AXIS Medical Education

Lowering Burden to Raise Adherence:

Optimizing Prophylaxis for Hemophilia A

DISCLAIMER

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Apply up-to-date evidence to enable optimal timing for prophylactic treatment initiation in patients with hemophilia A to minimize long-term complications
- Select appropriate prophylactic therapy for patients with hemophilia A based on clinical evidence, bleeding episode frequency, and patient preferences
- Implement shared decision-making strategies when discussing appropriate prophylactic treatment that prevents undue bleeding episodes and increases adherence in patients with hemophilia A

Optimizing Prophylaxis to Mitigate Long-Term Disease Complications

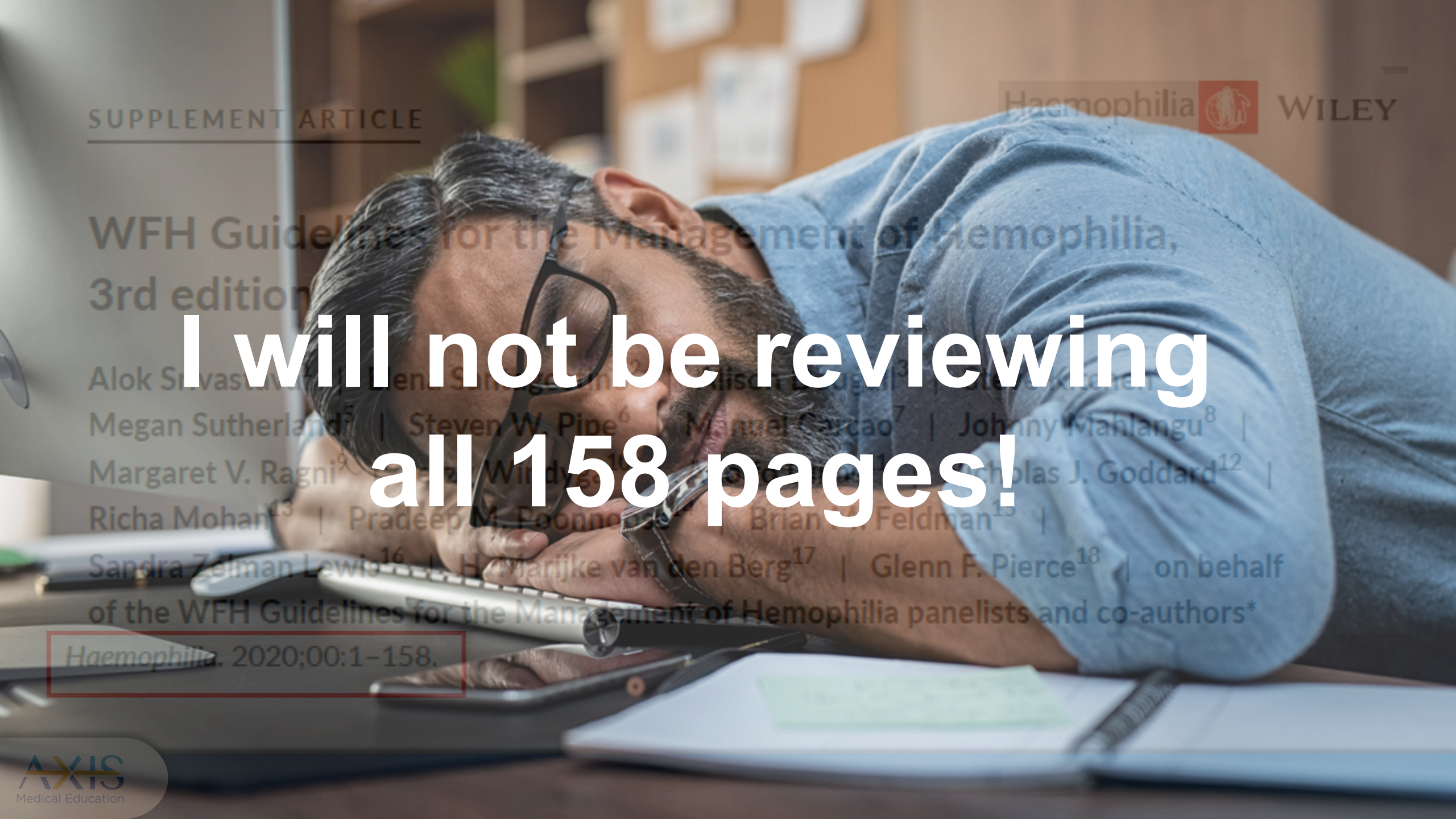
SUPPLEMENT ARTICLE

Haemophilia WILEY

WFH Guidelines for the Management of Hemophilia, 3rd edition

Alok Srivastava[1] | Elena Santagostino[2] | Alison Dougall[3] | Steve Kitchen[4] | Megan Sutherland[5] | Steven W. Pipe[6] | Manuel Carcao[7] | Johnny Mahlangu[8] | Margaret V. Ragni[9] | Jerzy Windyga[10] | Adolfo Llinás[11] | Nicholas J. Goddard[12] | Richa Mohan[13] | Pradeep M. Poonnoose[14] | Brian M. Feldman[15] | Sandra Zelman Lewis[16] | H. Marijke van den Berg[17] | Glenn F. Pierce[18] | on behalf of the WFH Guidelines for the Management of Hemophilia panelists and co-authors*

Haemophilia. 2020;00:1–158.


SUPPLEMENT ARTICLE
Haemophilia
WILEY
WFH Guidelines for the Management of Hemophilia,
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Haemophilia. 2020;00:1–158.
I will not be reviewing
all 158 pages!
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Modifications to WFH Guidelines, 3rd Edition

Sections Added

- Principles of care
- Genetic diagnosis
- Prophylaxis (emphasizing it's the only way to treat)
- Management of inhibitors
- Outcomes assessment

Sections Removed

- Transfusion-transmitted infections

Srivastava A, et al. *Haemophilia.* 2020;26(S6):1-158.
WFH, World Federation of Hemophilia.

Prophylaxis

- All patients with severe hemophilia A and B should be on prophylaxis sufficient to prevent bleeds at all times
- In countries with less access to factor concentrates, WFH recommends prophylaxis with less intensive regimens
- When prophylaxis is not available, on demand treatment must be available for treating bleeds early

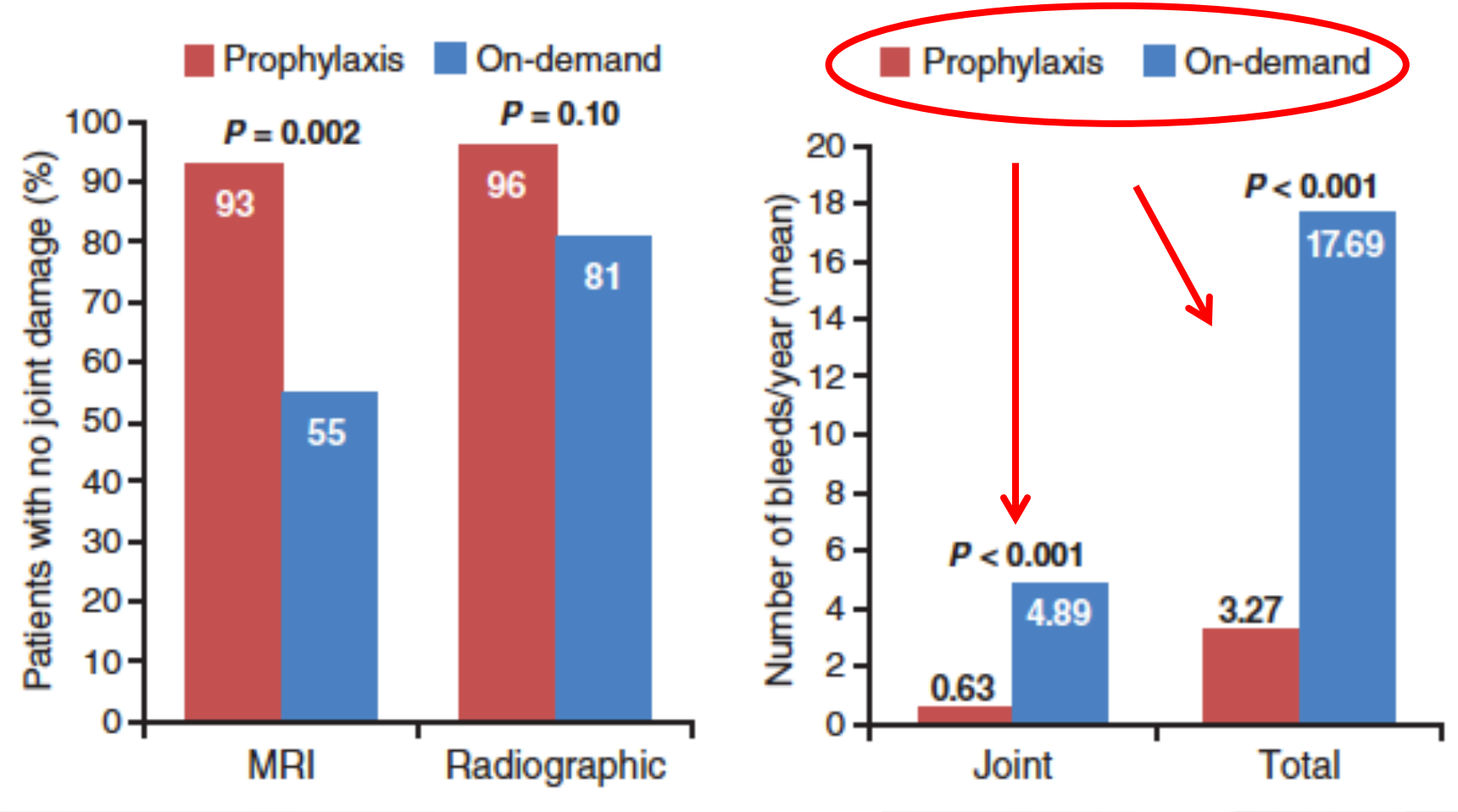
- Early initiation of primary prophylaxis is recommended with clotting factor concentrates or other agents prior to the onset of joint bleeding or by age 3 years
- This is primary prophylaxis
- All forms of prophylaxis are superior to episodic therapy
  - pdFVIII/FIX
  - rFVIII/FIX
  - SHL
  - EHL
  - Emicizumab

Srivastava A, et al. *Haemophilia.* 2020;26(S6):1-158.

pdFVIII/FIX, plasma-derived factor VII/IX; rFVIII/FIX, recombinant factor VII/IX; SHL, standard half-life; EHL, extended half-life; WFH, World Federation of Hemophilia.

Joint Outcome Study

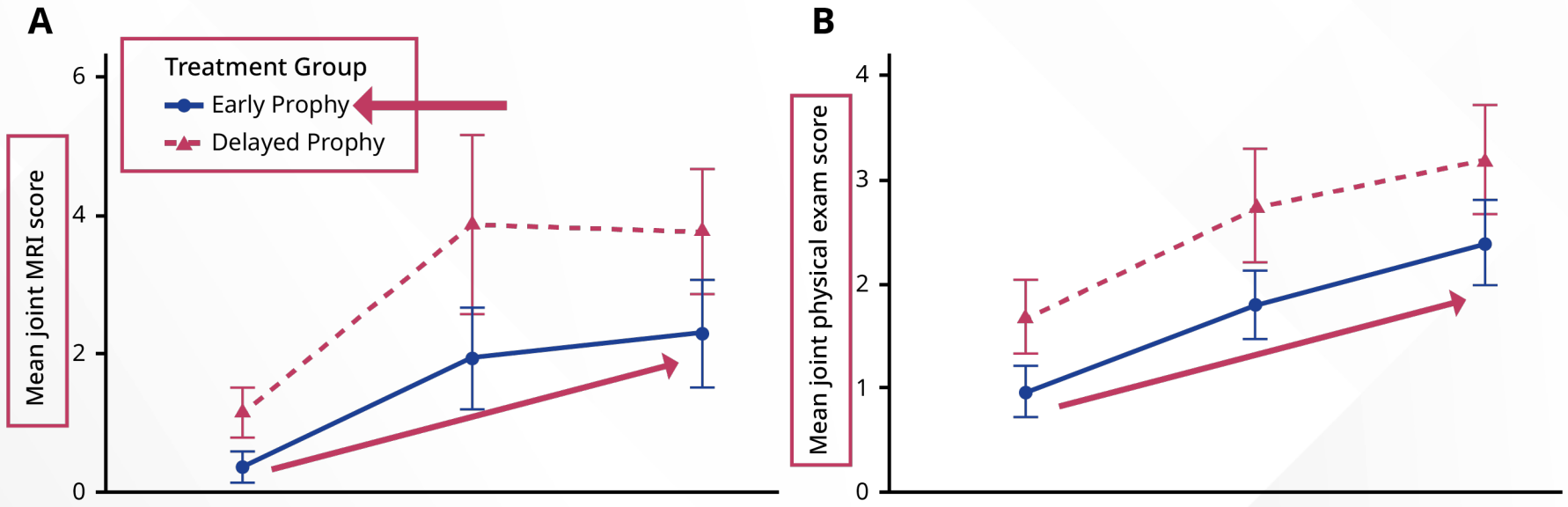
Prophylaxis Versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia



Manco-Johnson MJ, et al. *N Engl J Med*. 2007;357:535-544.

