AXIS Medical Education

Hemophilia A:

Strategies for Improving Long-Term Holistic Management, Adherence and Quality of Life

DISCLAIMER

This slide deck in its original and unaltered format is for educational purposes and is current as of December 2021. All materials contained herein reflect the views of the faculty, and not those of AXIS Medical Education, the CME provider, or the commercial supporter. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

DISCLOSURE OF UNLABELED USE

This activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

USAGE RIGHTS

This slide deck is provided for educational purposes and individual slides may be used for personal, non-commercial presentations only if the content and references remain unchanged. No part of this slide deck may be published in print or electronically as a promotional or certified educational activity without prior written permission from AXIS. Additional terms may apply. See Terms of Service on www.axismeded.com for details.

Disclosure of Conflicts of Interest

Miguel A. Escobar, MD, reported a financial interest/relationship or affiliation in the form of *Consultant*: Biomarin; Kedrion Biopharma; Rani Therapeutics; Magellan Pharmaceuticals; Takeda Pharmaceutical Co, Ltd; sanofi; uniQure; CSL Bering; Genentech, Inc; Novo Nordisk; and Pfizer, Inc. *Serve(d) as a speaker or a member of a speakers bureau for*: CSL Bering; Novo Nordisk; Pfizer, Inc; Kedrion Biopharma; Roche; and Bayer HealthCare, Inc. *Contracted research*: Takeda Pharmaceutical Co, Ltd; Novo Nordisk; uniQure; sanofi; Pfizer, Inc; Opto Biologics; and Genentech, Inc.

Cindy Leissinger, MD, reported a financial interest/relationship or affiliation in the form of *Advisory board*: Bayer HealthCare, Inc; CSL Bering; Catalyst Pharmaceuticals; Genentech, Inc; uniQure; sanofi; and Takeda Oncology. *Contracted research*: BioMarin Pharmaceutical, Inc.

Guy A. Young, MD, reported a financial interest/relationship or affiliation in the form of *Serve(d) as a speaker or a member of a speaker's bureau for*: Genentech, Inc; BioMarin Pharmaceutical, Inc; sanofi; Takeda Oncology; and Grifols. *Consultant*: BioMarin Pharmaceutical, Inc; Genentech, Inc; Spark Therapeutics; sanofi; Novo Nordisk; and Takeda Oncology.

AXIS Medical Education

Learning Objectives

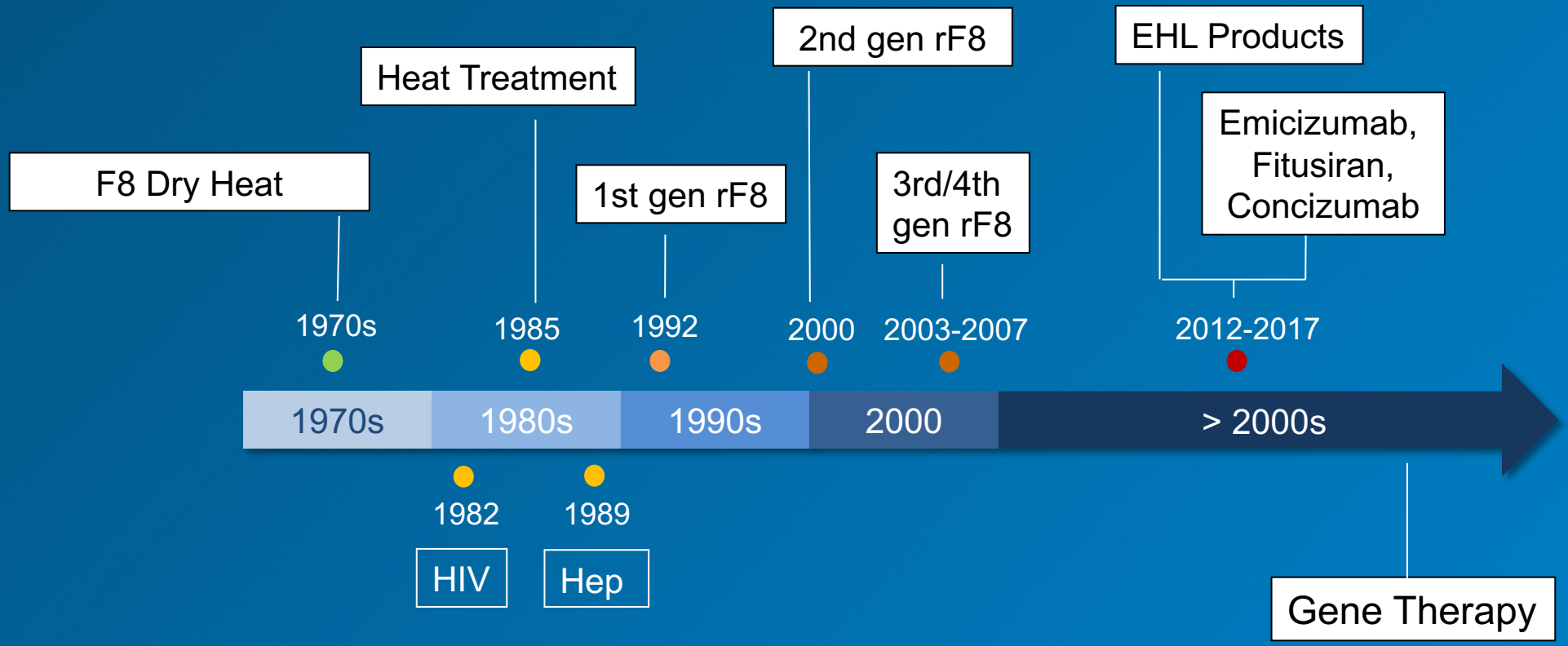
Upon completion of this activity, participants should be better able to:

