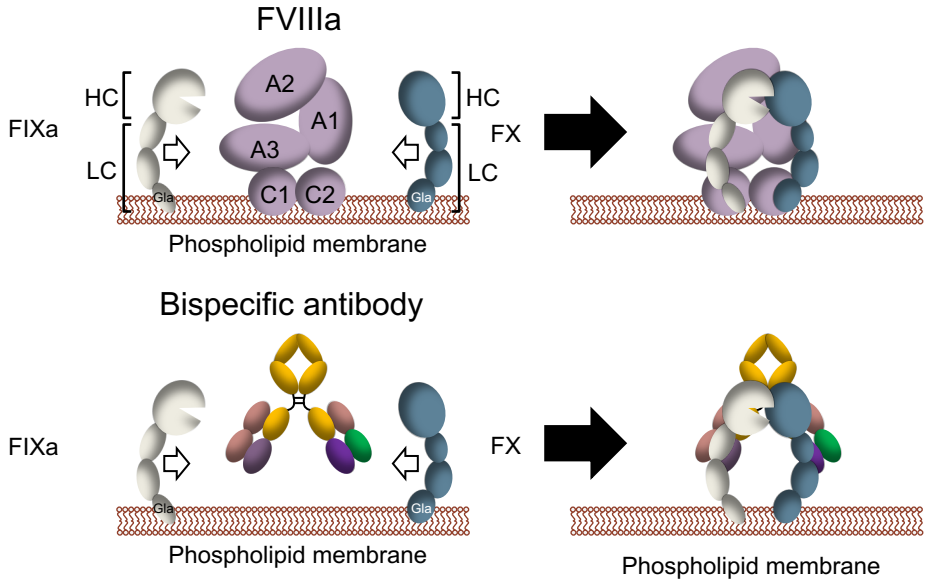
FIX, factor IX; FVIII, factor VIII

Srivastava A, et al. Haemophilia. 2020; 2020;26(Suppl 6):1-158; Morfini M, et al. Blood Transfus. 2013;11 Suppl 4(Suppl 4):s55-63; Löfqvist T, et al. J Intern Med. 1997;241(5):395-400; Collins P, et al. Haemophilia. 2016;22:487-498; Astermark J, et al. Br J Haematol. 1999;105(4):1109-13; Aledort LM, et al. J Intern Med. 1994;236(4):391-9

FACTOR VIIIa MIMETIC: EMICIZUMAB

- Bispecific IgG antibody, which is FVIIIa mimetic that binds to FIXa and FX
- Hypothesis – Spatial co-location of FIXa and FX should result in activation of the FX
- Distance between two antigen-binding sites of human IgG similar to the distance between FIXa and FX binding sites of FVIIIa
- 40,000 bispecific antibodies for FX activation in the presence of FIXa and phospholipid were screened

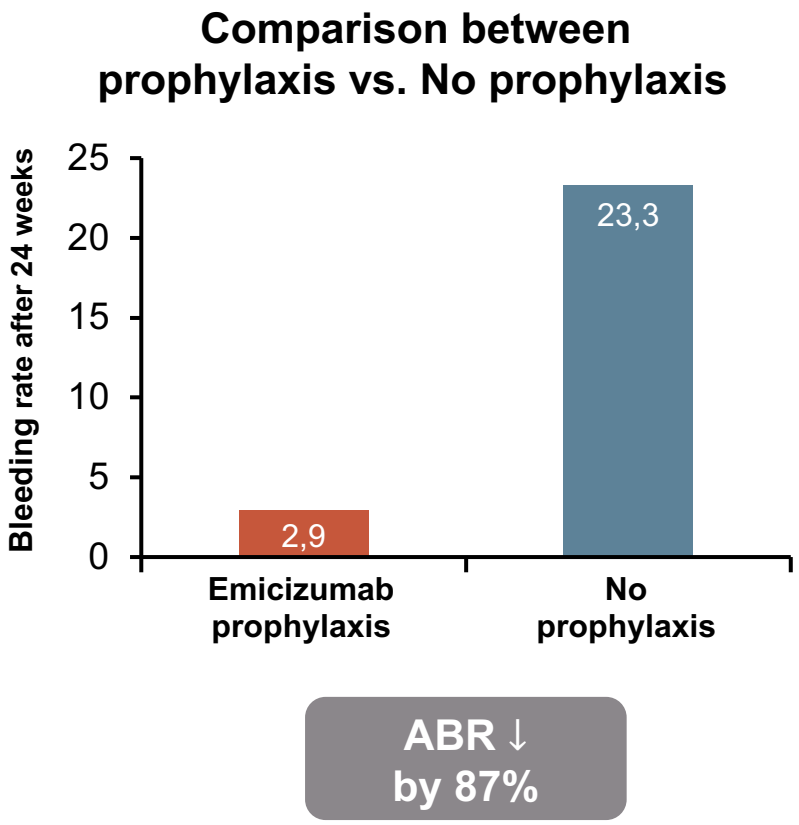




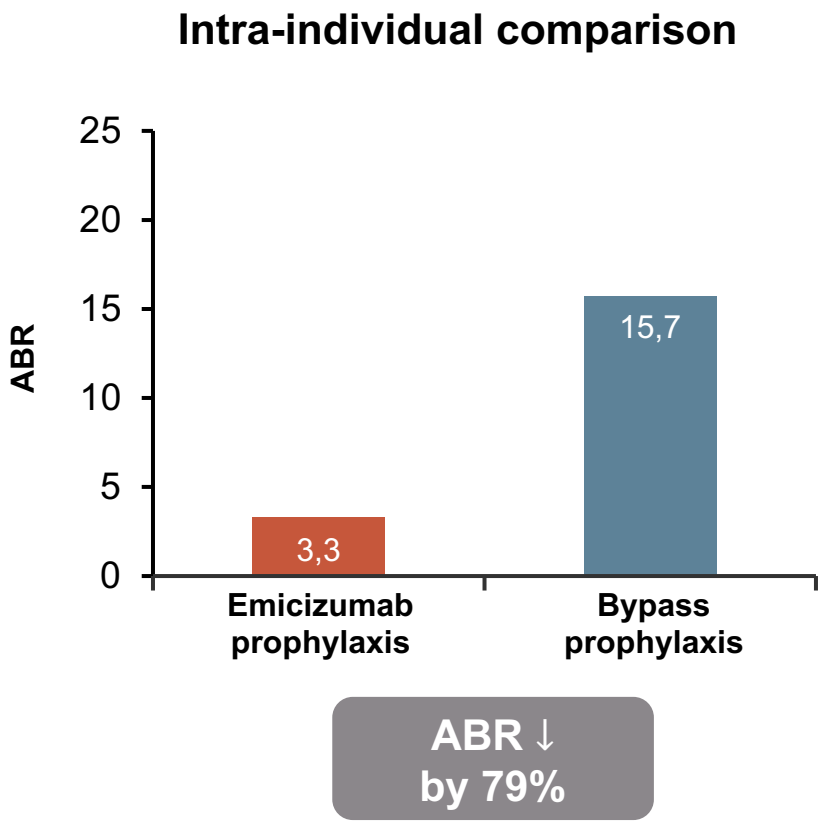
FIXa, activated factor IX; FVIIIa, activated FVIII; FX, factor X; HC, heavy chain; IgG, immunoglobulin G; LC, light chain

Adapted from Kitazawa T, et al. Nat Med. 2012;18(10):1570-4

PHASE 3 STUDY OF EMICIZUMAB IN SHA WITH INHIBITORS



ABR ↓ by 87%



ABR ↓ by 79%

On emicizumab prophylaxis - 63% had no bleeds
On episodic treatment - 6% had no bleeds

Emicizumab prophylaxis superior to on-demand treatment & prophylaxis with bypassing agents