Joint Outcome Continuation Study

Average Joint MRI Scores and Physical Examination Scores



Average Scores (Mean (SD))	JOS Entry MRI	JOS Exit eMRI		JOS-C Entry eMRI		JOS-C Exit eMRI		JOS Exit CPJAS		JOS-C Entry CPJAS		JOS-C Exit CPJAS	
Mean Age (Yrs)	1.5	6.1		13.8		18.0		6.0		14.1		18.1	
Early Prophylaxis	0	0.4 (0.9) n = 15		1.9 (2.2) n = 10		2.3 (2.8) n = 14		1.0 (0.9) n = 15		1.8 (1.2) n =13		2.4 (1.6) n =15	
Delayed Prophylaxis	0	1.2 (1.5) n = 18		3.9 (4.1) n = 11		3.8 (3.7) n = 18		1.7 (1.4) n = 18		2.7 (1.8) n = 12		3.2 (2.2) n = 18	

Adapted from Boulden Warren B, et al. *Blood Adv.* 2020;4(11):2451-2459.

CPJAS, Colorado Pediatric Joint Assessment Scale; eMRI, extended magnetic resonance imaging; JOS, Joint Outcome Study; SD, standard deviation.

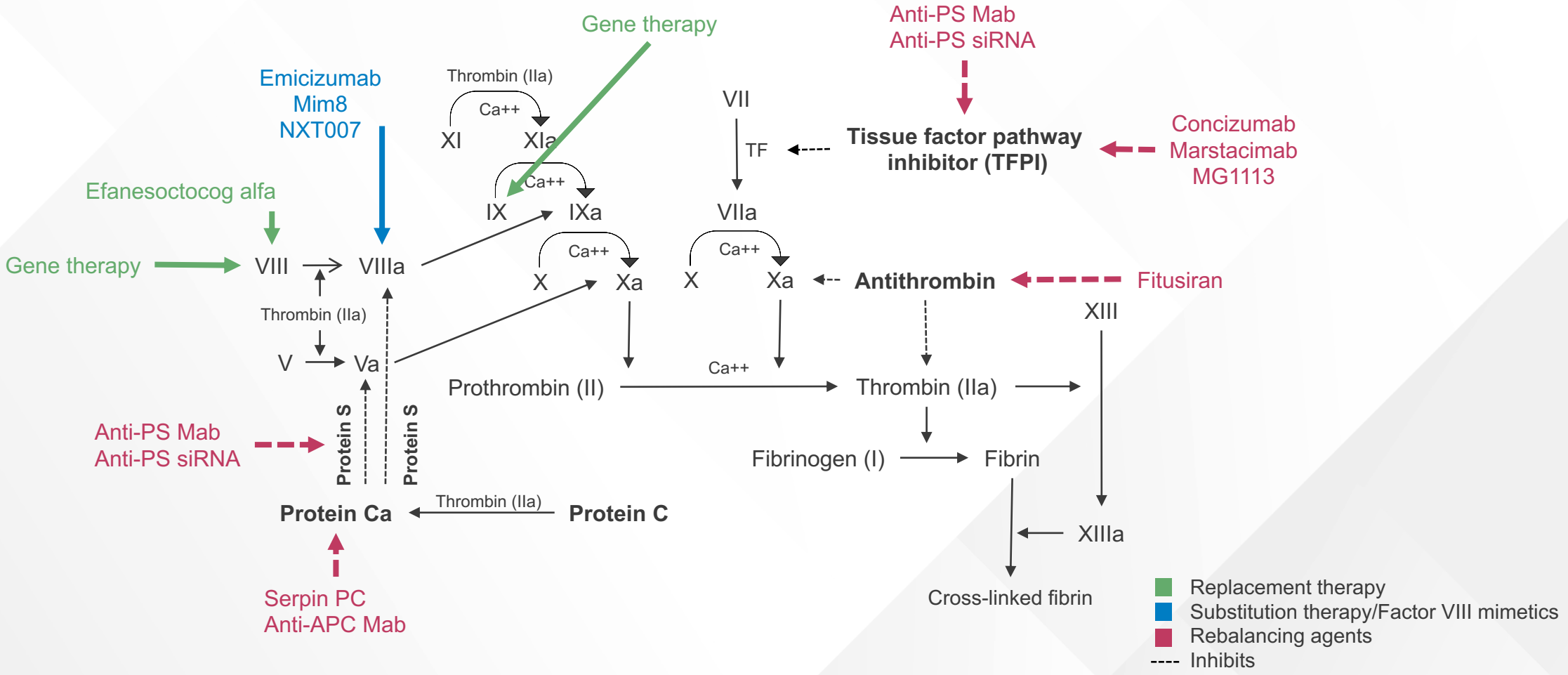
Factor-Mimetic and Rebalancing Therapies in Hemophilia A

Nonfactor Therapies

- They are all given subcutaneously and most of them less/much less frequently than factor therapy
- They are (based on trial data) more effective at preventing bleeding than factor therapy
- They therefore may be more effective at preventing joint disease

- What are nonfactor therapies?
  - Factor VIII mimetics
  - Rebalancing agents

Novel Therapeutics Mechanisms of Action



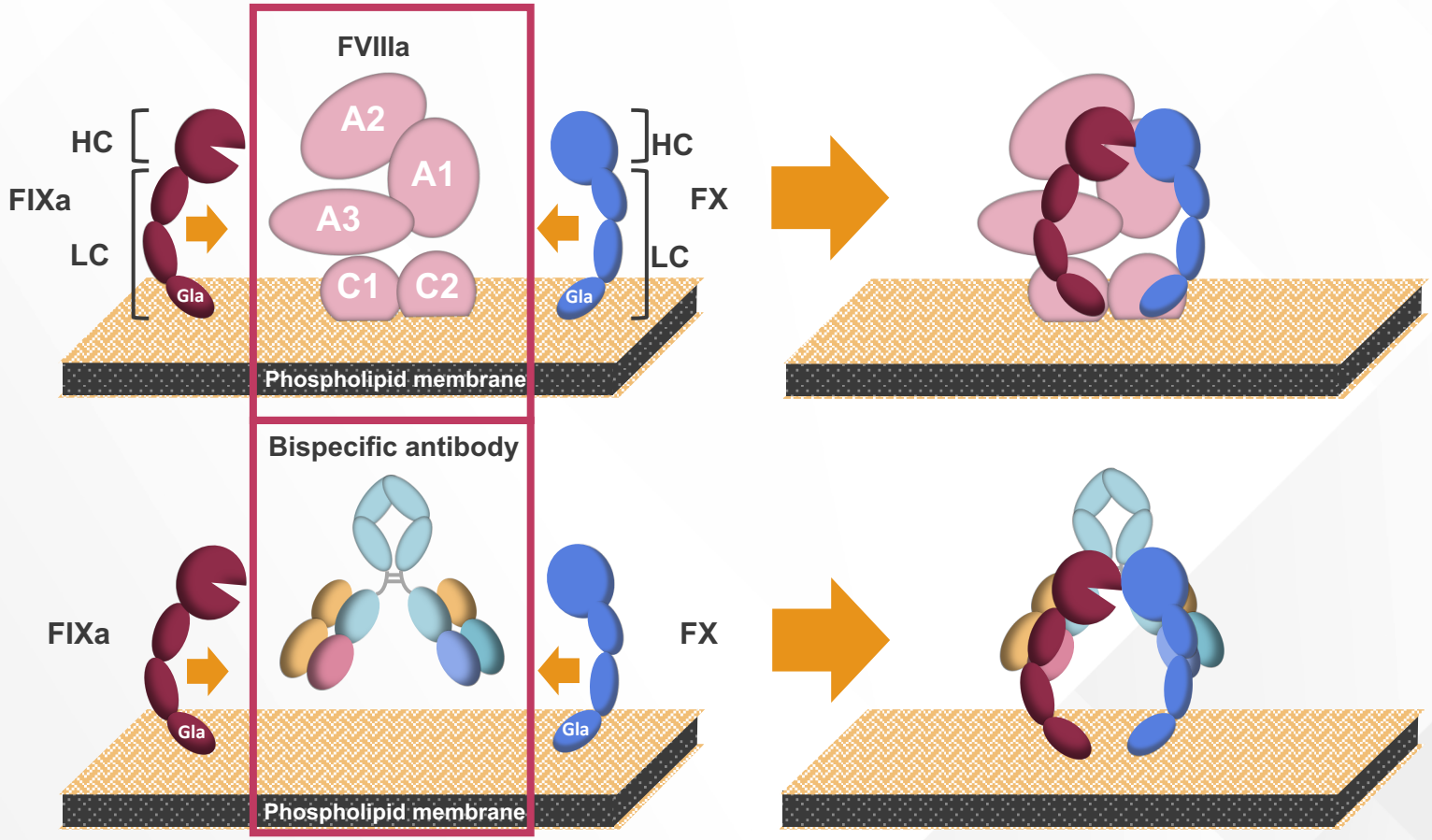
Courtesy of Guy Young, MD.

MAB, monoclonal antibody; PS, protein S; siRNA, small interfering ribonucleic acid.

Factor VIII Mimetics

What Do We Mean By Mimetic?

Factor VIII Mimetics for Hemophilia A



Adapted from Kitazawa T, et al. *Nat Med*. 2012;18:1570-1574.
a, activated; F, factor; HC, heavy chain; LC, light chain.

Factor VIII Mimetics for Hemophilia A

MOA	Drug	Dosing Regimen	Development Phase	Comments
Substitute for the function of activated FVIII	Emicizumab	SC q1, 2, or 4 weeks **Loading dose:** 3 mg/kg SC once weekly for the first 4 weeks Followed by a **maintenance dose** of: • 1.5 mg/kg q1 week, or • 3 mg/kg q2 weeks, or • 6 mg/kg q4 weeks	FDA-approved	Most commonly prescribed medication for prophylaxis in Hemophilia A Indication: routine 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 inhibitors
	Mim8	SC q1 week or q1 month	3	Pre-clinical studies show increased thrombin generation compared to emicizumab
	NXT007	SC q1, 2, or 4 weeks	1	

HEMLIBRA (emicizumab-kxwh). Prescribing information. Genentech, Inc.; 2023.
FDA, US Food and Drug Administration; MOA, mechanism of action; q, every; SC, subcutaneous.