- Evaluate currently available prophylactic therapies for hemophilia A to select the treatment best suited to the individual patient
- Analyze currently available safety and efficacy data from clinical trials and real-world studies on bispecific antibody non–factor replacement therapy to make informed management decisions
- Incorporate quality of life and cost data into shared decision making with patients to maximize treatment adherence

AXIS Medical Education

Overview of Hemophilia A

Historical Overview of Therapies in Hemophilia

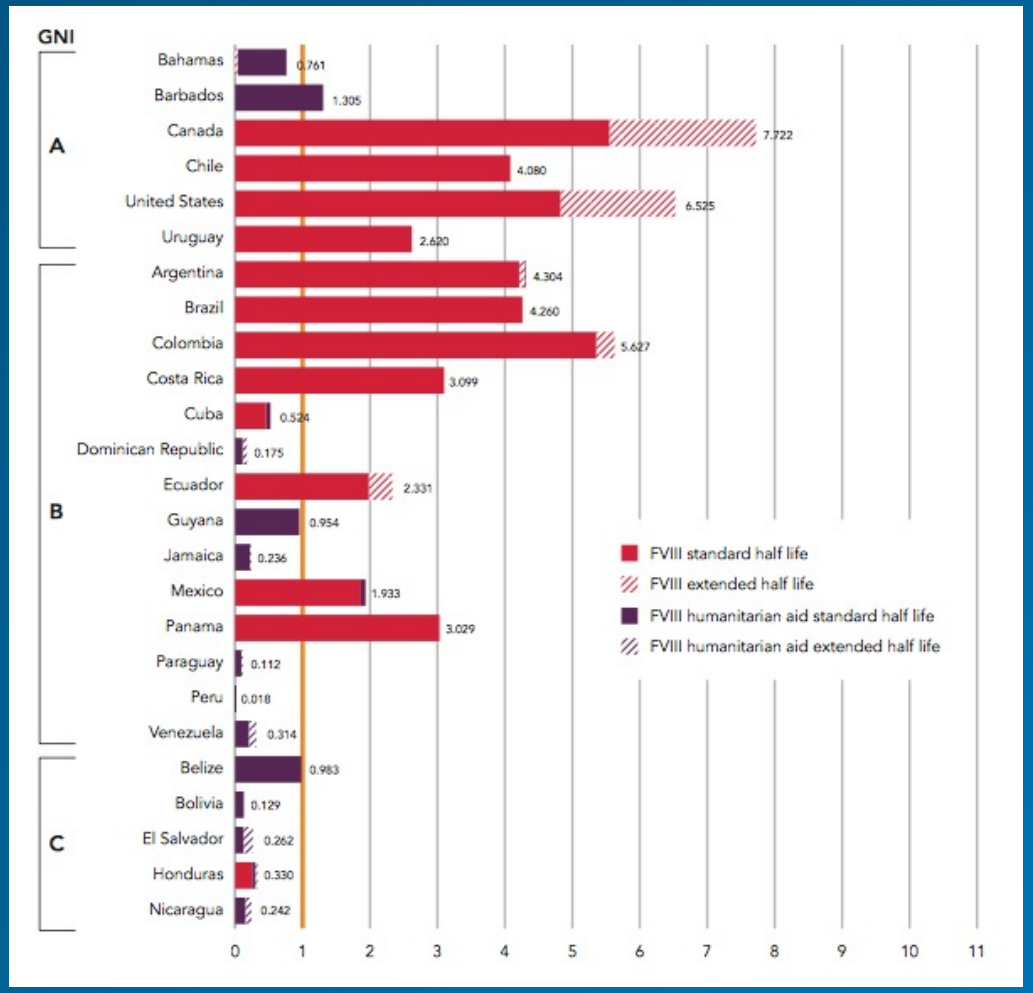


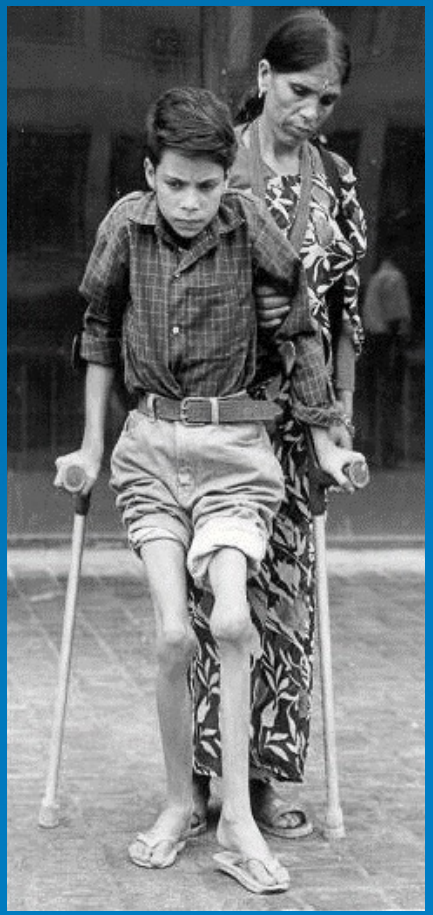
F8, factor 8; rF8, recombinant factor 8; EHL, extended-half life.