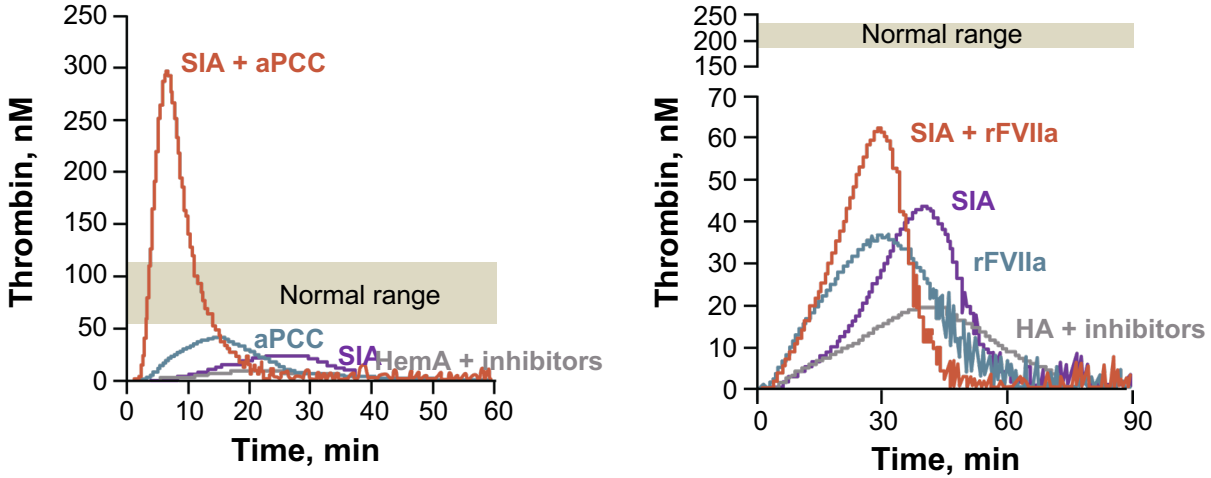
ABR, annualised bleeding rate; SHA, severe haemophilia A

Oldenburg J, et al. N Engl J Med. 2017;377:809-18

THROMBOSIS WAS AN UNEXPECTED ADVERSE EVENT DUE TO A DRUG- DRUG INTERACTION WITH APCC!

- Five episodes of thrombotic microangiopathy and thrombotic events were reported in SHA with inhibitor trial[1,2]
- Restricted to patients receiving activated prothrombin complex concentrates (aPCC) >100 U/kg daily for ≥24 hours[2]
- Unexpected drug-drug interaction[1]
- No events were seen with rFVIIa[2]

In vitro spiking experiments with Sequence-identical analogue of emicizumab (SIA) with aPCC and rFVIIa[3]



SIA with aPCC (0.5 U/mL) increased the peak thrombin level 17-fold over SIA alone, 4.2-fold greater than reference[3]

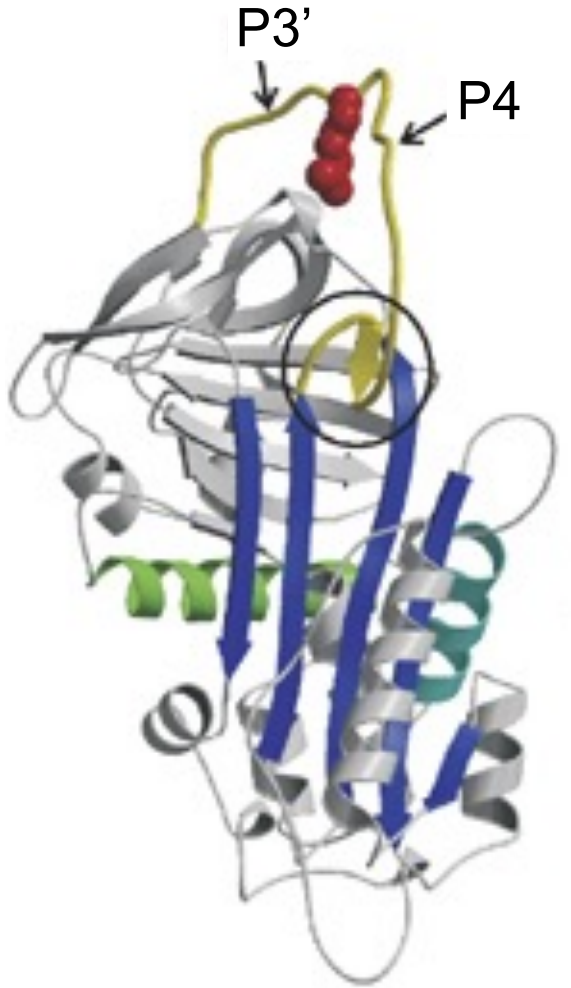
Emicizumab has only partial co-factor activity, with low affinity for enzyme and substrate, and no on/off regulation; the amount of FIXa is rate limiting[4]

APCC, activated prothrombin complex concentrate; FIXa, activated factor IX; rFVIIa, recombinant activated factor VII; HA, haemophilia A; SHA, severe haemophilia A

1. Oldenburg J, et al. N Engl J Med. 2017;377:809-18; 2. Levy GG, et al. J Thromb Haemost. 2019;17(9):1470-1477; 3. Hartmann R, et al. J Thromb Haemost. 2018. doi: 10.1111/jth.14203. Online ahead of print 4. Lenting PJ, et al. Blood. 2017;130(23):2463-2468

ANTITHROMBIN (AT)

- AT is the principal inhibitor of the coagulation serine proteases – irreversible inhibition
- The primary targets are FXa and thrombin
- AT also inactivates FIXa, FXIa, and FXIIa
- Thrombin is 10-fold more sensitive to inhibition than FXa
- *In vivo* activation of AT is mediated by heparan sulphate and other glycosaminoglycans



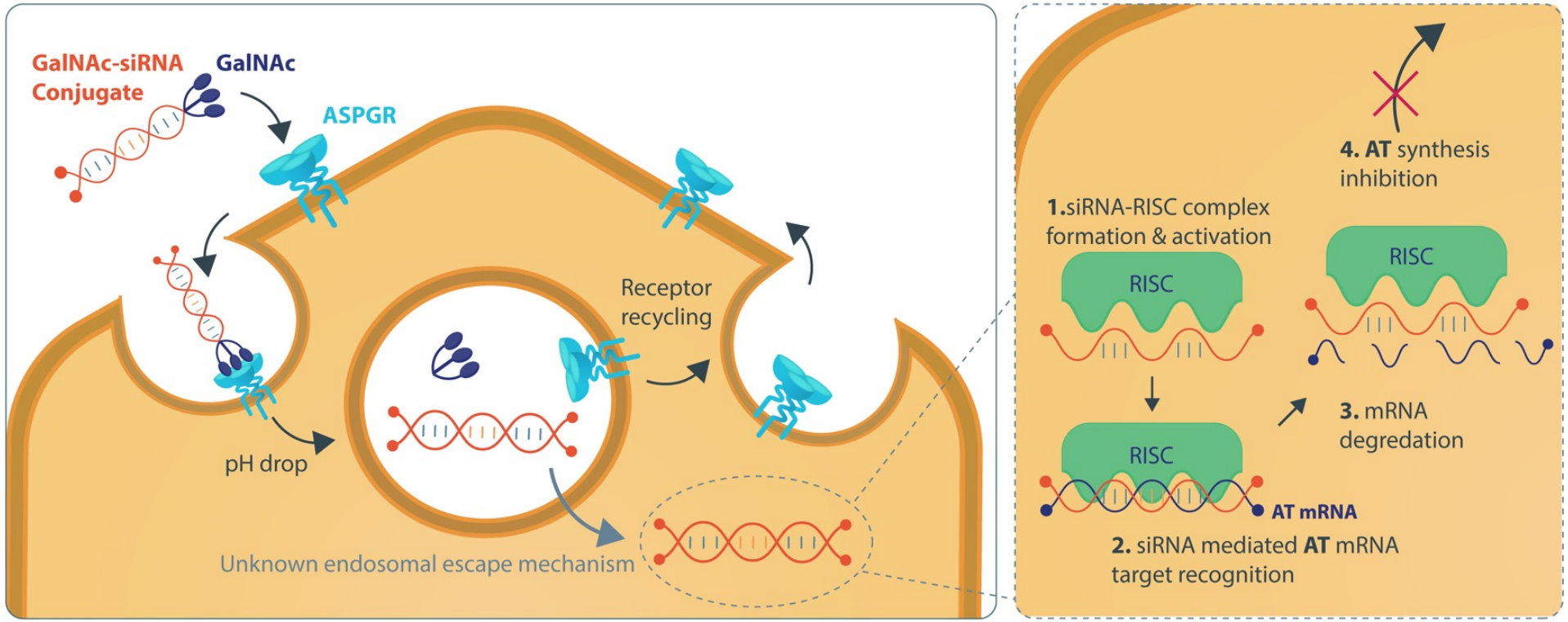
AT, antithrombin; FIXa, activated factor IX; FXa, activated factor X; FXIa, activated factor XI