Emicizumab Clinical Trials

Clinical Trial	Population	ABR, Treated Bleeds: Emicizumab Prophylaxis vs No Prophylaxis	% Patients With Zero Treated Bleeds	ABR, Treated Bleeds: Emicizumab Prophylaxis vs Prior Prophylaxis in NIS
HAVEN 1 (NCT02622321)	PwHA ≥12 years with FVIII inhibitors	• 87% reduction (QW)*	• 63% (QW) • 6% (no prophylaxis)	• 79% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 2 (NCT02795767)	PwHA <12 years with FVIII inhibitors	• N/A (no comparator)	• 76.9% (QW)	• 99% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 3 (NCT02847637)	PwHA ≥12 years without FVIII inhibitors	• 96% reduction (QW) • 97% reduction (Q2W)	• 56% (QW), 60% (Q2W), • 0% (no prophylaxis)	• 68% reduction with emicizumab QW vs prior FVIII prophylaxis
HAVEN 4 (NCT03020160)	PwHA ≥12 years with or without FVIII inhibitors	• Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, PK		

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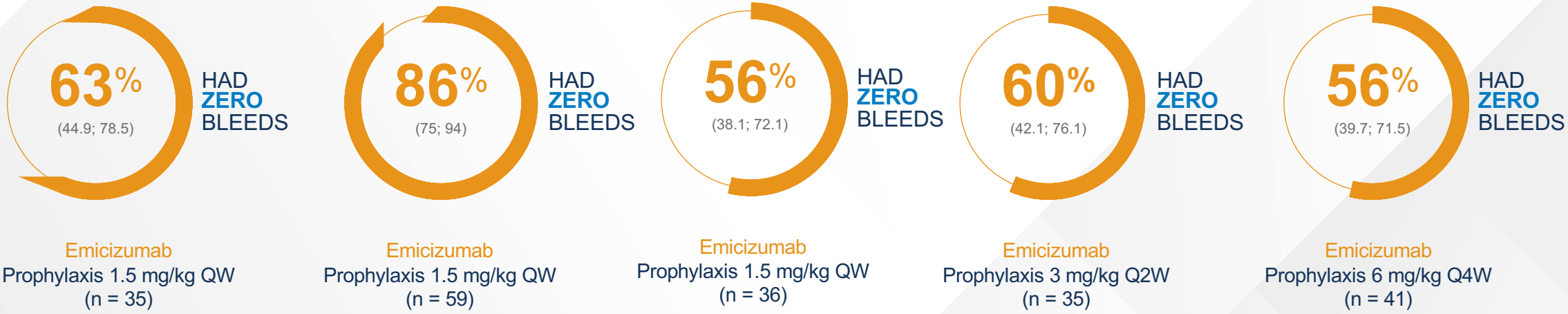
Oldenburg J, et al. *N Engl J Med*. 2017;377:809-818. Young G, *et al. Blood*. 2019;134:2127-2138.
Mahlangu J, et al. *N Eng J Med*. 2018;379:811-822. Pipe SW, et al. *Lancet Haematol*. 2019;6:e295-e305.
ABR, annualized bleeding rate; BPA, bypassing agent; NIS, noninterventional study; PK, pharmacokinetic; PwHA, patients with hemophilia A; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Emicizumab: Clinically Meaningful Bleed Protection in All Dosing Options

Patients With Zero Treated Bleeds With Emicizumab Prophylaxis (95% CI)

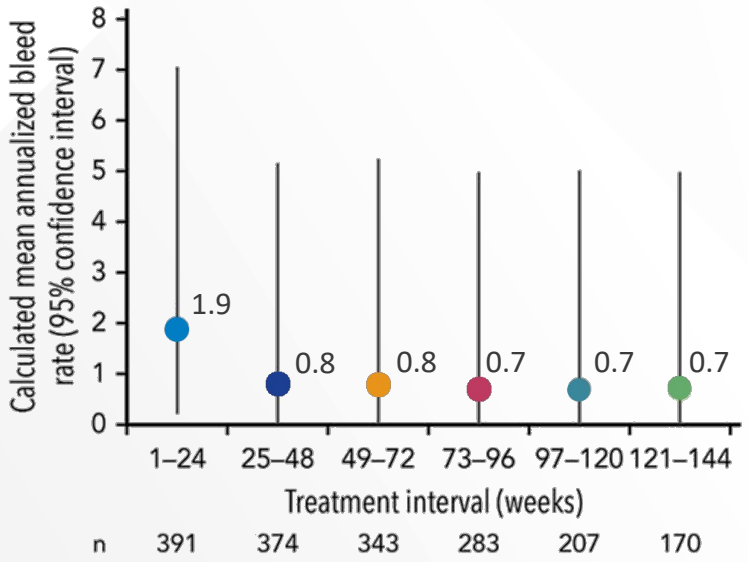


Oldenburg J, et al. *N Engl J Med.* 2017;377:809-818. Young G, et al. *Blood.* 2019;134:2127-2138.
Mahlangu J, et al. *N Eng J Med.* 2018;379:811-822. Pipe SW, et al. *Lancet Haematol.* 2019;6:e295-e305.
QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

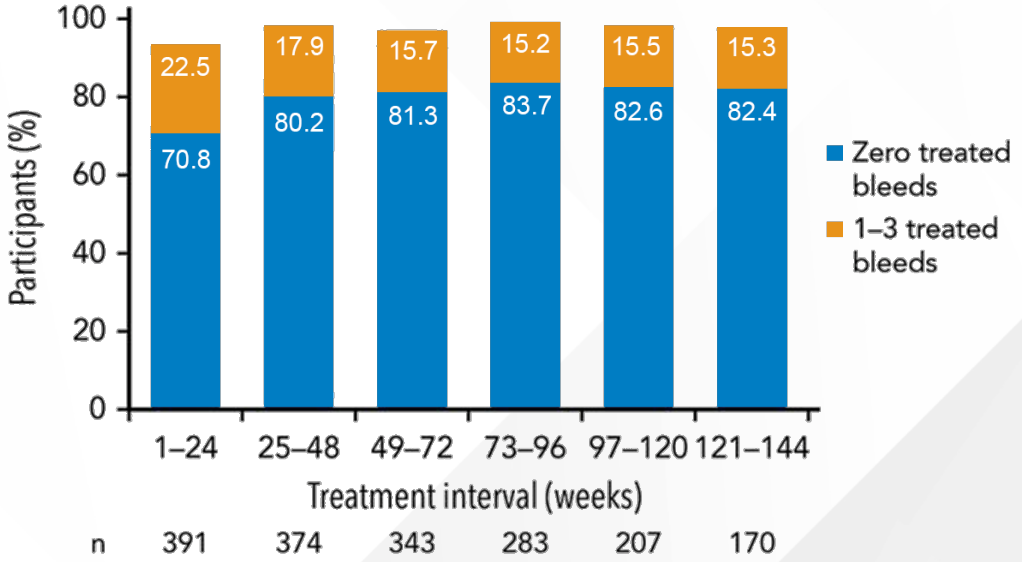
Emicizumab: Pooled Analysis of HAVEN 1-4 Trials

A pooled analysis of long-term results from Phase III studies of emicizumab prophylaxis (HAVEN 1-4) in persons with hemophilia A

Annualized bleed rates (treated bleeds; mean values with 95% confidence intervals)



Percentages of participants with zero and 1-3 treated bleeds (%)



- With nearly 3 years of follow-up, low bleed rates were maintained with emicizumab prophylaxis
- After week 24, at least 97% of participants had ≤3 bleeds in each treatment interval
- Emicizumab remained well tolerated over long-term follow-up

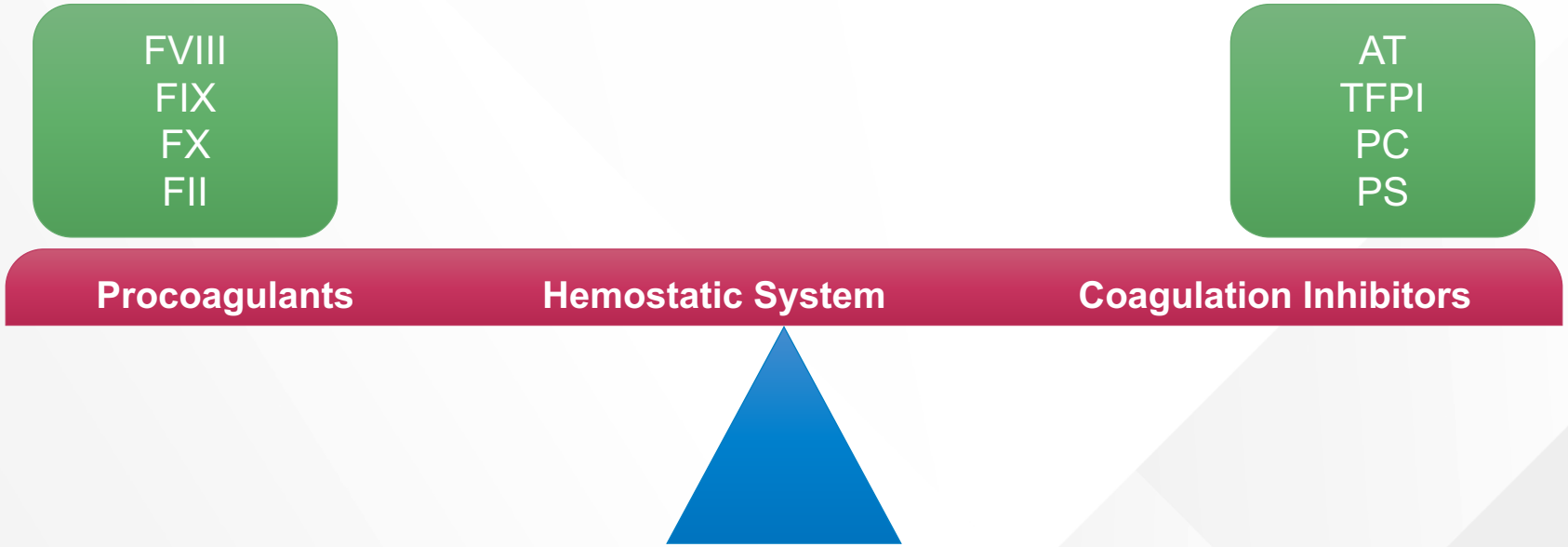
Adapted from Callaghan MU, et al. *Blood*. 2021;137:2231-2242.

Additional Emicizumab Clinical Trials

Clinical Trial	Phase	Population	Results/Comments
HAVEN 6 (NCT04158648)	3	Emicizumab prophylaxis in patients with **mild or moderate** hemophilia A without factor VIII inhibitors	Treatment with emicizumab maintained low bleed rates across the study period (N = 72, median follow-up of 55.6 weeks) • 66.7% experienced no bleeds that required treatment • 81.9% experienced no spontaneous bleeds that required treatment • 88.9% experienced no joint bleeds that required treatment • Model-based ABR remained low throughout the evaluation period at 0.9
HAVEN 7 (NCT04431726)	3	Emicizumab in **infants** with severe hemophilia A without FVIII inhibitors from birth to 12 months of age	Interim results indicated efficacy and confirmed safety of emicizumab with sustained PK and PK data (N = 54) • 31 (57.4%) had at least 1 bleed; total number of bleeds: 77 • 12 (22%) had at least one treated bleed; total number of treated bleeds: 14 • Treated spontaneous bleeds: 0 • Treated joint bleeds: 2 (14.3%) • Mean model-based ABR: 1.9 all bleeds
STASEY (NCT03191799)	3	**Safety** of emicizumab prophylaxis in patients with hemophilia A with inhibitors	Confirmed safety profile reported in previous HAVEN studies with no new safety signals and the majority of patients having zero bleeding episodes (N = 193) • Thromboembolic events (TEs): 2 (1.0%) • Thrombotic microangiopathies (TMAs): 0 • Hypersensitivity reactions: 0 • Most common AEs (≥10% of PwHA): arthralgia (17.1%), nasopharyngitis (15.5%), headache (15.0%), ISR (11.4%), pyrexia (10.9%)

Hermans C, et al. ISTH Annual Congress 2022. Abstract OC 30.5. Pipe SW, et al. ASH 2022 Annual Meeting & Exposition. Abstract 187; *Blood.* 2022;140(Supplement 1):457-459.
Jimenez-Yuste V, et al. ISTH Annual Congress 2021. Abstract PB0521.
ABR, annualized bleed rates; AEs, adverse events; ISR, injection-site reactions; PK, pharmacokinetic; PwHA, patients with hemophilia A.