AXIS Medical Education

2020 WFH Annual Global Survey
Mean per Capita Factor VIII Use in 2020: Americas

Regional and GNI Comparisons of IU/total Population





GNI, gross national income; IU, international unit; WFH, World Federation of Hemophilia.

World Federation of Hemophilia. 2020. Annual Global Survey.

AXIS Medical Education

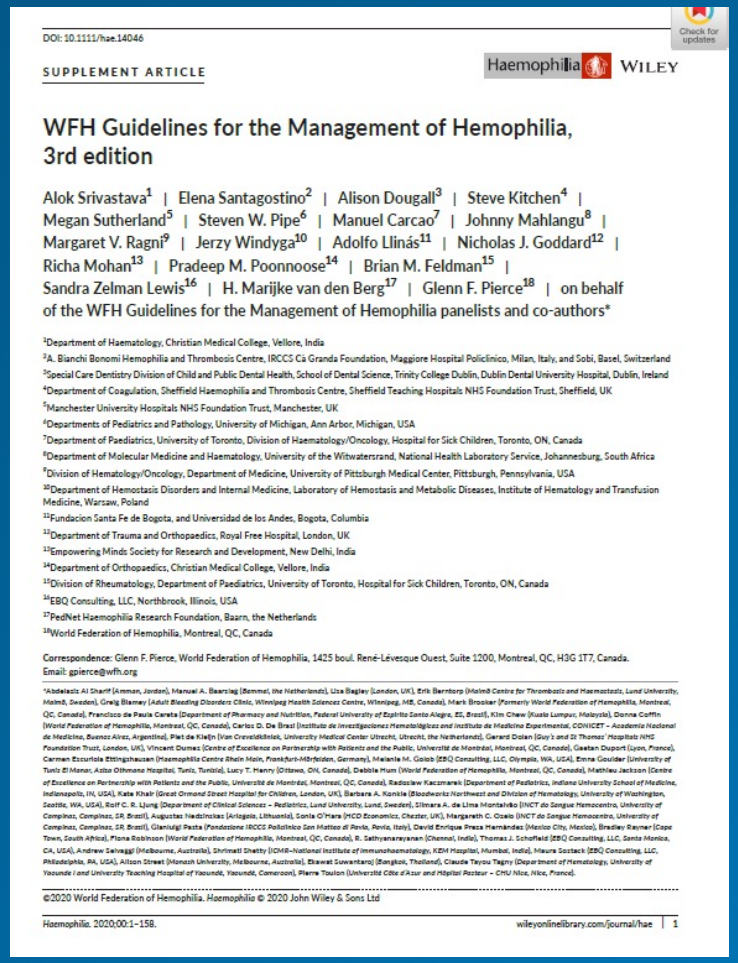
2020 WFH Annual Global Survey
Percentage of Patients on Prophylaxis (95 Countries)

Country	Percent under 18 on prophylaxis	Precise or estimate	Percent over 18 on prophylaxis	Precise or estimate
Argentina	80	Estimate	15	Estimate
Armenia	50	Estimate	25	Estimate
Australia	92	Estimate	76	Estimate
Austria	88	Precise	74	Precise
Bahamas	0	Precise	0	Precise
Barbados	6	Estimate	1	Estimate
Belarus	100	Estimate	2	Estimate
Belgium	90	Estimate	75	Estimate
Brazil	87	Precise	64	Precise
Cambodia	2	Estimate	1	Estimate
Cameroon	0	Precise	0	Precise
Canada	91	Estimate	82	Estimate
Chile	100	Estimate	50	Estimate
Colombia	97	Precise	85	Precise
Costa Rica	50	Precise	50	Precise
Georgia	30	Estimate	-	-
Germany	100	Estimate	-	-
Ghana	60	Estimate	50	Estimate
Greece	93	Precise	67	Precise
Ireland	96	Estimate	95	Estimate
Israel	95	Precise	72	Precise

WFH, World Federation of Hemophilia.
Adapted from World Federation of Hemophilia. 2020. Annual Global Survey.

AXIS Medical Education

WFH Guidelines for the Management of Hemophilia, 3rd Edition



DOI: 10.1111/hae.14046

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*

[1]Department of Haematology, Christian Medical College, Vellore, India
[2]A. Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Cà Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy, and Sobi, Basel, Switzerland
[3]Special Care Dentistry Division of Child and Public Dental Health, School of Dental Science, Trinity College Dublin, Dublin Dental University Hospital, Dublin, Ireland
[4]Department of Coagulation, Sheffield Haemophilia and Thrombosis Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[5]Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[6]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, Michigan, USA
[7]Department of Paediatrics, University of Toronto, Division of Haematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada
[8]Department of Molecular Medicine and Haematology, University of the Witwatersrand, National Health Laboratory Service, Johannesburg, South Africa
[9]Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[10]Department of Hemostasis Disorders and Internal Medicine, Laboratory of Hemostasis and Metabolic Diseases, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[11]Fundacion Santa Fe de Bogota, and Universidad de los Andes, Bogota, Columbia
[12]Department of Trauma and Orthopaedics, Royal Free Hospital, London, UK
[13]Empowering Minds Society for Research and Development, New Delhi, India
[14]Department of Orthopaedics, Christian Medical College, Vellore, India
[15]Division of Rheumatology, Department of Paediatrics, University of Toronto, Hospital for Sick Children, Toronto, ON, Canada
[16]EBQ Consulting, LLC, Northbrook, Illinois, USA
[17]PedNet Haemophilia Research Foundation, Baarn, the Netherlands
[18]World Federation of Hemophilia, Montreal, QC, Canada