Almonte AG, Sweatt JD. Brain Res. 2011;1407:107-22; Bäck J et al.. Biomaterials. 2009;30(34):6573-80; Johnson DJ, et al. EMBO J. 2006;25(9):2029-37.

Figure adapted from: Johnson DJ, et al. EMBO J. 2006;25(9):2029-37

FITUSIRAN IS A NUCLEIC ACID THERAPY BASED ON RNAi THAT DECREASES ANTITHROMBIN (AT)

- RNA interference (RNAi) - intracellular regulatory process that results in post-transcriptional gene silencing[1]
- Small interfering RNA (siRNA) are double-stranded RNAs (21–23 base pairs) that trigger RNAi machinery with degradation of target mRNA[1,2]
- Fitusiran is double-stranded siRNA, modified (GalNAc-siRNA conjugate) to facilitate hepatocyte entry via specific receptors (ASGPRs)[3,4]
- Targets AT mRNA for degradation through RNA-induced silencing complex (RISC) and the reduction in AT is dose dependent[3,5]



ASGPR, asialoglycoprotein receptor; AT, antithrombin; mRNA, messenger RNA; RNAi, RNA interference. Adapted from: Springer AD, Dowdy SF. Nucleic Acid Ther. 2018 Jun;28(3):109-118; Okaygoun D, et al. J Biomed Sci. 2021;28(1):64; Jeon JY. Pharm Res 2022.1. Zhang L, et al. Front Pharmacol. 2022;13:1090237; 2. Robinson R. PLoS Biol. 2004;2(1):E28; 3. Butterfield JSS, et al. Mol Ther. 2020;28(4):997-1015; 4. Springer AD, Dowdy SF. Nucleic Acid Ther. 2018 Jun;28(3):109-118; 5. Okaygoun D, et al. J Biomed Sci. 2021;28(1):64

AT KNOCKDOWN IN HAEMOPHILIA A OR B *WITH* INHIBITORS – FITUSIRAN PHASE 3 RESULTS

Randomised, open-label study (n=57)

- Fitusiran 80 mg, (N=38)
- Bypassing agents on-demand, (N=19)

All treated bleeds Fitusiran vs. bypass

Estimated mean ABR 1.67 vs. 18.07

(p<0.0001)

Treated spontaneous bleeds

Estimated mean ABR 0.87 vs. 15.68

(p<0.0001)

Patients with Zero treated bleeding events

On fitusiran prophylaxis 65.8%

Adverse events

- Thrombotic events in two patients
- Elevated liver function tests

ABR, annualised bleeding rate; AT, antithrombin;

Young G, et al. Blood (2021) 138 (Supplement 1): 4. Presented at ASH December 2021. https://doi.org/10.1182/blood-2021-150273 (last accessed: August 2023);
Young G, et al. Lancet. 2023;401(10386):1427-1437.

FITUSIRAN DOSING AMENDED TO MITIGATE THROMBOSIS RISK

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

Thromboembolism	Possible cause and associated factor
5 events:	
1 cerebral sinus thrombosis	AT 10-20%, concomitant repeated FVIII, tobacco use
1 atrial thrombosis	AT 10-20%, concomitant repeated FVIIa
1 cerebral infarct	AT <10%, recent prostate cancer
1 cerebrovascular accident	AT <10%, history of DVT, diabetes, active smoker
1 spinal artery thrombosis	AT <10%, spinal injury, vascular disorder

Starting dose
- 50 mg dose every other month

Target steady-state AT levels
- 15% and 35%

Dosing is to be discontinued
- Two AT levels <15%

Dosing to be increased
- AT > 35% at steady state

Two potential regimens
- 50 mg or 80 mg monthly

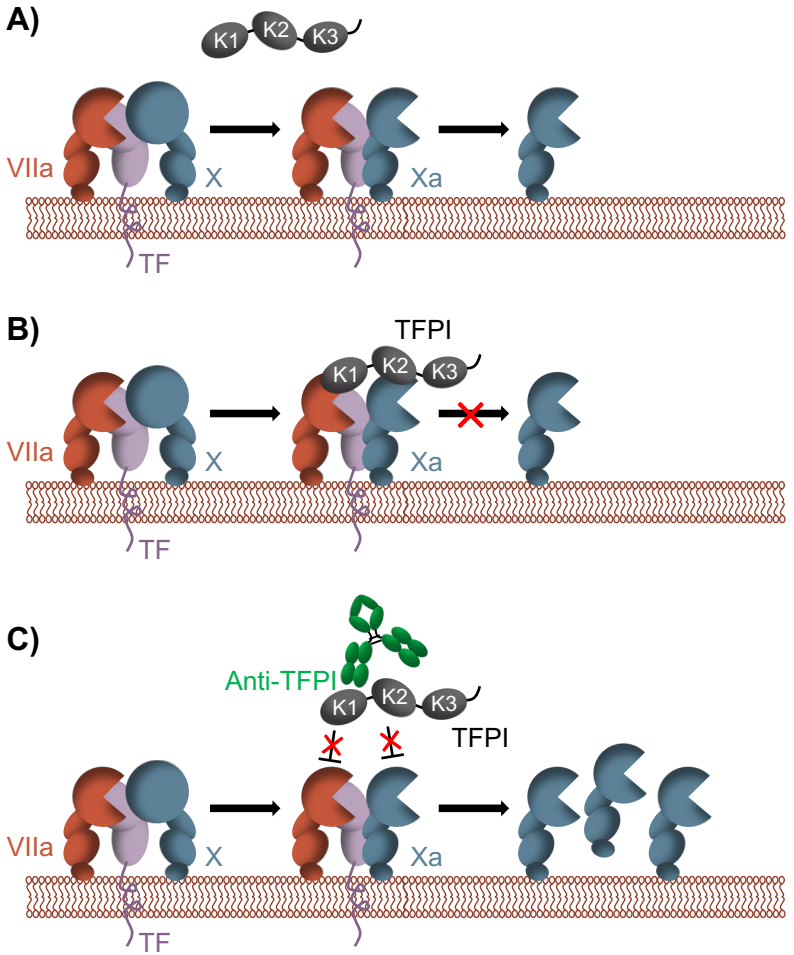
AT, antithrombin; DVT, deep vein thrombosis; FVIIa, activated FVII; FVIII(a), (activated) factor VIII

https://www.hemophilia.org/news/sanofi-revises-fitusiran-dosing-regimen-to-mitigate-risk-of-vascular-thrombosis (last accessed: August 2023)

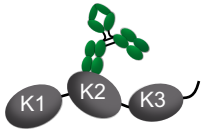
Gualtierotti R, et al. Pharmaceuticals (Basel). 2022;15(10):1183; Pipe S. W., et al. ISTH 2022