Rebalancing Agents

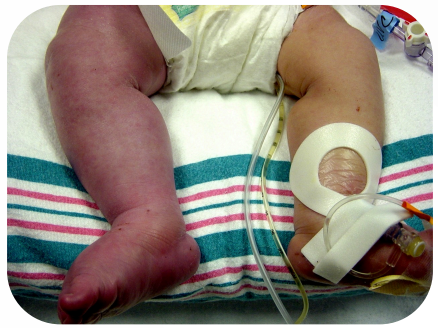


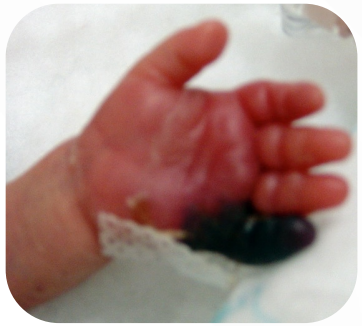
Courtesy of Guy Young, MD.
AT, antithrombin; F, factor; PC, protein C; PS, protein S; TFPI, tissue factor pathway inhibitor.

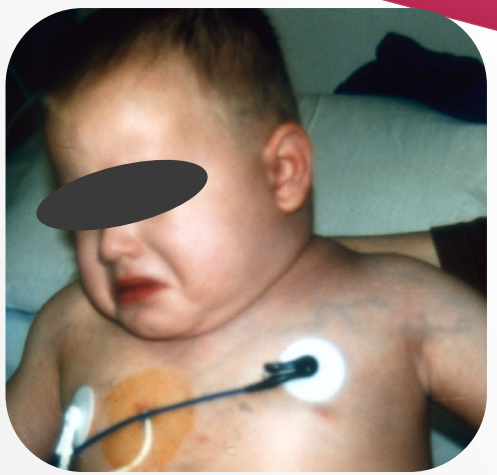
Bleeding Disorder

Courtesy of Guy Young, MD.
AT, antithrombin; F, factor; PC, protein C; PS, protein S; TFPI, tissue factor pathway inhibitor.

Thrombotic Disorder

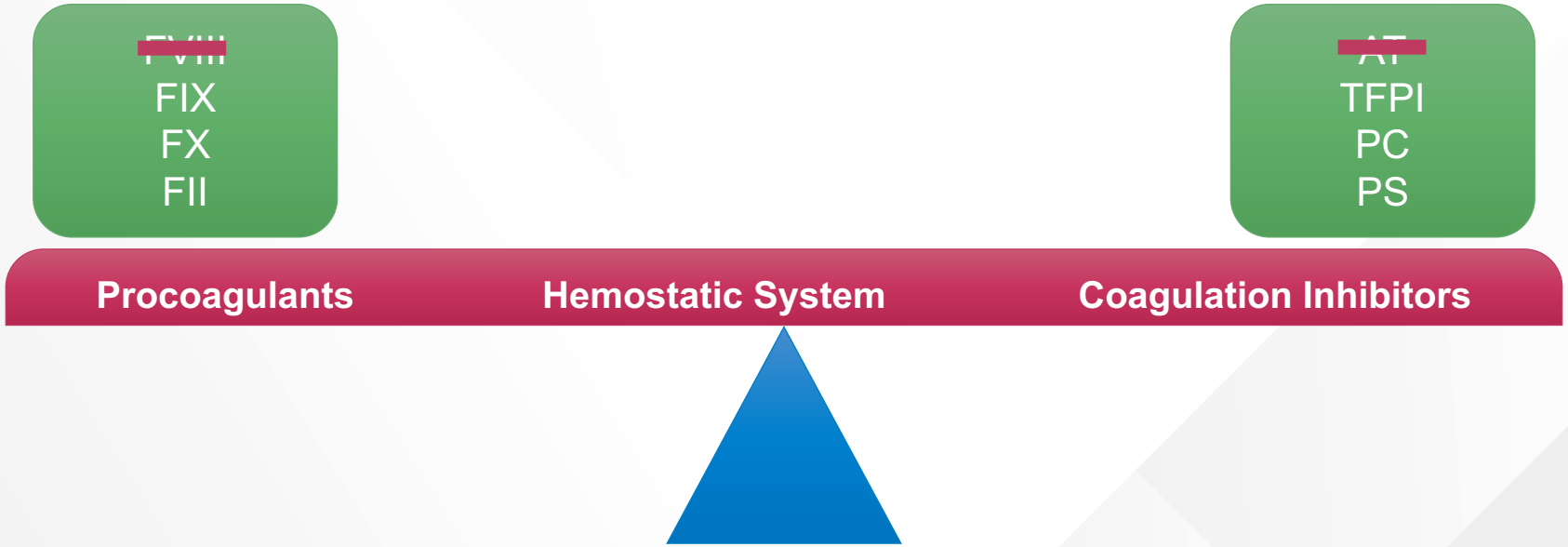






Courtesy of Guy Young, MD.
AT, antithrombin; F, factor; PC, protein C; PS, protein S; TFPI, tissue factor pathway inhibitor.

Balance Restored – No Bleeding/No Clotting



Courtesy of Guy Young, MD.
AT, antithrombin; F, factor; PC, protein C; PS, protein S; TFPI, tissue factor pathway inhibitor.

Rebalancing Agents

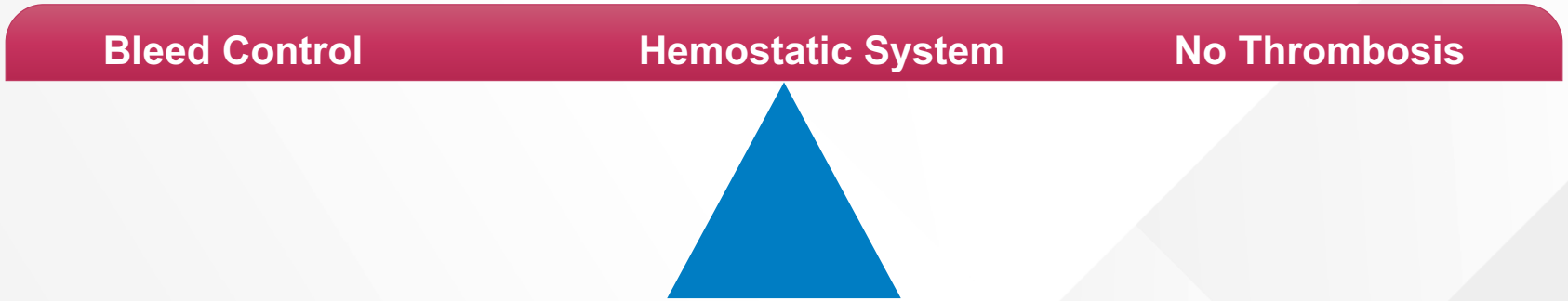
PROS

- Same medication for hemophilia A and B with/without inhibitors
- Several mechanisms of action
  - Can be used in different types of patients
- Efficacious
- Safe (mostly)
- Subcutaneously administered
- Potential to be used in other bleeding disorders

CONS

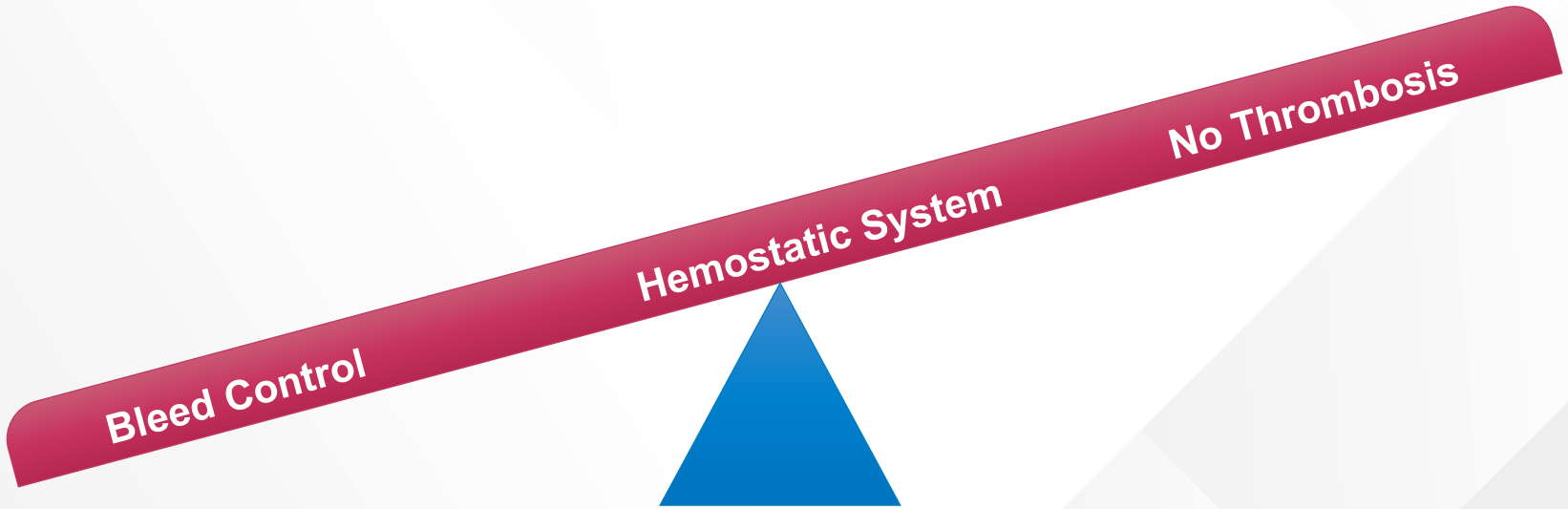
- Novel mechanisms of action
  - Treaters/patients have to learn about another part of the coagulation cascade
- Therapeutic drug monitoring with dose adjustments will be required (at least for some)
- Safety concerns (thrombosis)
- Lack of antidote for some

Can We Get The Balance Right?



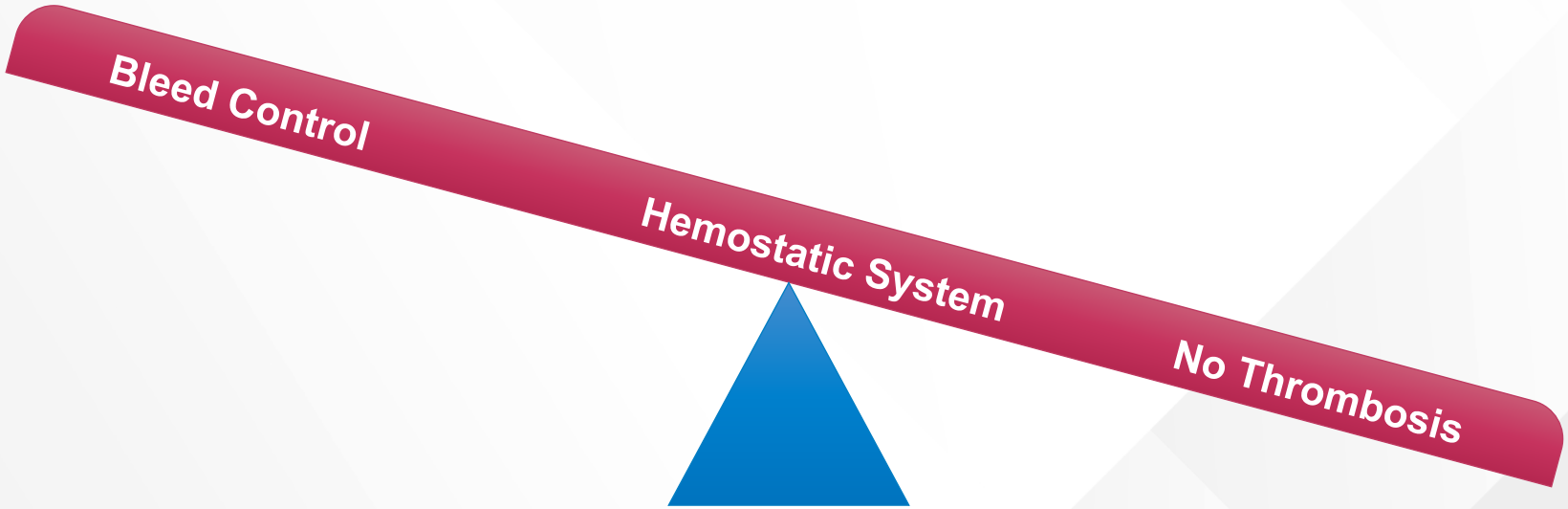
Courtesy of Guy Young, MD.

Poor Bleed Control – No Thrombosis



Courtesy of Guy Young, MD.

Good Bleed Control – Thrombotic Events



Courtesy of Guy Young, MD.