Correspondence: Glenn F. Pierce, World Federation of Hemophilia, 1425 boul. René-Lévesque Ouest, Suite 1200, Montreal, QC, H3G 1T7, Canada.
Email: gpierce@wfh.org

*Abdelaziz Al Sharif (Amman, Jordan), Manuel A. Baarslag (Bemmel, the Netherlands), Liza Bagley (London, UK), Erik Berntorp (Malmö Centre for Thrombosis and Haemostasis, Lund University, Malmö, Sweden), Greig Blamey (Adult Bleeding Disorders Clinic, Winnipeg Health Sciences Centre, Winnipeg, MB, Canada), Mark Brooker (Formerly World Federation of Hemophilia, Montreal, QC, Canada), Francisco de Paula Careta (Department of Pharmacy and Nutrition, Federal University of Espírito Santo Alegre, ES, Brazil), Kim Chew (Kuala Lumpur, Malaysia), Donna Coffin (World Federation of Hemophilia, Montreal, QC, Canada), Carlos D. De Brasi (Instituto de Investigaciones Hematológicas and Instituto de Medicina Experimental, CONICET – Academia Nacional de Medicina, Buenos Aires, Argentina), Piet de Kleijn (Van Creveldkliniek, University Medical Center Utrecht, Utrecht, the Netherlands), Gerard Dolan (Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK), Vincent Dumez (Centre of Excellence on Partnership with Patients and the Public, Université de Montréal, Montreal, QC, Canada), Gaetan Duport (Lyon, France), Carmen Escuriola Ettinghausen (Haemophilia Centre Rhein Main, Frankfurt-Höchstden, Germany), Melanie M. Golob (EBQ Consulting, LLC, Olympia, WA, USA), Enna Gaulder (University of Tunis El Manar, Aziza Othmana Hospital, Tunis, Tunisia), Lucy T. Henry (Ottawa, ON, Canada), Debbie Hum (World Federation of Hemophilia, Montreal, QC, Canada), Mathieu Jackson (Centre of Excellence on Partnership with Patients and the Public, Université de Montréal, Montreal, QC, Canada), Radoslaw Kaczmarek (Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA), Kate Khair (Great Ormond Street Hospital for Children, London, UK), Barbara A. Konkle (Bloodworks Northwest and Division of Hematology, University of Washington, Seattle, WA, USA), Rolf C. R. Ljung (Department of Clinical Sciences – Pediatrics, Lund University, Lund, Sweden), Silmara A. de Lima Montalvão (INCT do Sangue Hemocentro, University of Campinas, Campinas, SP, Brazil), Augustas Nedzinskas (Ariogala, Lithuania), Sonia O'Hara (HCD Economics, Chester, UK), Margareth C. Ozelo (INCT do Sangue Hemocentro, University of Campinas, Campinas, SP, Brazil), Gianluigi Pasta (Fondazione IRCCS Policlinico San Matteo di Pavia, Pavia, Italy), David Enrique Presa Hernández (Mexico City, Mexico), Bradley Rayner (Cape Town, South Africa), Fiona Robinson (World Federation of Hemophilia, Montreal, QC, Canada), R. Sathyanarayanan (Chennai, India), Thomas J. Schofield (EBQ Consulting, LLC, Santa Monica, CA, USA), Andrew Selvaggi (Melbourne, Australia), Shrimati Shetty (ICMR–National Institute of Immunohaematology, KEM Hospital, Mumbai, India), Maura Szostack (EBQ Consulting, LLC, Philadelphia, PA, USA), Alison Street (Monash University, Melbourne, Australia), Ekawat Suwantaroo (Bangkok, Thailand), Claude Tayou Tagny (Department of Hematology, University of Yaounde I and University Teaching Hospital of Yaounde, Yaounde, Cameroon), Pierre Toulon (Université Côte d'Azur and Hôpital Pasteur – CHU Nice, Nice, France).

©2020 World Federation of Hemophilia. Haemophilia © 2020 John Wiley & Sons Ltd

- 12 Chapters
- >50 Participants
- 338 Recommendations

WFH, World Federation of Hemophilia.
Srivastava et al. *Haemophilia* 2020:00;1-158.

AXIS Medical Education

Definition of Prophylaxis

Old Definition

- Regular infusion of clotting factor concentrates to prevent bleeds in people with hemophilia A and B

New Definition

- Regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding
- Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical activities (at home, school, work, and in the community), similar to the non-hemophilic population

Berntorp. *Haemophilia* 2003; 9(suppl 1):1-4.
Carcao et al. *Haemophilia* 2018; 24(6):845-848.
Srivastava et al. *Haemophilia* 2020:26(suppl 6):1-158.