MONOCLONAL ANTIBODIES AGAINST TFPI

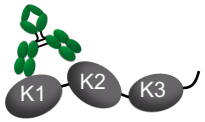
- Concizumab (Novo Nordisk), Marstacimab (Pfizer) and Befovacimab (Bayer)[1]
- Inhibition of TFPI increases thrombin output through the initiation pathway[1-3]



Anti-TFPI antibody against K2 domain
Concizumab and PF-06741086 from Pfizer



Anti-TFPI antibody against K1 and K2 domain
BAY-1093884 from Bayer



TFPI mechanism of action and inhibition by anti-TFPI antibodies; **A)** Tissue factor (TF) based initiation of coagulation and generation of FXa by the extrinsic tenase complex (FVIIa.TF.FX); **B)** Inhibition of FXa and FVIIa by TFPI; **C)** Binding of the different Kunitz (K) domains by the various anti-TFPI antibodies

FVIIa, activated factor VII; FX(a), (activated) factor X; K, Kunitz domain; TF, tissue factor; TFPI, tissue factor pathway inhibitor Adapted from Chowdary P. (2018) 1. Chowdary P. Drugs. 2018;78(9):881-890; 2. Wood JP, et al. Proc Natl Acad Sci U S A. 2013;110(44):17838-43; 3. Mast AE. Arterioscler Thromb Vasc Biol. 2016;36(1):9-14

OVERVIEW OF THROMBOTIC CASES IN CONCIZUMAB EXPLORER7 AND EXPLORER8 TRIALS

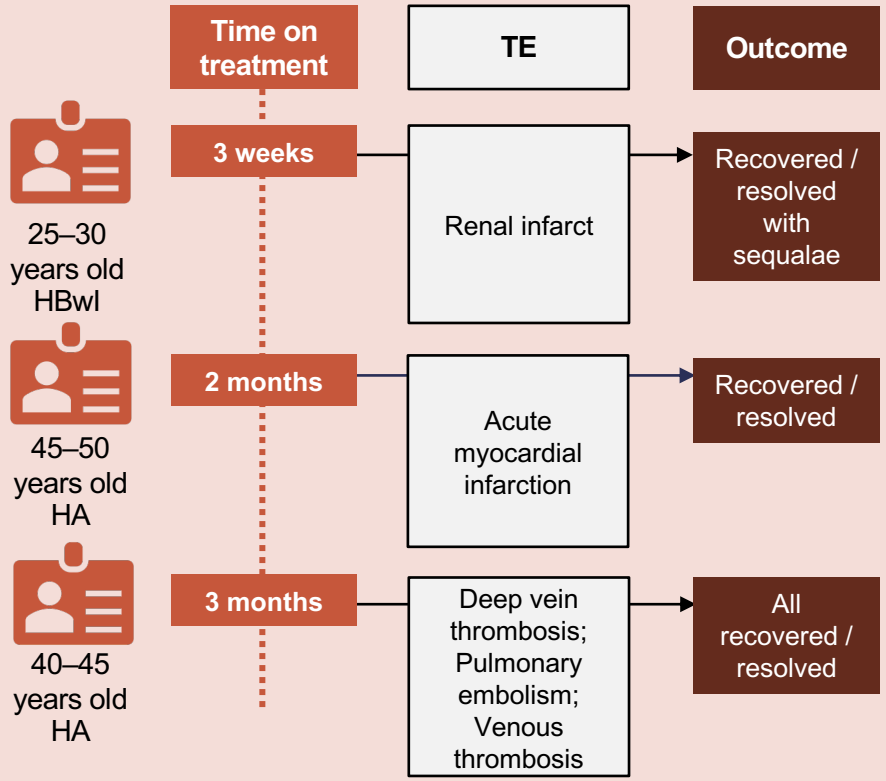
Phase 3 pivotal study[1]

Dosing strategy[1] – Loading dose of 1 mg/kg and maintenance dose of 0.25 mg/kg

Three patients reported three thrombotic events, resulting in a study pause and evaluation of the trial data[1]

All had thrombotic risk factors at baseline and had used concomitant haemostatic medication on the day of/days up to event onset[1]

Overview of thrombotic cases in concizumab explorer7 and explorer8 trials[2]



A risk mitigation strategy was developed, and the study restarted

HA, haemophilia A; HBwI, haemophilia B with inhibitors; TE, thrombotic event

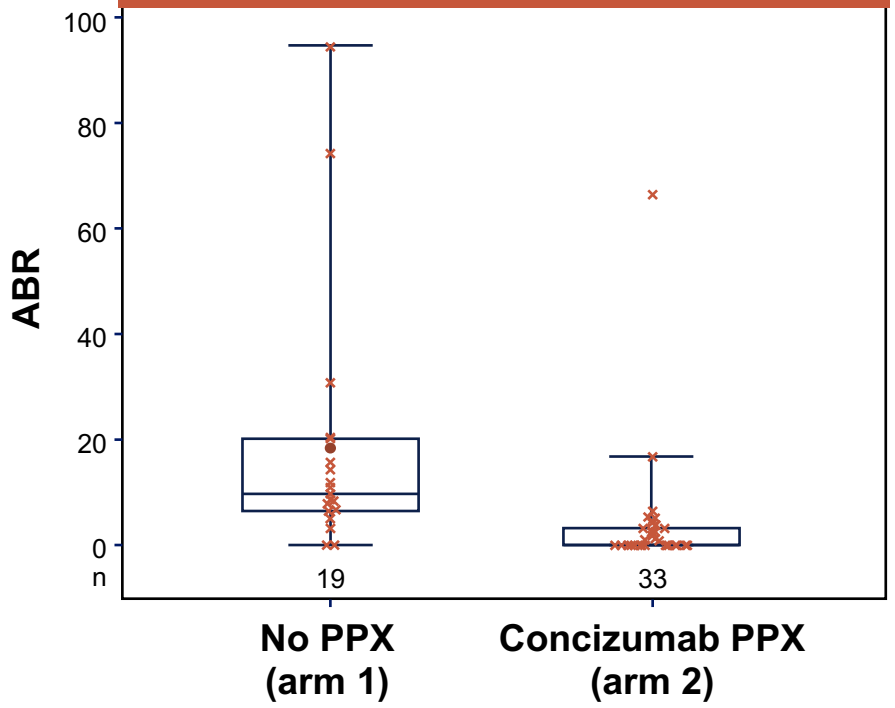
1. Seremetis SV, et al. Blood 2020;136(S1):40; 2. Seremetis S, et al. Poster 1796 presented at the 62nd American Society of Hematology Annual Meeting 2020. https://doi.org/10.1182/blood-2020-139563 (last accessed: August 2023). Patient-specific thrombotic data from poster not verified.

CONCIZUMAB – PHASE 3 CLINICAL TRIAL RESULTS IN HA AND HB PATIENTS *WITH* INHIBITORS

	No PPX	Concizumab PPX	
Treatment arm	**Arm 1**	**Arm 2**	**Arms 2–4[a]**
Patients in FAS, n	19	33	114
Median ABR (IQR)	**9.8 (6.5–20.2)**	**0 (0–3.3)**	0 (0–3.3)
Estimated mean ABR (95% CI)	**11.8 (7.0–19.9)**	**1.7 (1.0–2.9)**	

63.6% of patients receiving concizumab prophylaxis had zero bleeding episodes

ABR – treated spontaneous and traumatic bleeding episodes



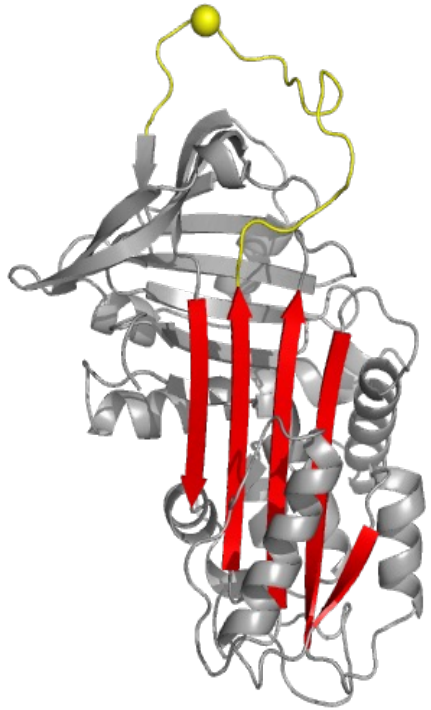
Min/Max Whiskers = 5th/95th percentile.

ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; HA/B, haemophilia A/B; IQR, interquartile range; PPX, prophylaxis.

Matsushita T, et al. N Engl J Med. 2023;389(9):783-794; Jiménez-Yuste V, et al. Presented at ISTH 2022. Abstract (LB 01.2) available at: https://abstracts.isth.org/abstract/concizumab-prophylaxis-in-patients-with-haemophilia-a-or-b-with-inhibitors-efficacy-and-safety-results-from-the-primary-analysis-of-the-phase-3-explorer7-trial/ (last accessed: August 2023); ClinicalTrials.gov/NCT04083781: Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04083781 (last accessed: September 2023)

ACTIVATED PROTEIN C (APC) AND SerpinPC

- APC is the principal inhibitor of co-factors FVa and FVIIIa
- The signalling and anticoagulant functions of APC are in spatially and kinetically distinct compartments
- Inhibition of APC restores thrombin generation



3D-model of SerpinPC

- SerpinPC – engineered serine protease inhibitor
  - Modified α1 anti-trypsin with substitution mutations and a replacement serpine scaffold to confer selective inhibition of APC
  - High degree of specificity for APC
  - Half-life of 5 to 7 days
  - Administered subcutaneously
- The inhibition of APC prolongs prothrombinase activity and sufficient thrombin generation
- Phase 1 studies (NCT04073498) have been completed

FVa, activated factor V; FVIII, activated factor VIII

Polderdijk SGI, et al. Curr Opin Hematol. 2017;24(5):446-452; Polderdijk SG, et al. Blood. 2017;129(1):105-113; Weyand AC, Blood 2019;133(5):389–398

BENEFITS OF NON-FACTOR THERAPIES

Increased access to effective treatment

- As effective as FVIII/FIX for bleed prevention[1]
- Effective prophylaxis in haemophilia A patients with FVIII inhibitors or FIX inhibitors[1]
- Can potentially convert from a severe to mild phenotype[1]

Decreased treatment burden

- Subcutaneous administration – ease of use
- Potentially longer half-life[1,2]
- Simpler regimens[1]
  - Less disruption
  - Fewer rules
  - Less burdensome to patients

FIX; factor IX; FVIII, factor VIII

1. Chowdary P. Hamostaseologie. 2021;41:47-256; 2. Laffan MA. Br J Haematol. 2016;172:23-31

CONCLUSIONS

- Restoration of thrombin generation is now an established treatment strategy
- Several gains – principally
  - Effective treatment for SHA and SHB patients with inhibitors
  - Reduction in treatment burden
- Potential challenges and pitfalls
  - Risk of thrombosis
  - Lack of new monitoring strategies and outcome tools to account for new treatment targets
  - Change in natural history of the disease
- More opportunities
  - Expansion of indications
  - Potential for combination therapies

HA/B, haemophilia A/B

INHIBITORS IN HEMOPHILIA – TOLERANCE TOWARDS THE DEFICIENT FACTOR?

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DISCLOSURES

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions.

Expert Disclosures:

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WHAT DO WE KNOW ABOUT INHIBITOR DEVELOPMENT (THE IMMUNE REACTION TOWARDS THE DEFICIENT FACTOR)

- **Inhibitor formation** is a frequent but multifactorial **immune reaction** of replacement therapy in patients providing immunogenic epitopes[1]
- Studies in **PUPs** with novel therapies require time to collect **meaningful clinical data**[2]
- **Non-replacement therapies** will not provide **normal haemostasis** and interindividual variations in haemostatic capacity are to be expected – additional **factor treatment** required in specific situations e.g. severe trauma / major surgery[3,4]
- So far, there is not enough evidence to support that **inhibitors** can be avoided by postponing **FVIII exposure** in the young child (e.g. by using rFVIIa)[5]
- **Mortality and morbidity** have been higher among severe and non-severe haemophilia A patients with inhibitor[2]
- Rate of **adverse events** in HB 10-fold higher than in HA, e.g. anaphylaxis and nephrosis[5]

FVIII, factor VIII; HA, haemophilia A; HB, haemophilia B; PUP: previously untreated patient

1. Astermark J, et al. Blood. 2015;125(13):2045-51; 2. Le Quellec S, et al. Drug Des Devel Ther. 2020;14: 469-81; 3. Parisi L and Kumar A. Treasure Island (FL): StatPearls Publishing; 2023 Jul; 4. Lewandowska M, et al. Haemophilia. 2021;27(1):90-99; 5. Rivard G, et al. Haemophilia. 2005;11(4):335-9

THEORIES ON WHY INHIBITORS DEVELOP

Discrimination of self vs non-self

- An immune response is triggered against all foreign (“non-self”) entities, whereas no immune response is triggered against the organism's own constituents (“self”)
- Immunologists still think of the immune system within this framework, even though this theory may be interpreted as fundamentally flawed

Danger Theory

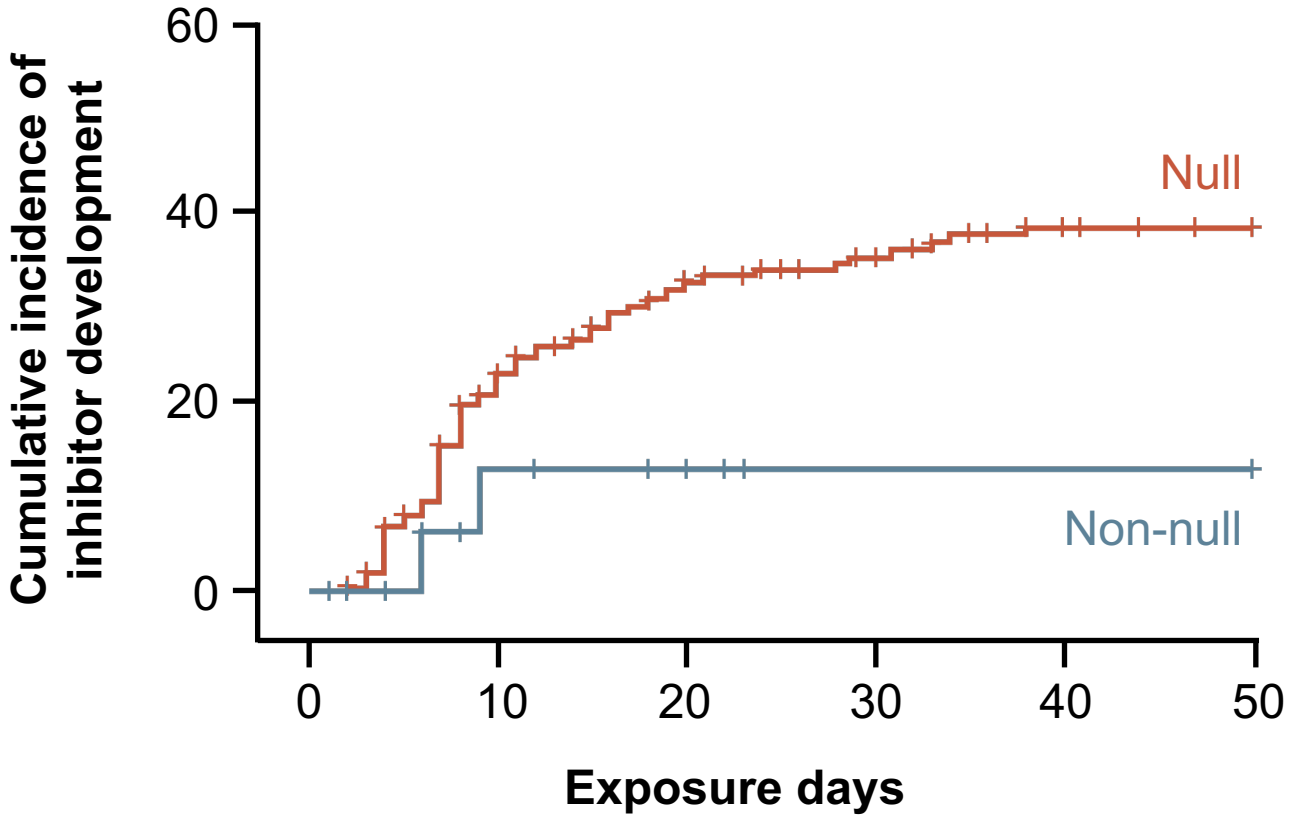
- Self constituents can trigger an immune response, if they are dangerous (e.g., cellular stress) and non-self constituents can be tolerated, if they are not dangerous (e.g., the fetus). The proper opposition to determine why an immune response is triggered is the presence or absence of danger, released by the body's own cells. According to the danger theory every immune response is not due to the presence of “non-self” (i.e., genetically foreign entities), but to the emission, within the organism, of “danger signals”