Rebalancing Agents

MOA	Drug	Dosing Regimen	Development Phase	Comments
Anti-AT siRNA	Fitusiran	SC monthly or every other month	3	Thrombotic events led to a new dosing regimen targeting AT levels between 15-35%
Anti-TFPI monoclonal antibodies	Concizumab	SC daily	3	Thrombotic events led to a new approach targeting range of concizumab levels
	Marstacimab	SC weekly	3	No reported thrombotic events so far
Anti-APC serpin	Serpin PC	SC q1, 2 or 4 weeks	3	Designed to improve hemostasis without risk for thrombosis

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AT, antithrombin; APC, activated protein C; q, every; SC, subcutaneous; serpin, serine protease inhibitor; siRNA, small interfering ribonucleic acid; TFPI, tissue factor pathway inhibitor.

Fitusiran Clinical Trials

Three Phase 3 Studies in Adults and Adolescents ≥12 years

ALN-AT3SC-003 (n = 54)

- Patients with Hem A or B aged ≥12 years
- ***With*** inhibitors
- Fitusiran 80mg QM
- Bleed managed by BPA on-demand

Plenary presentation[1]

ALN-AT3SC-004 (n = 120)

- Patients with Hem A or B aged ≥12 years
- ***Without*** inhibitors
- Fitusiran 80mg QM
- Bleed managed by factor on-demand

Late breaker[2]

ALN-AT3SC-009 (n = 80)

- Patients with Hem A or B aged ≥12 years
- ***With or without*** inhibitors
- Fitusiran 80mg QM
- Compared with factor / BPA prophylaxis

Late breaker[3]

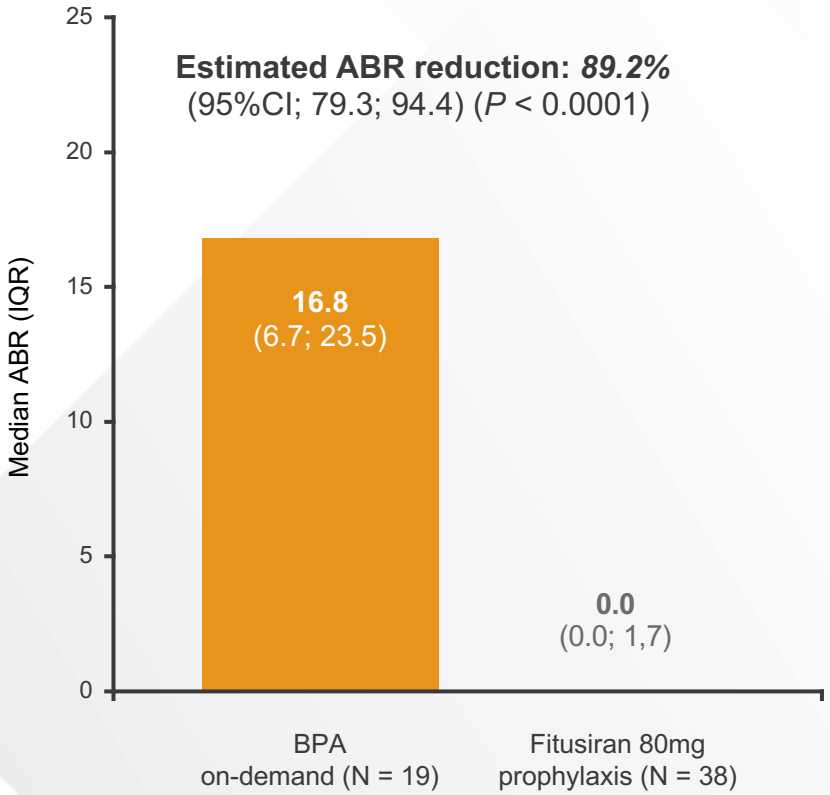
BPA, bypassing agent; Hem A or B, hemophilia A or B; QM, once monthly.

1. Young G, et al. *Lancet*. 2023;401(10386):1427-1437.
2. Srivastava A, et al. *Lancet Haematol*. 2023;10(5):e322.
3. Kenet G, et al. *Res prac throm haemost*. 2022;6(S1):LB01.1.

Fitusiran Phase 3 Efficacy Data

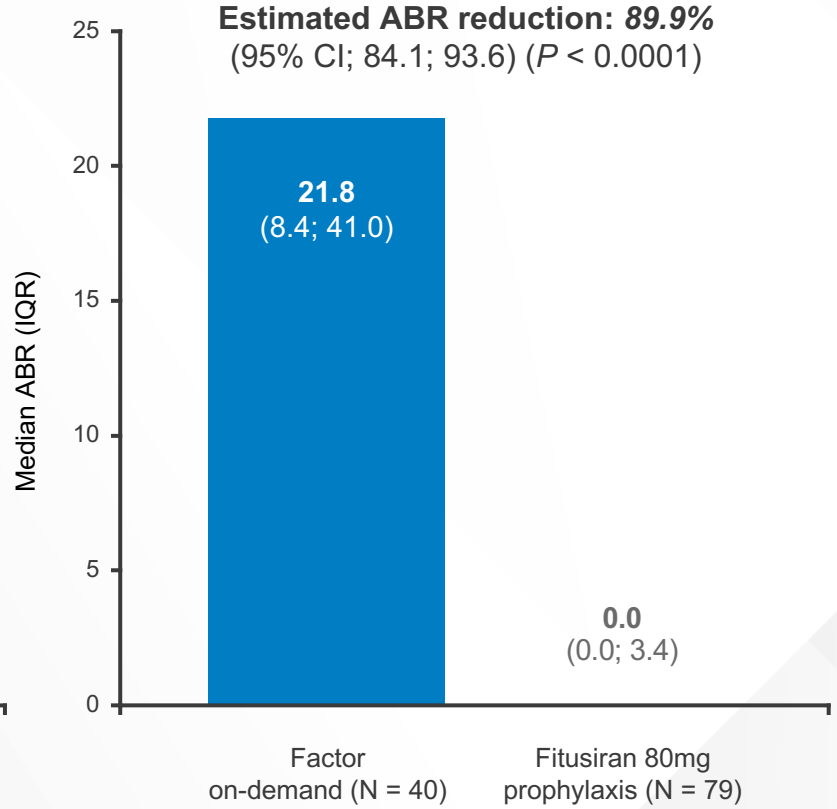
ATLAS-INH[1]

Fitusiran vs on-demand bypassing agents: hem A or B with inhibitors



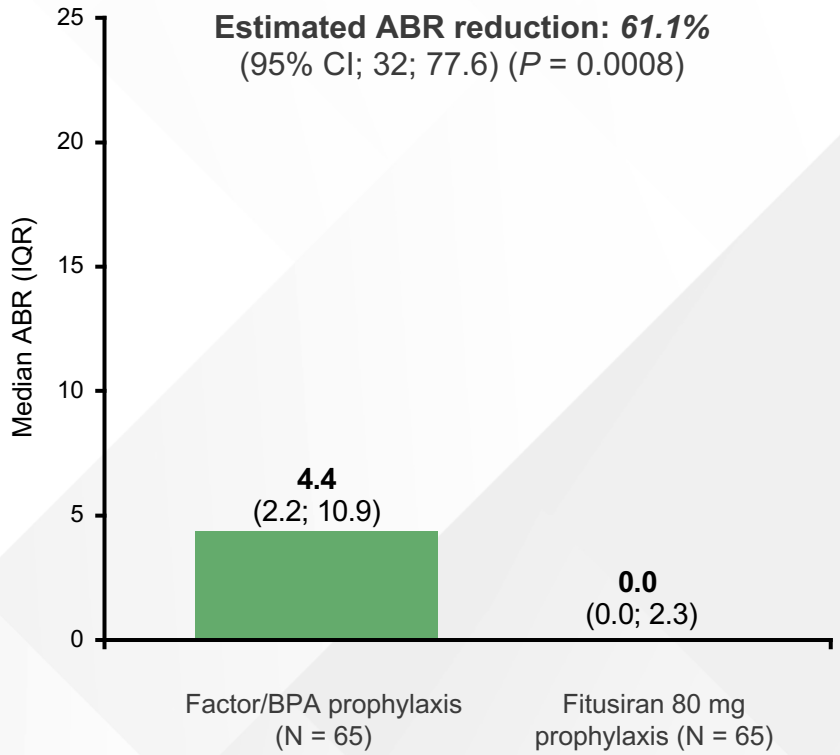
ATLAS-A/B[2]

Fitusiran vs on demand factor: hem A or B without inhibitors



ATLAS-PPX[3]

Fitusiran vs prior factor/BPA prophylaxis with or without inhibitors



Information presented here is intended as a summary of these studies only – direct comparisons cannot be made between the studies.

1. Young G, et al. *Lancet*. 2023;401(10386):1427-1437. 2. Srivastava A, et al. *Lancet Haematol*. 2023;10(5):e322. 3. Kenet G, et al. *Res prac throm haemost*. 2022;6(S1):LB01.1.

ABR, annualized bleeding rate; BPA, bypassing agent; CI, confidence interval; Hem A or B, hemophilia A or B; IQR, interquartile range.

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Concizumab Clinical Trials

- Safety
- PK and PD

→

- Efficacy
- Safety

Phase 1
Explorer™1[1,2]
Healthy (N = 28), PwHA (N = 21), PwHB (N = 3)
18–65 years of age

Phase 1
Explorer™2[2,3]
Healthy (N = 4)
18–64 years of age

Phase 1b
Explorer™3[4,5]
PwHA–inh (N = 24)
18–64 years of age

Phase 2
Explorer™4[6]
PwHA/B+inh (N = 26)
≥18 years of age

Phase 2
Explorer™5[7]
PwHA–inh (N = 36)
≥18 years of age

Phase 3
Explorer™6[8]
PwHA/B±inh (N = 231)
≥12 years of age

Phase 3
Explorer™7[9]
PwHA/B+inh (N = 136)
≥18 years of age

Phase 3
Explorer™8[10]
PwHA/B–inh (N = 158)
≥12 years of age

Phase 3
Explorer™10[11]
PwHA/B±inh (N = 90)
<12 years of age

✓ Trial complete → Trial ongoing X Trial terminated

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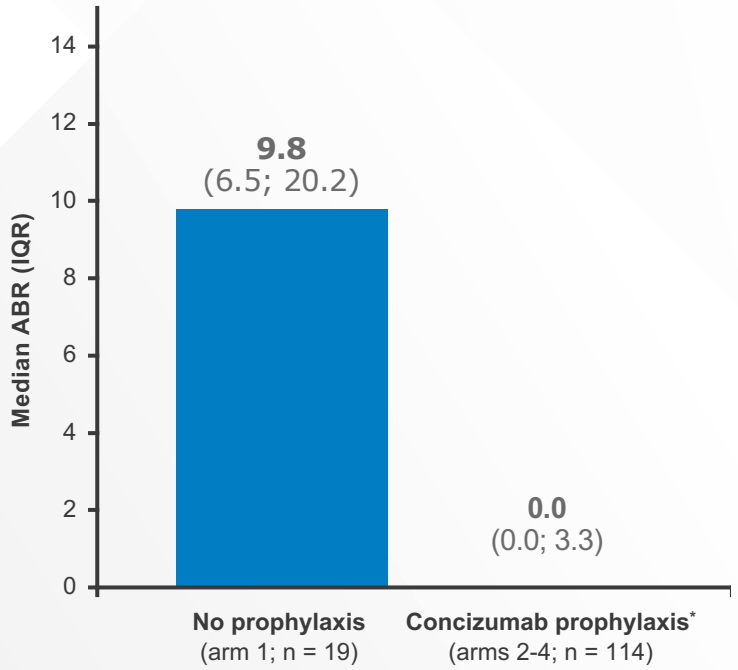
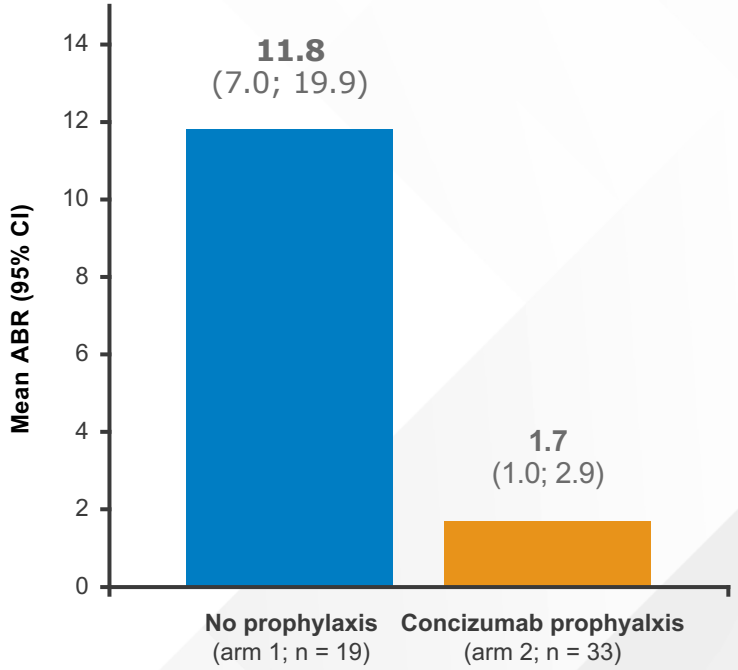
PD, pharmacodynamic; PK, pharmacokinetic; PwHA/B, people with hemophilia A or B; PwHA/B+inh, people with hemophilia A or B with inhibitors; PwHA-inh, people with hemophilia A without inhibitors; PwHA/B-inh, people with hemophilia A or B without inhibitors.