AXIS Medical Education

Definition of Prophylaxis

Primary prophylaxis	Regular continuous prophylaxis **started in the absence of documented joint disease**, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and 3 years of age
Secondary prophylaxis	Regular continuous prophylaxis **initiated after 2 or more joint bleeds** but before the onset of joint disease; this is usually at 3 or more years of age
Tertiary prophylaxis	Regular continuous prophylaxis **initiated after the onset of documented joint disease**. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood

Prophylaxis Defined According to Intensity		
Prophylaxis Intensity	**Hemophilia A**	**Hemophilia B**
High-dose prophylaxis	25-40 IU FVIII/kg every 2 days (>4,000 IU/kg per year)	40-60 IU FIX/kg twice per week (>4,000 IU/kg per year)
Intermediate-dose prophylaxis	15-25 IU FVIII/kg 3 days per week (1,500-4,000 IU/kg per year)	20-40 IU FIX/kg twice per week (2,000-4,000 IU/kg per year)
Low-dose prophylaxis (with escalation of dose intensity, as needed)	10-15 IU FVIII/kg 2-3 days per week (1,000-1,500 IU/kg per year)	10-15 IU FIX/kg 2 days per week (1,000-1,500 IU/kg per year)

Srivastava et al. *Haemophilia* 2020:26(suppl 6):1-158.

AXIS Medical Education

Factor VIII Concentrates

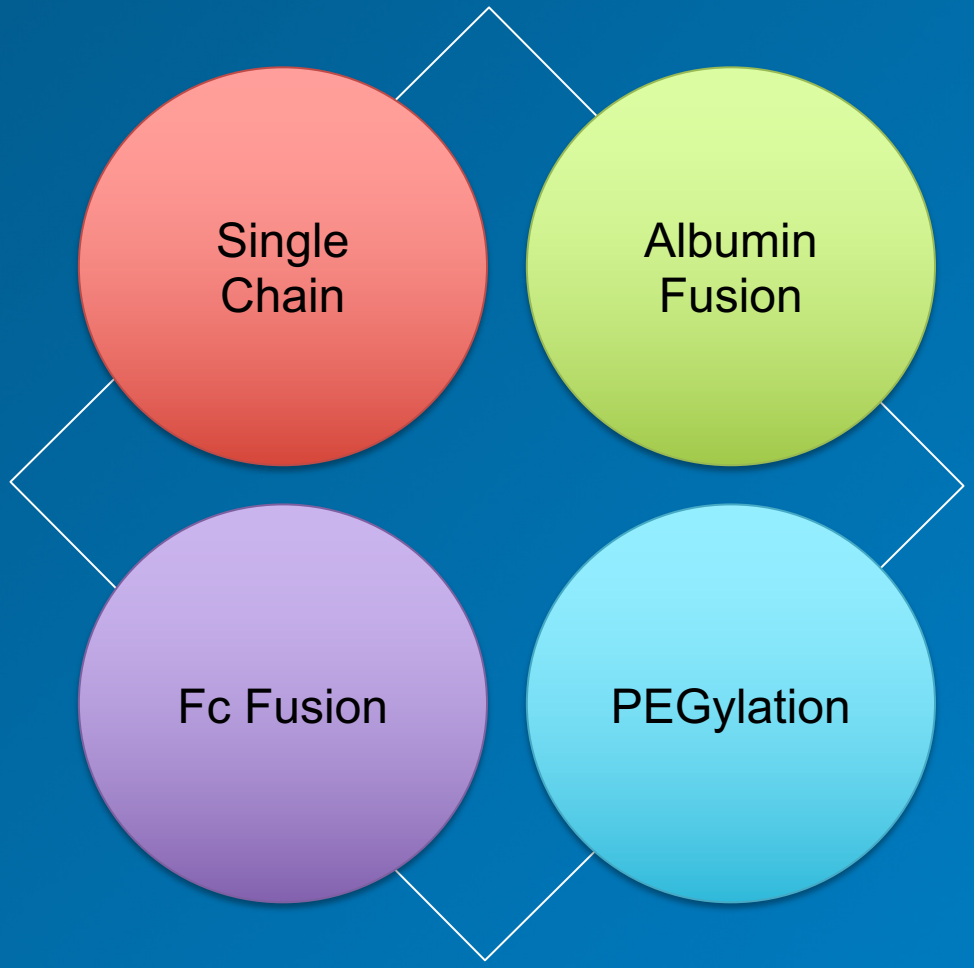
Product	Cell Line	FVIII Construct	Additional Features	Mean Adult Half-life ± SD, hr
Turoctocog alfa	CHO	B-domain truncated		10.8 ± 4.9
Ionoctocog alfa	CHO	B-domain truncated	Single-chain, FVIII activity by 1-stage clotting assay, multiply by 2x conversion factor	14.2 ± 3.7
Octocog alfa	BHK	Full-length	Includes human chaperone protein HSP70 to assist protein folding	14.3 ± 3.7
Rurioctocog alfa pegol	CHO	Full-length	Random pegylation with branched 20kDa PEG, most covalently bind to B-domain	14.7 ± 3.8
Simoctocog alfa	HEK-293	B-domain deleted		17.1 ± 11.2
Damoctocog alfa pegol	BHK	B-domain deleted	Site-directed pegylation with 60kDa PEG, linked to introduced cysteine residue	18.7
Efmoroctocog alfa	HEK-293	B-domain deleted	Fusion with IgG1 Fc at carboxy-terminus	19.7 ± 2.3
Turoctocog alfa pegol	CHO	B-domain truncated	Site-directed pegylation with 40kDa PEG, conjugated to 21 amino acid B-domain sequence	19

FVIII, factor VIII; HSP, heat shock protein; IgG, immunoglobulin G; PEG, polyethylene glycol.