Discontinuity Theory

- The immune system responds to sudden changes in antigenic stimulation and is rendered tolerant by slow or continuous stimulation

Pradeau T and Cooper EL. Front Immunol. 2012;3:287
Pradeau T and Vivier E. Sci Immunol. 2016 Jul 14;1(1):AAG0479

A RESIDUAL FACTOR VIII SYNTHESIS IS LIKELY TO BE PROTECTIVE TOWARDS INHIBITOR DEVELOPMENT



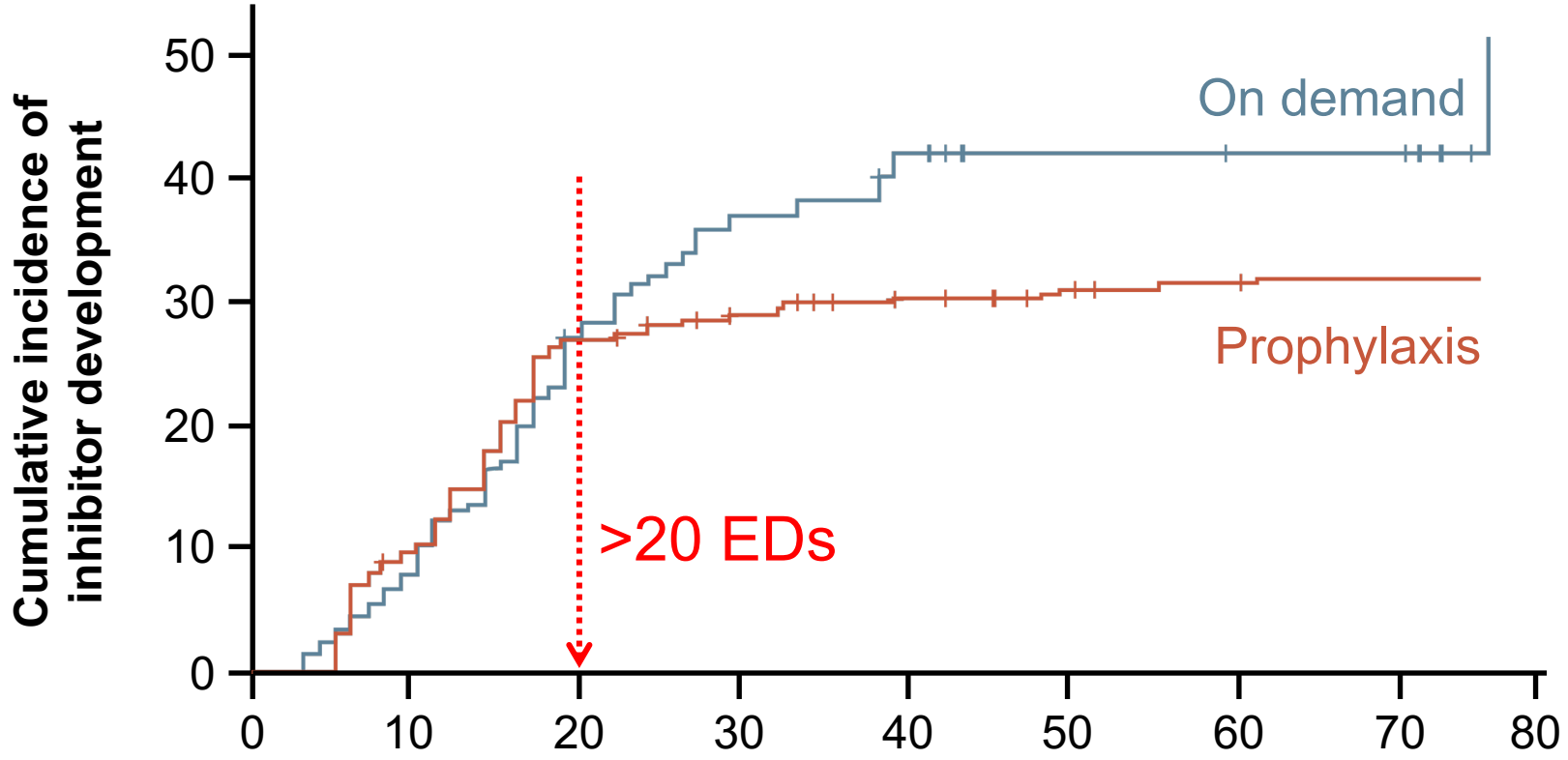
- **Null mutations** = FVIII:Ag <1%
- **Non-null mutations** = FVIII:Ag ≥1%

- Three times higher **risk** of developing **inhibitor** if unmeasurable FVIII: Ag in plasma

FVIII:Ag, factor VIII coagulant antigen

Spena S, et al. J Thromb Haemost. 2018;16:778-790. Data from the SIPPET study.