1. ClinicalTrials.gov. NCT01228669. 2. Pasca S. *J Blood Med.* 2022;13:191-199. 3. ClinicalTrials.gov. NCT01631942. 4. ClinicalTrials.gov. NCT02490787. 5. Eichler H, et al. *J Thromb Haemost.* 2018;16(11):2184-2195. 6. ClinicalTrials.gov. NCT03196284. 7. ClinicalTrials.gov. NCT03196297. 8. ClinicalTrials.gov. NCT03741881. 9. ClinicalTrials.gov. NCT04083781. 10. ClinicalTrials.gov. NCT04082429. 11. ClinicalTrials.gov. NCT05135559.

Concizumab Phase 3 Efficacy Data Explorer7 (main period)

ABR at primary analysis cut off* in people with hemophilia A or B with inhibitors





Mean ABR was **1.7** and **median ABR was 0**, and **64% of participants** who received concizumab (arm 2; n = 33) **had zero treated bleeds** at 24 weeks

*Includes participants previously on demand that were randomized to receive concizumab prophylaxis (arm 2; n = 33), participants that transferred from the explorer4 trial, and an additional group of participants that were on prior prophylaxis or on demand (arms 3 and 4, respectively; n = 81).
ABR, annualized bleeding rate.
Jiménez Yuste V, et al. ISTH 2022 Congress. Abstract LB 01.2. Mathias M, et al. *Haemophilia.* 2023;29(S1):OR06.

Marstacimab Phase 2 Efficacy Data

	Total 300 mg (N = 10)	Total 300 mg Loading + 150 mg (N = 10)
Pre-treatment* ABR, mean (SD)	20.2 (5.7)	17.4 (9.0)
Median (range)	19.0 (12.0–30.0)	15.0 (12.0–42.0)
On study ABR, mean (SD)	1.5 (2.4)	2.7 (4.5)
Median (range)	0 (0–6.0)	1.0 (0–14.4)

- Across all dose cohorts, mean and median on-study **ABRs** ranged from **0 to 3.6 and 0 to 2.5** respectively, demonstrating comparable efficacy to that observed in the 1b/2 study
- **Nine out of 18 participants (50%)** who completed the study **had no bleeding events**

Phase 3 BASIS trial of adolescent and adult participants between ages 12 to <75 years with severe hemophilia A demonstrated statistically significant and clinically relevant reduction in ABR compared to prophylaxis and on-demand intravenous regimens

AXIS Medical Education

*Participants from previous study (Cohort 1 and 4; n = 10) continued to receive 300mg marstacimab weekly; participants (Cohort 2 and 3; n = 8) received 300mg loading dose followed by 150mg weekly dose. De novo participants (Cohort 5; n = 0 and Cohort 6; n = 2) received 300mg loading dose followed by 150mg weekly dose. Treatment was administered for up to 365 days. Pre-treatment summarized data up to 6 months prior to participation in the long-term study for de novo participants, and up to 6 months prior to participation in the prior phase 1b/2 short-term multiple ascending dose study for rollover participants.
ABR, annualized bleeding rate; SD, standard deviation.
Mahlangu J, et al. *Br J Haematol.* 2023;200:240-248.

Novel Agents by Administrations Per Year

Drug	Administrations Per Year	Comments
Factor replacement	52-183 (IV)	Only IV. Other administration methods have been tried but have not worked well
Emicizumab/Mim8	13-52 (SC)	Very long washout (months) with no antidote
Fitusiran	6-12 (SC)	Very long washout (months) but antidote (AT infusion) is available
Concizumab	365 (SC)	Daily injection, but advantage of rapid washout No antidote
Marstacimab	52 (SC)	No antidote
Serpin PC	13-52 (SC)	Dosing still being worked out

AT, antithrombin; IV, intravenous; PC, protein C; SC, subcutaneous.

Novel Replacement Therapy

Efanesoctocog alfa

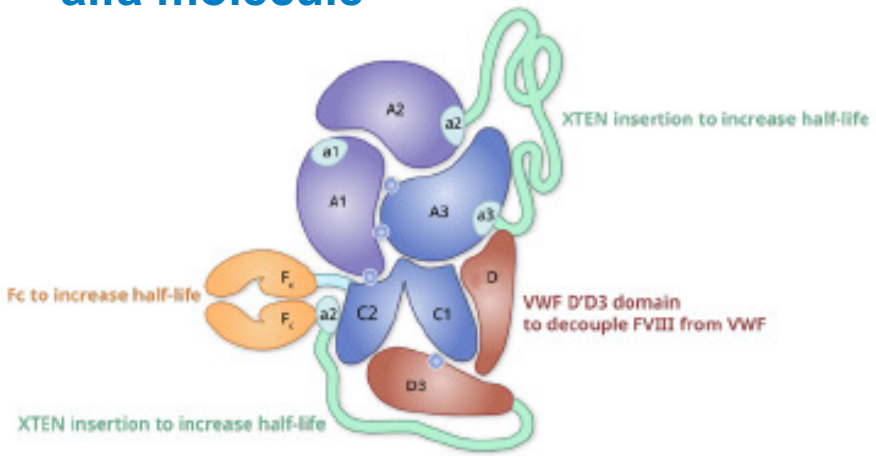
- Recombinant coagulation factor VIII Fc-VWF-XTEN fusion protein
- New class of factor VIII replacement therapy for hemophilia
- Designed to decouple recombinant factor VIII from endogenous VWF and thus overcome the VWF-imposed half-life ceiling on factor VIII replacement
  - Provides high sustained factor VIII activity by overcoming the VWF-imposed half-life ceiling

Fc, fragment crystallizable; VWF, von Willebrand factor.

von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318.

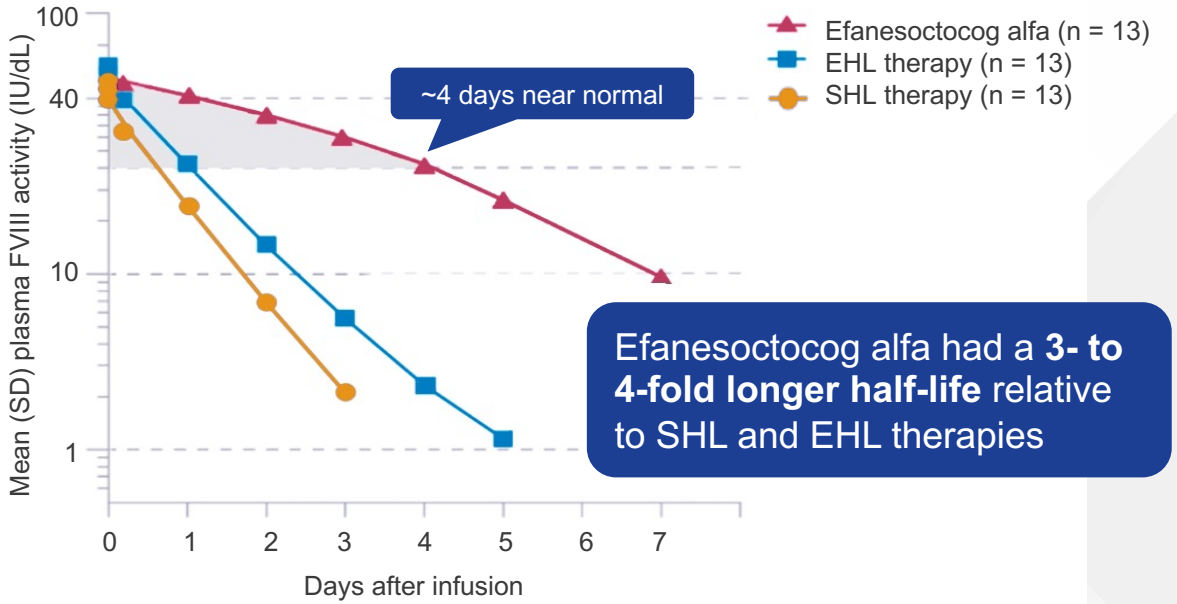
Efanesoctocog alfa

Molecular design of efanesoctocog alfa molecule



- Composed of a single recombinant factor VIII protein and 3 additional components that contribute to increased half-life:
  - An Fc domain that facilitates recycling through the neonatal Fc receptor pathway
  - Covalent linkage to a VWF D′D3 factor VIII binding domain to decouple recombinant factor VIII from endogenous VWF
  - Two XTEN polypeptides to shield efanesoctocog alfa from proteolytic degradation and clearance

Factor VIII activity levels in the normal to near-normal (>40%) range for most of the week in the Phase 1 PK study



Adapted from von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318. ALTUVIIIO. Prescribing information. Sanofi; 2023.
a1, a2, a3, acidic region 1, 2, 3; EHL, extended half-life; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; F, factor; PK, pharmacokinetic; SD, standard deviation; SHL, standard half-life; VWF, von Willebrand factor.

Novel Replacement Therapy

MOA	Drug	Dosing Regimen	Development Phase	Comments
Recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein	Efanesoctocog alfa	IV **For routine prophylaxis:** 50 IU/kg once weekly **For on-demand treatment and control of bleeding episodes:** single dose of 50 IU/kg	FDA-approved	Indication: for use in adults and children with hemophilia A (congenital factor VIII deficiency) for: • Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment & control of bleeding episodes • Perioperative management of bleeding

ALTUVIIIO. Prescribing information. Sanofi; 2023.
Fc, fragment crystallizable; FDA, US Food and Drug Administration; IV, intravenous; MOA, mechanism of action.