Croteau. *Pediatr Clin North Am*. 2018;65:407. Peyvandi et al. *J Thromb Haemost*. 2013;11:84.

AXIS Medical Education

Strategies to Extend the Half-Life of Recombinant Clotting Factors



Pipe. *Hematol Am Soc Hematol Educ Program* 2016;2016(1):650-656.

AXIS Medical Education

Extended Half-Life Factors for Hemophilia A

Half-life prolongation is limited by the dependence of FVIII on VWF

	rVIII-SingleChain[2] (50 IU/kg)	hrFVIII[3] (50 IU/kg)	rFVIIIFc[4] (50 IU/kg)	BAX 855[5] (45 ± 5 IU/kg)	BAY 94-9027[6,7] (60 IU/kg)	N8-GP[8] (25-75 IU/kg)
AUC, IU*hr/dL	1,830 (34.9)	2,260 (8.0)	2,800 (1,980-3,970)*	2,073 (778)	4,329 (3,087-8,578)	3,885 (1,141)
Half-life, hr	**14.1** (27.1)	**14.7** (10.4)	**19.0** (17.0-21.1)	**14.3**	**18.5** (15.1-23.4)	**23.08** (5.24)
Clearance, mL/hr/kg	3.15 (38.2)	3.0 (1.2)	2.0 (1.7-2.2)	2.76 (2.03)	1.4 (0.7-1.9)	1.39 (0.42)

All results are mean (SD) or median (range)
*Dosed at 65 IU/kg
ABR, annualized bleeding rate; AUC, area under the curve.

1. Pipe et al. *Blood* 2016;128:2007-2016.
2. Mahlangu et al. *Blood* 2016;128:630-637.
3. Octapharma. Nuwiq Summary of Product Characteristics 2016.
4. Mahlangu et al. *Blood* 2014;123:317-325.
5. Powell et al. *Blood* 2012;119:3031-3037.
6. SOBI Biosciences. Adynovate Prescribing Information. 2016.
7. Coyle et al. *J Thromb Haemost* 2014;12:488-496.
8. Tiede et al. *J Thromb Haemost* 2013;11:670-678.

AXIS Medical Education

Efficacy of Extended Half-Life FVIII Products

rFVIIIFc	≥12 years			6-12 years	<6 years
	Modified	Individualized	Weekly	Individualized	Individualized
ABR	1.97 (0.96-7.03)	0.66 (0.00-2.63)	2.03 (0.60-4.39)	1.54 (0.00-3.41)	0.00 (0.00-2.00)
AsBR	0.96 (0.00-5.51)	0.00 (0.00-1.23)	0.76 (0.00-2.6)	0.00 (0.00-1.75)	0.00 (0.00-0.00)

	N8-GP		BAX 855		BAY 94-9027 (Median [Q1, Q3])			
	12-66 years	<12 years	12-65 years	0- <12 years	15-67 years			<12 years
	1-2 × weekly	2 × weekly	2 × weekly	2 × weekly	2 × weekly	Every 5 days	Every 7 days	1-2 × weekly
ABR	1.18 (0.00–4.25)	1.95 (0-2.79)	1.9 (0.0-5.8)	2.0 (0.0-3.9)	1.8 (0.3-4.6)	1.3 (0.0-4.6)	0.7 (0.0-1.6)	2.87 (1-7)
AsBR	0.00 (0.00–1.82)	0 (0-0)	0.0 (0.0-2.2)	0 (0-1.9)	-	-	-	-

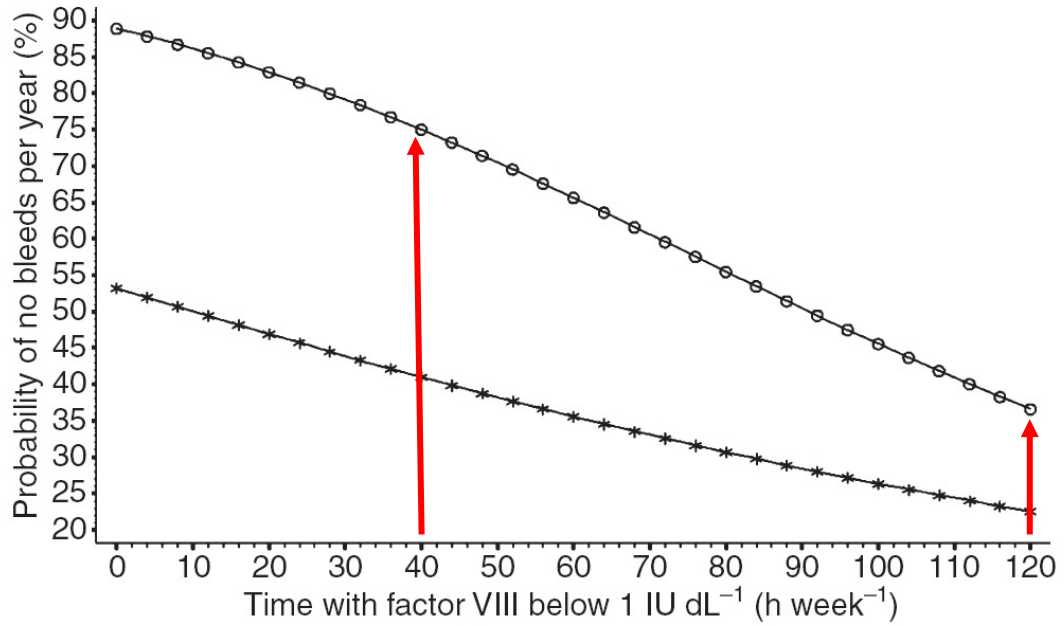
ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate.