THE EFFECT OF PROPHYLAXIS ON INHIBITOR RISK

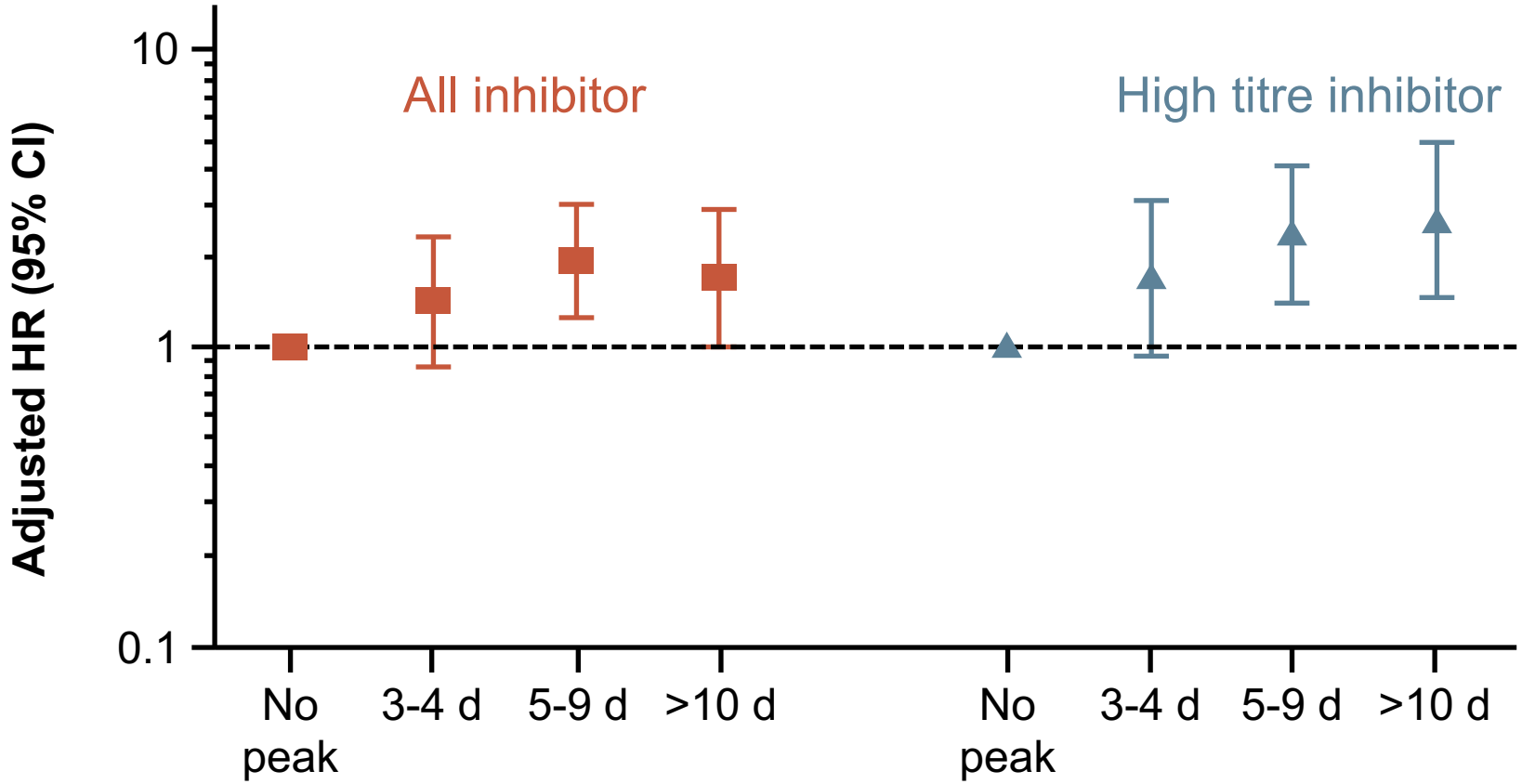


Patients at risk:									
On demand	513	254	109	56	28	18	10	10	6
Prophylaxis	0	123	218	274	298	311	320	327	329

ED, exposure day

Gouw SC, et al. Blood. 2013;121(20):4046-55

INTENSITY OF TREATMENT AT FIRST EXPOSURE VS INHIBITOR DEVELOPMENT



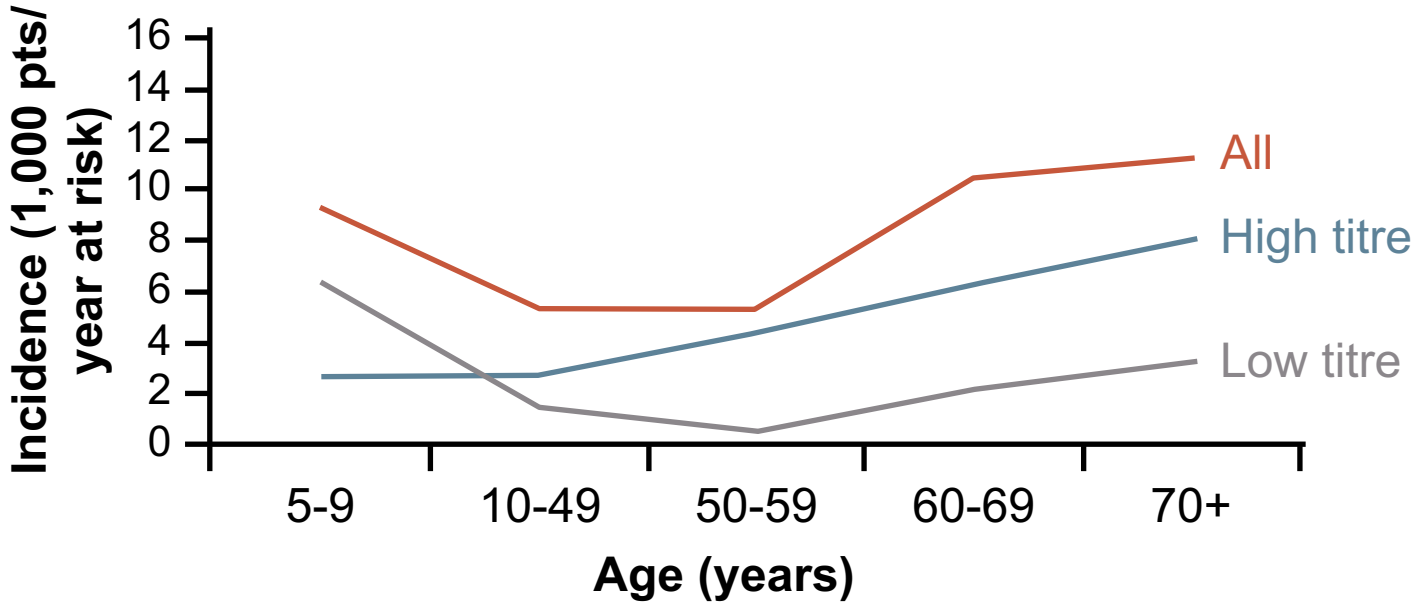
- Adjusted for ethnicity, *F8* gene mutation type, family history inhibitors, factor VIII product type, surgery

CI, confidence interval; d, days; F8, factor VIII (gene); HR, hazard ratio

Gouw SC, et al. Blood. 2013;121(20):4046-55

FACTOR VIII INHIBITORS IN THE ELDERLY

A **second peak** of **inhibitors** has been reported in patients with severe HA **aged >50 yrs** in the United Kingdom[1]



- A retrospective survey-based study of all patients with HA or HB aged ≥40 yrs treated at Advance Haemophilia Treatment Centres in Europe did not identify a second peak of inhibitors[2]
- Most patients with a late-onset inhibitor in the study had undergone surgery or had an infection or significant trauma in the 3 months preceding the inhibitor detection[2]
- Prophylaxis with a FVIII replacement in patients with severe, and possibly also moderate haemophilia A, may help to retain a tolerant state during older age[1,2]

FVIII, factor VIII; HA, haemophilia A; HB, haemophilia B; yrs, years

1. Hay CR, et al. Blood. 2011 Jun 9;117(23):6367-70; 2. Astermark J, et al. Thromb Haemost. 2022 Jun;122(6):905-912

VALUE OF INHIBITOR RISK STRATIFICATION – POTENTIAL APPROACH?

- ***FVIII mutations***
- ***HLA Class II***
- ***Immunoregulatory genes***

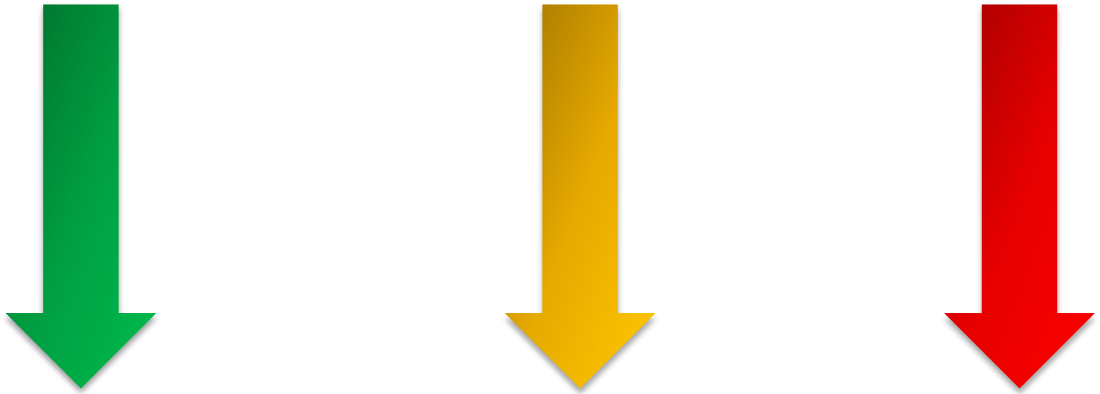
GENETIC risk factor

NON-GENETIC risk factor

- ***Immune challenge***
- ***Intensity of treatment***
- ***Type of concentrate***