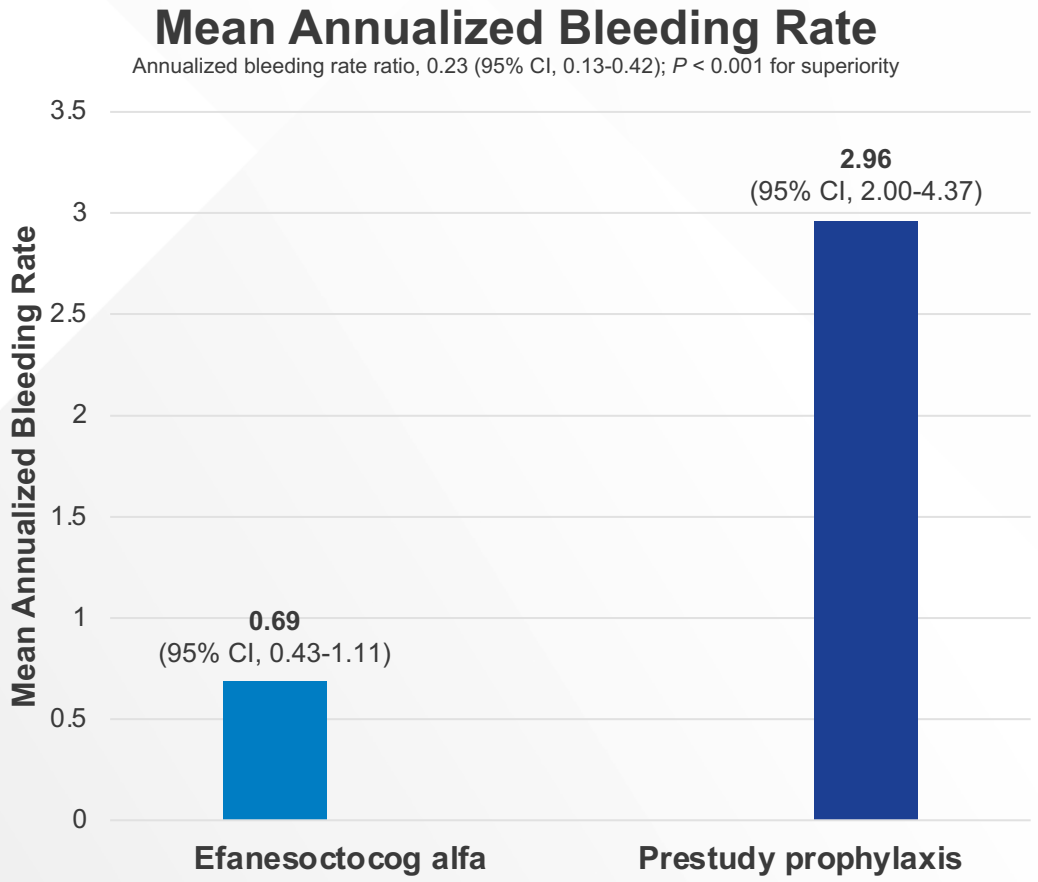
Efanesoctocog alfa Clinical Trials

Clinical trial	Phase	Population	ABR	Comments
XTEND-1 (NCT04161495)	3	Safety, efficacy, and pharmacokinetics in previously treated patients **≥12 years** of age with severe hemophilia A • Group A (N = 133): patients received once-weekly prophylaxis with efanesoctocog alfa (50 IU/kg of body weight) for 52 weeks • Group B (N = 26): patients received on-demand treatment for 26 weeks, followed by once-weekly prophylaxis for 26 weeks	Group A: • Mean: 0.7 • Median: 0.0 • Patients with 0 bleeding episodes: 86 (65%)	• Mean ABR decreased from 2.96 to 0.69, a finding that showed superiority over pre-study factor VIII prophylaxis - Significant reduction of 77% • In the overall population: - Nearly all bleeding episodes (97%) resolved with 1 injection - Acceptable side-effect profile - Development of inhibitors to factor VIII not detected • Prophylaxis with efanesoctocog alfa improved physical health ($P < 0.001$), pain intensity ($P = 0.03$), and joint health ($P = 0.01$) • ~4 days with mean factor VIII levels above 40% (normal to near-normal range)
XTEND-Kids (NCT04759131)	3	Safety, efficacy, and pharmacokinetics of once-weekly prophylaxis in previously treated pediatric patients **<12 years** of age with severe hemophilia A	• Mean: 0.89 • Median: 0.0	• Primary endpoint: occurrence of inhibitor development (baseline to 52 weeks) - No FVIII inhibitors detected in 74 children, with more than 50 children experiencing at least 50 exposure days, nearly a full year of treatment
XTEND-ed (NCT04644575)	3	Long-term extension study in previously treated patients with severe Hemophilia A		

Most common side effects (>10%): headache and arthralgia

von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318. Sanofi. https://www.sanofi.com/en/media-room/press-releases/2023/2023-03-02-07-00-00-2618928#.
ABR, annualized bleeding rate; FVIII, factor VIII.

XTEND-1 Trial



Annualized Bleeding Rates	Group A (N = 133)	
Endpoint	**Pre-study Prophylaxis**	**Efanesoctocog alfa Prophylaxis**
Primary Endpoint – ABR for efanesoctocog alfa prophylaxis		
Median ABR	-	0
Mean ABR, model based	-	0.71
Patients with zero bleeding episodes	-	86 (65%)
Key Secondary Endpoint – Intrapatient ABR comparison		
No. of patients evaluated	78	78
Median ABR	1.06	0
Mean ABR, model based	2.96	0.69
Rate ratio vs. pre-study prophylaxis	-	0.23
P value for superiority	-	<0.001

Adapted from von Drygalski A, et al. *N Engl J Med*. 2023;388:310-318.
ABR, annualized bleeding rate.

XTEND-Kids Trial

	N = 74
Occurrence of inhibitor development	0.0%
Median ABR	0.0
Estimated mean ABR	0.89
Zero bleeding episodes	64%
Zero joint bleeds	82%
Zero spontaneous bleeds	88%

- No development of inhibitors to FVIII or anti-drug antibodies was detected following treatment with efanesoctocog alfa
- Efanesoctocog alfa prophylaxis provided high sustained FVIII activity throughout the weekly dosing interval and in the normal to near-normal range (>40 IU/dL for ~3 days)
- Once-weekly prophylaxis provided effective bleed protection and treatment

Malec L, et al; XTEND-Kids Trial Group. ISTH 2023 Congress. Abstract LB01.1.
ABR, annualized bleeding rate; FVIII, factor VIII.

What Clinicians Need to Know About Shared Decision-Making in Hemophilia A

So, how do we choose?

SHARE Decision-Making Model

STEP 1 **Seek** your patient's participation.

STEP 2 **Help** your patient explore & compare treatment options.

STEP 3 **Assess** your patient's values and preferences.

STEP 4 **Reach** a decision with your patient.

STEP 5 **Evaluate** your patient's decision.

AHRQ. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html

Treatment Considerations

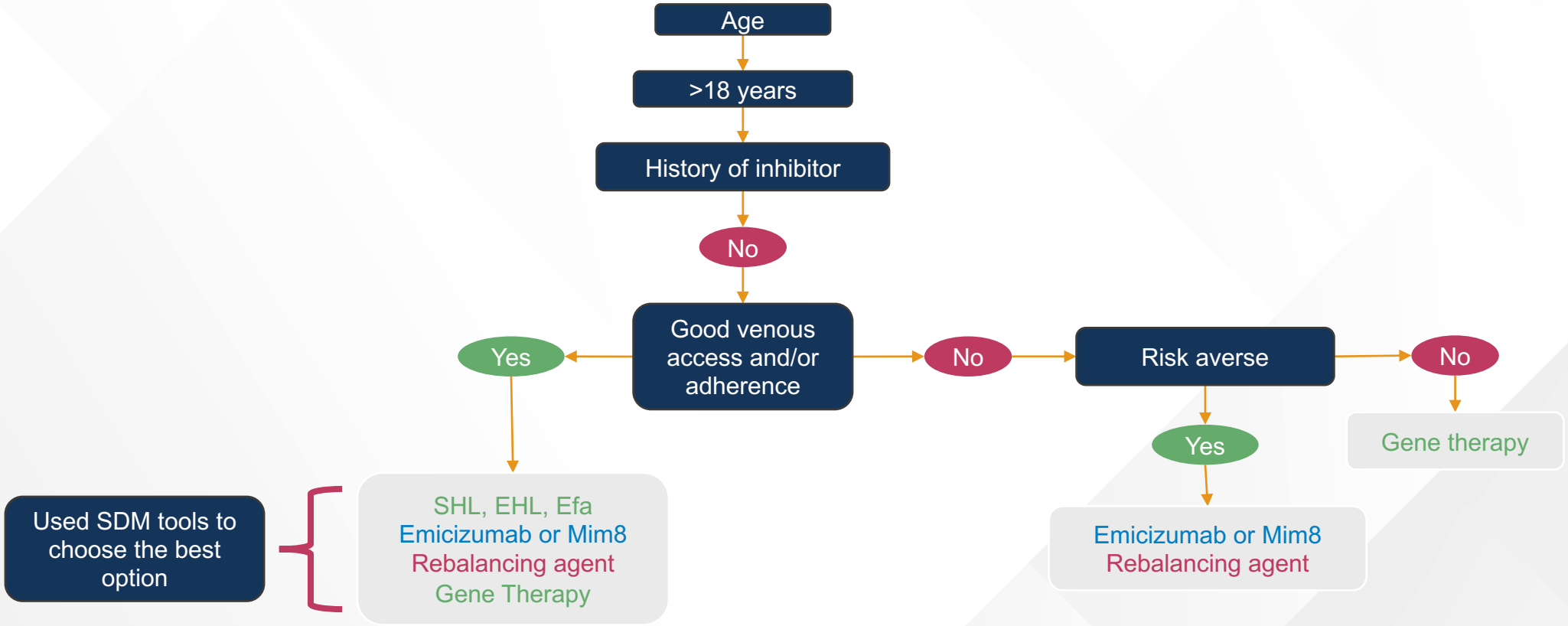
Patient Categories								
Age		Hemophilia type		Severity			Inhibitor status	
<18 years	>18 years	Hem A	Hem B	Severe	Moderate	Mild	Positive	Negative

Patient Categories								
Venous access		Adherence		Risk averse			Lifestyle (work or play)	
Good	Poor	Good	Bad	No	Med	Yes	Higher risk job/active	Sedentary

Patient Categories				
Age		Cardiovascular risk factors		Individual patient values
<58	>58	Yes	No	High efficacy v. Low treatment burden

Courtesy of Guy Young, MD.

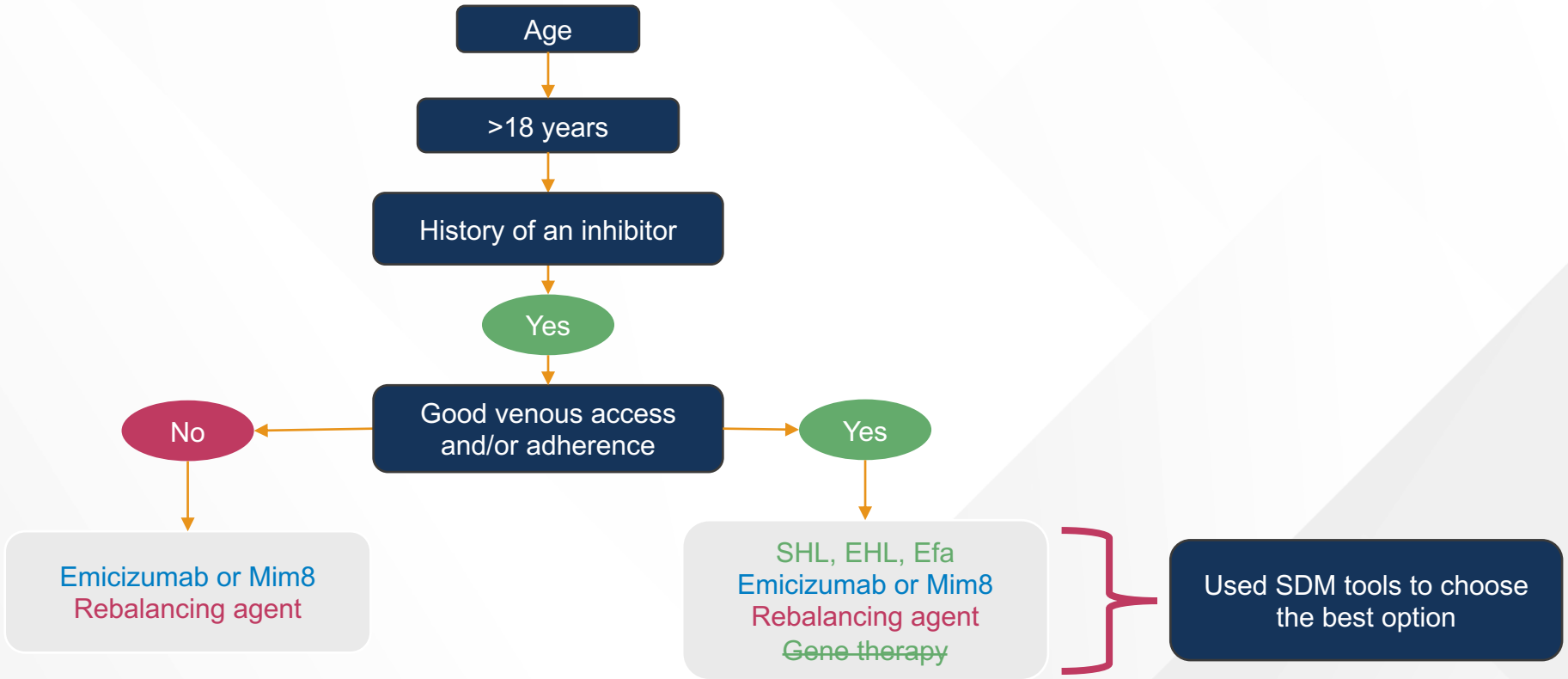
Hemophilia A—No Current Inhibitor



Courtesy of Guy Young, MD.