1. Nolan et al. *Haemophilia* 2016;22:72-80.
2. Pasi et al. *Thromb Haemost* 2017;117:508-518.
3. Fischer et al. *Lancet Haematol* 2017;4:e75-82.

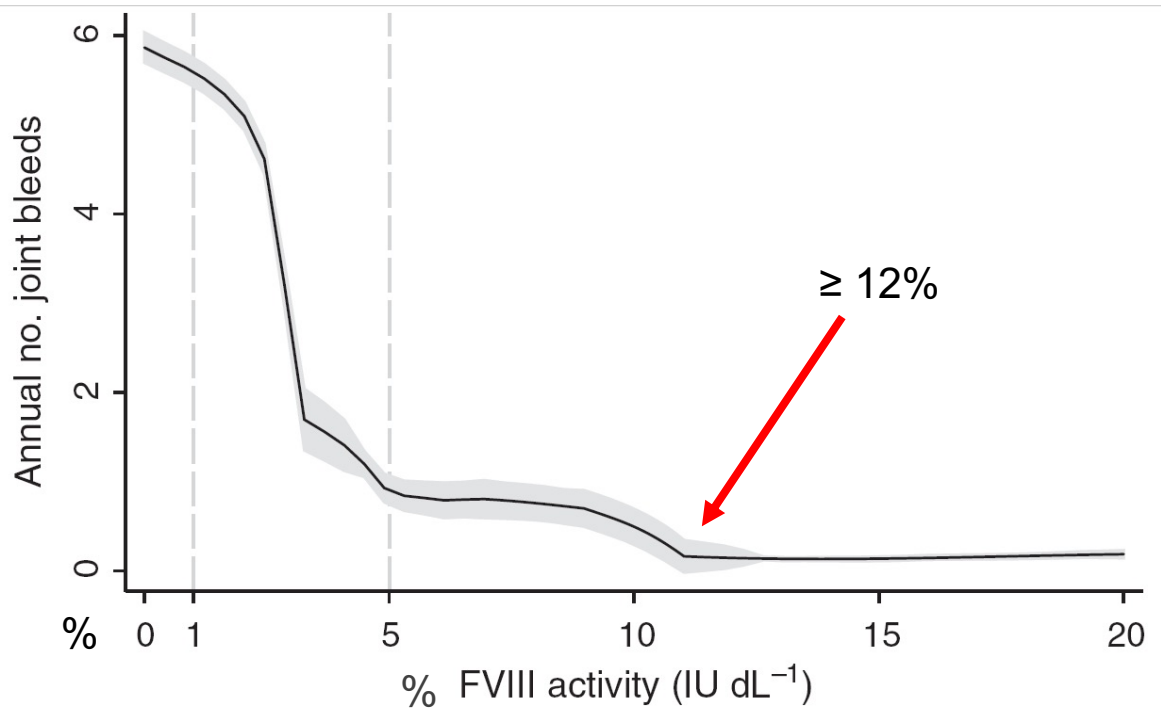
AXIS Medical Education

Correlation Between Factor Levels and Bleeding

Annual probability of zero bleeds by time below 1%



Annual number of joint bleeds by FVIII activity

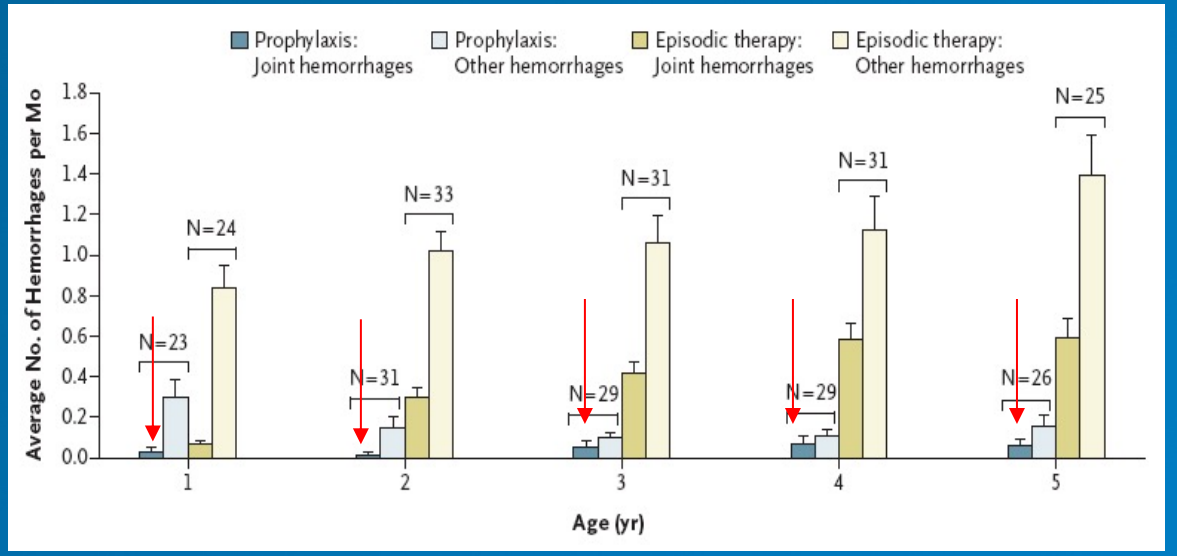


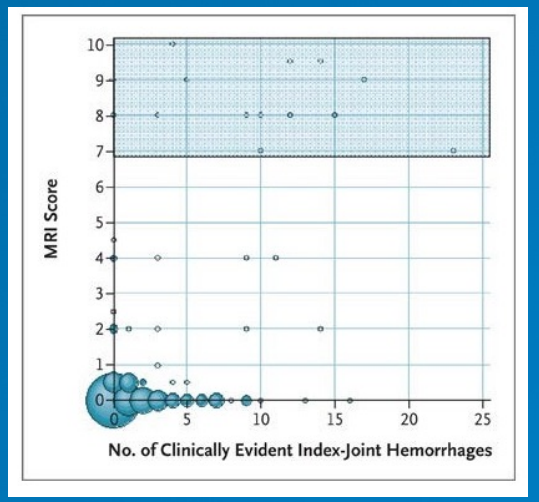
Collins et al. *J Thromb Haemost*. 2009;7(3):413-420.
den Uijl et al. *Haemophilia* 2011;17:849-853.

AXIS Medical Education

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

- **Prophylaxis:** 25 IU/kg every other day
- **Episodic/On-demand:** 40 IU/kg followed by 20 IU/kg
- Considered to have normal index-joint structure on MRI (*P* = .006) when boys reached 6 years of age:
  - 93% in the prophylaxis group
  - 55% in the episodic-therapy group



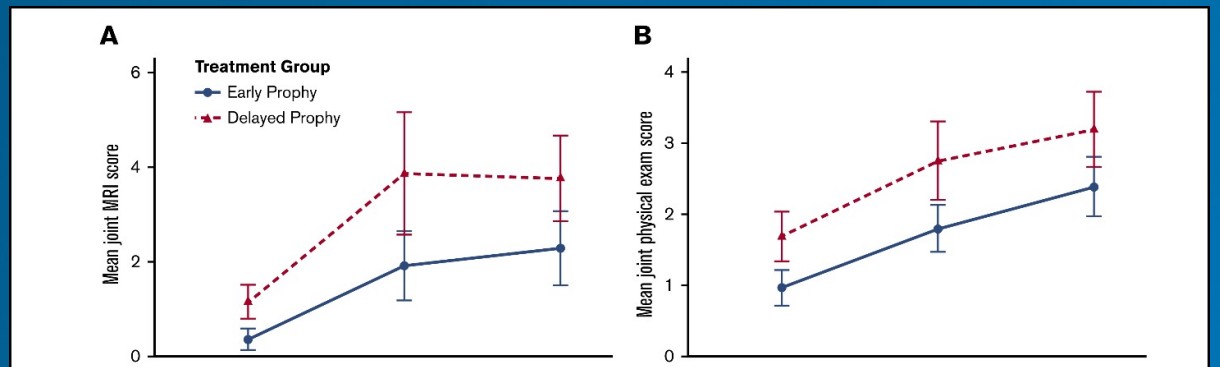


Manco-Jonson et al. *N Engl J Med*. 2007;357:535-544.

AXIS Medical Education

Young Adult Outcomes of Childhood Prophylaxis for Severe Hemophilia A: Results of the Joint Outcome Continuation Study