Low inhibitor risk

- Ethnicity (Caucasian)
- Brother without inhibitor
- Low-risk *F8* mutation
- Immune gene/HLA low risk
- Prophylaxis first 10 ED



Factor therapy

Factor +/- Non-factor therapy

Non-replacement therapy

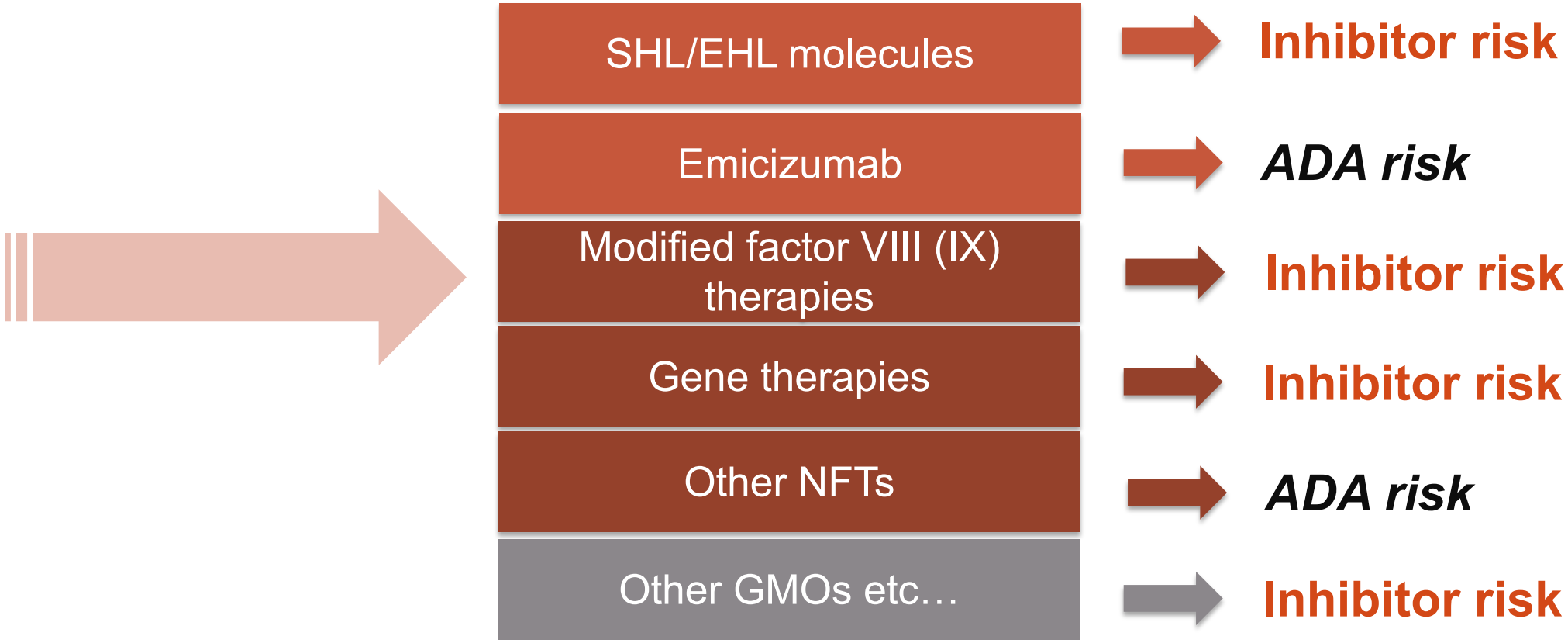
High inhibitor risk

- Ethnicity (Black/Latino)
- Brother with inhibitor
- High-risk *F8* mutation
- Immune gene/HLA risk variants
- Intensive treatment first 10 ED

ED, exposure day; F8, factor VIII gene; FVIII, factor VIII; HLA: human leukocyte antigen

Speaker's own concept

IMMUNE RESPONSE TO TREATMENT IN HAEMOPHILIA MANAGEMENT



ADA, anti-drug antibody; EHL, extended half-life; GMO, genetically modified organism; NFT, non-factor therapy; GMO, Genetic Modified Organism

Speaker's own concept

ITI THERAPY PROTOCOLS

High dose protocol (Bonn protocol)	100–150 IU FVIII/kg bw every 12 hours; according to the bleeding tendency concomitant treatment with FEIBA 50 U/kg or rFVIIa twice daily
High dose protocol	100–200 IU FVIII/kg every 24 hours
Intermediate dose protocol	50–100 IU FVIII/kg daily
Low dose protocol(s)	25(–50) IU FVIII/kg every other day or three times weekly
Malmö protocol	Extracorporeal immune adsorption with protein A, immunosuppression (cyclophosphamide), immunomodulation (IVIG), FVIII every 8–12 hours
Protocols including immunosuppressive agents	Rituximab, MMF, dexamethasone, IVIG, FVIII

bw, bodyweight; FEIBA, factor eight inhibitor bypassing activity; FVIII, factor VIII; ITI, immune tolerance induction; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; rFVIIa, recombinant factor VIIa

Ljung RCR. Br J Haematol. 2018;180:501-510; Mariani G, et al. Semin Thromb Hemost. 2003;29:69-76

ITI PROTOCOLS COMBINED WITH EMICIZUMAB PROPHYLAXIS IN CLINICAL STUDIES FOR OPTIMAL BLEED PREVENTION

Low dose[1]	**25-50 IU FVIII/kg 3 x weekly** + emicizumab QW sc
Low-intermediate dose[1] (Atlanta protocol)[2]	**100 IU FVIII/kg 3 x weekly** + emicizumab QW sc
High dose[1] (Bonn protocol)	**200 IU FVIII/kg 1 x day** + emicizumab QW sc

FVIII, factor VIII; ITI, immune tolerance induction; QW, every week; sc, subcutaneous

Ljung RCR. Br J Haematol. 2018;180:501-510; Mariani G, et al. Semin Thromb Hemost. 2003;29:69-76; Escuriola C, et al. Haemophilia. 2021;27(3):e305-e313; Batsuli G, et al. Haemophilia. 2019;25(5):789-796

CONCLUSIONS

- Despite significant progress in **haemophilia management** and more to come …, **factor concentrates** will still be required for a long time and **inhibitors** will develop
- The current **goal** of haemophilia management should be **tolerance** towards the deficient factor and ≥1 ITI attempt should be considered in all **patients with inhibitors**
- In **inhibitor resistant patients** and if ITI is not available/not undertaken for specific reasons – NRT will **significantly improve** the outcome
- Future clinical management should be **individualised** to minimise treatment burden – if possible by **predictive tools**
- **New treatment options** for improved bleed protection/potential cure may require a tolerant state

ITI, immune tolerance induction; NRT, non-replacement therapy

CLINICAL TAKEAWAYS – PART 1

- Factor replacement therapy is a flexible and effective therapeutic option, both for prophylaxis and treatment of bleeds
- Non-factor therapy is an effective treatment for severe hemophilia A and severe hemophilia B patients with inhibitors and can reduce the treatment burden compared to factor replacement therapy
- The goal of hemophilia management should in the era of available non-factor therapies still be tolerance towards the deficient factor and ≥1 immune tolerance induction attempt should be considered in patients with persistent inhibitors
- Future clinical management should be individualised to minimise treatment burden, possibly by predictive tools