Efa, efanesoctocog alfa; EHL, extended half-life; SDM, shared decision-making; SHL, standard half-life.

Hemophilia A—No Current Inhibitor



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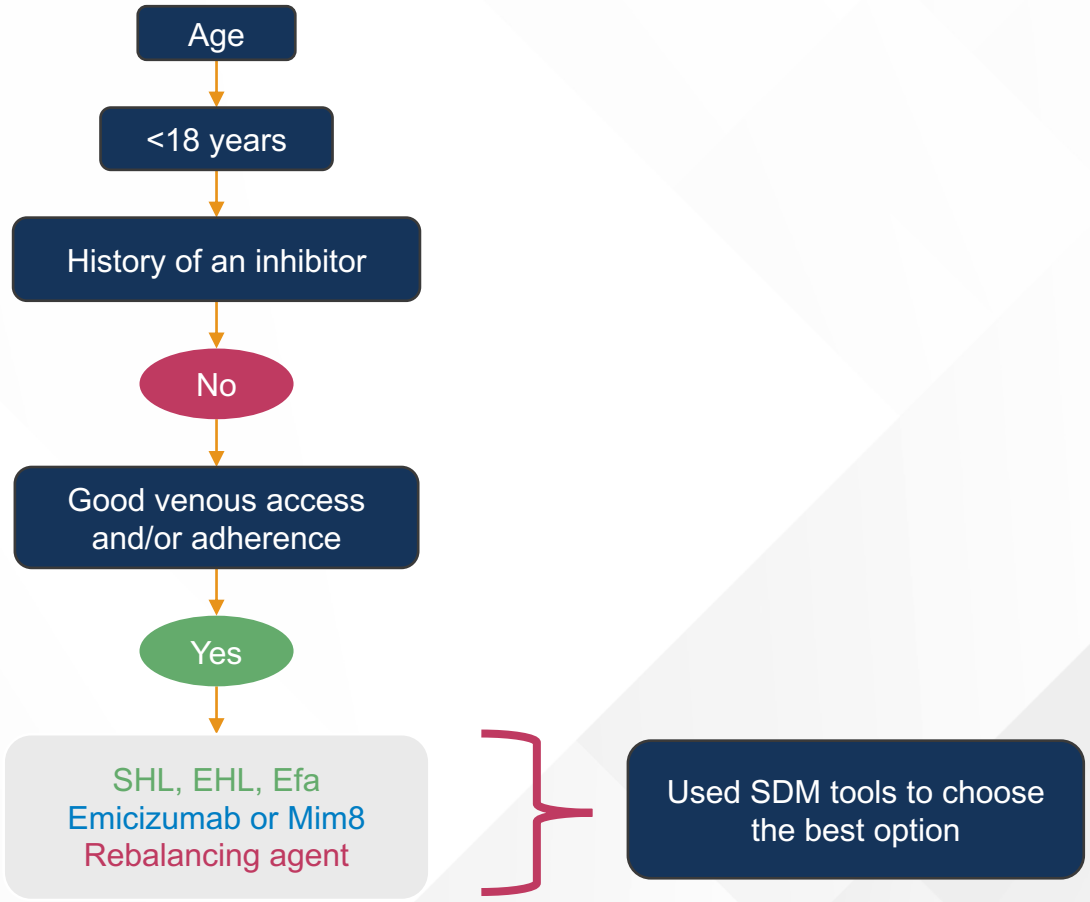
Hemophilia A—No Current Inhibitor



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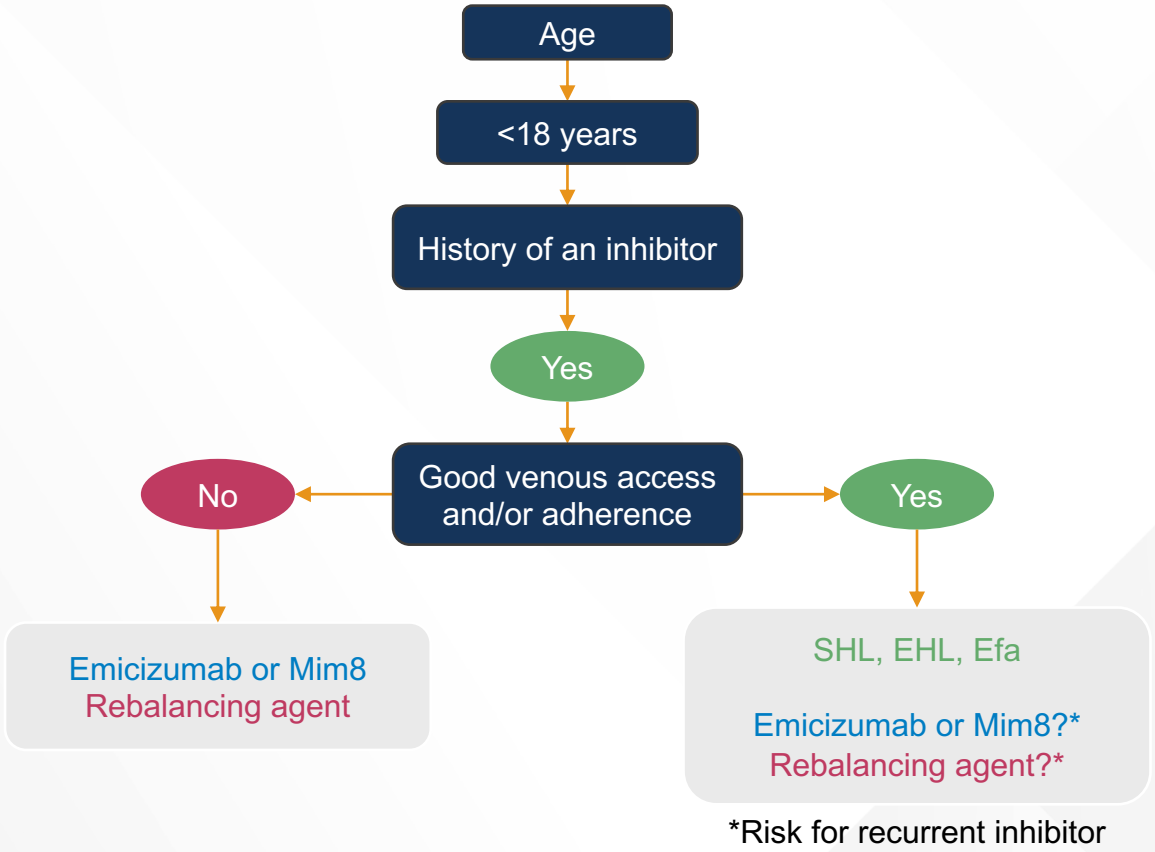
Hemophilia A—No Current Inhibitor

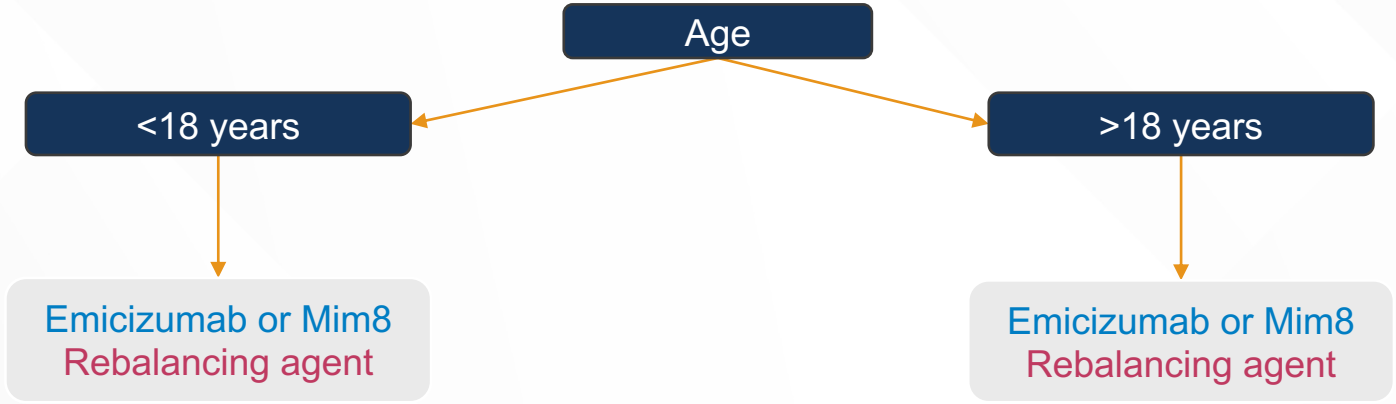


*Risk for recurrent inhibitor

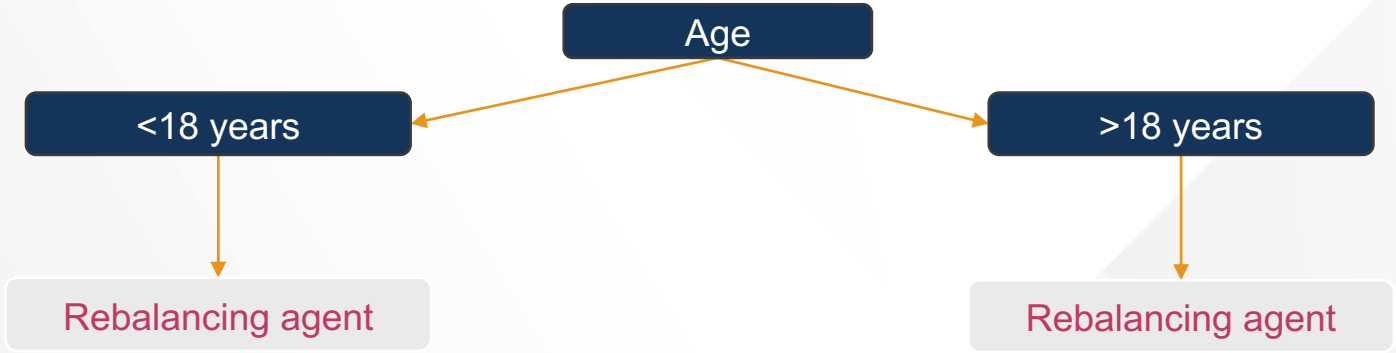
Courtesy of Guy Young, MD.

Efa, efanesoctocog alfa; EHL, extended half-life; SHL, standard half-life.

Hemophilia A—Active Inhibitor



Hemophilia B—Active Inhibitor



Courtesy of Guy Young, MD.

Questions to Ask Patients

- What is their definition of well controlled (in terms of bleeding)?
  - Does it agree with your definition?
  - If not, discuss what well-controlled should mean for them
- What are their goals and preferences?
  - Lifestyle issues discussed earlier
- What aspects of treatment are most important to them?
  - Is bleed prevention the ONLY thing that matters?
  - Is ease of administration the ONLY thing that matters?
  - What combination of improving their disease burden and treatment burden is ideal for them?

- Co-create treatment plans to improve adherence and reduce bleeding episodes
- Using SDM to help improve the level of health equity in persons with HA that is similar to their unaffected peers

HA, hemophilia A; SDM, shared decision making.

Steps to Improve Outcomes

- Make a treatment plan patients/caregivers agree with
  - This will improve their buy-in and improve their adherence
  - Don’t dictate to them what you think they should do
- Explain health equity to your patients
  - That your goal is for them to live a normal life like their non-hemophilia relatives
  - Convince them that is achievable
  - Your optimism will be reflected in theirs and including them in the decision making will result in the best outcomes and best quality of life

AXIS Medical Education

Lowering Burden to Raise Adherence:

Optimizing Prophylaxis for Hemophilia A