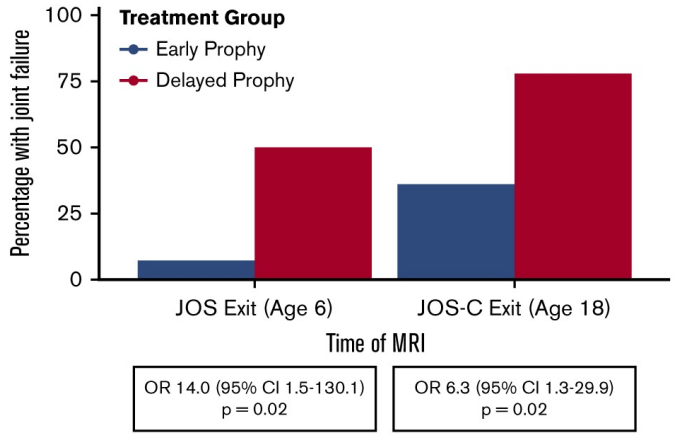
- Initiation of prophylaxis prior to age 2.5 years is critical to protect the joints of patients with severe hemophilia
- Those who delay initiation of prophylaxis have higher bleeding rates and increased development of arthropathy



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	

Follow-up patients from the JOS

In late adolescence, children with Severe Hemophilia A started on prophylactic factor VIII after age 6 years had higher rates of osteochondral damage on MRI ("joint failure") than those started on prophylactic factor VIII before age 2 years.



JOS, Joint Outcome Study.

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

AXIS Medical Education

WFH Recommendation for Pediatric Patients

"For **pediatric patients** with severe haemophilia A or B, the WFH recommends **early initiation of prophylaxis** with clotting factor concentrates (standard or extended half-life) or other hemostatic agent(s) **prior to the onset of joint disease** and ideally before age 3."

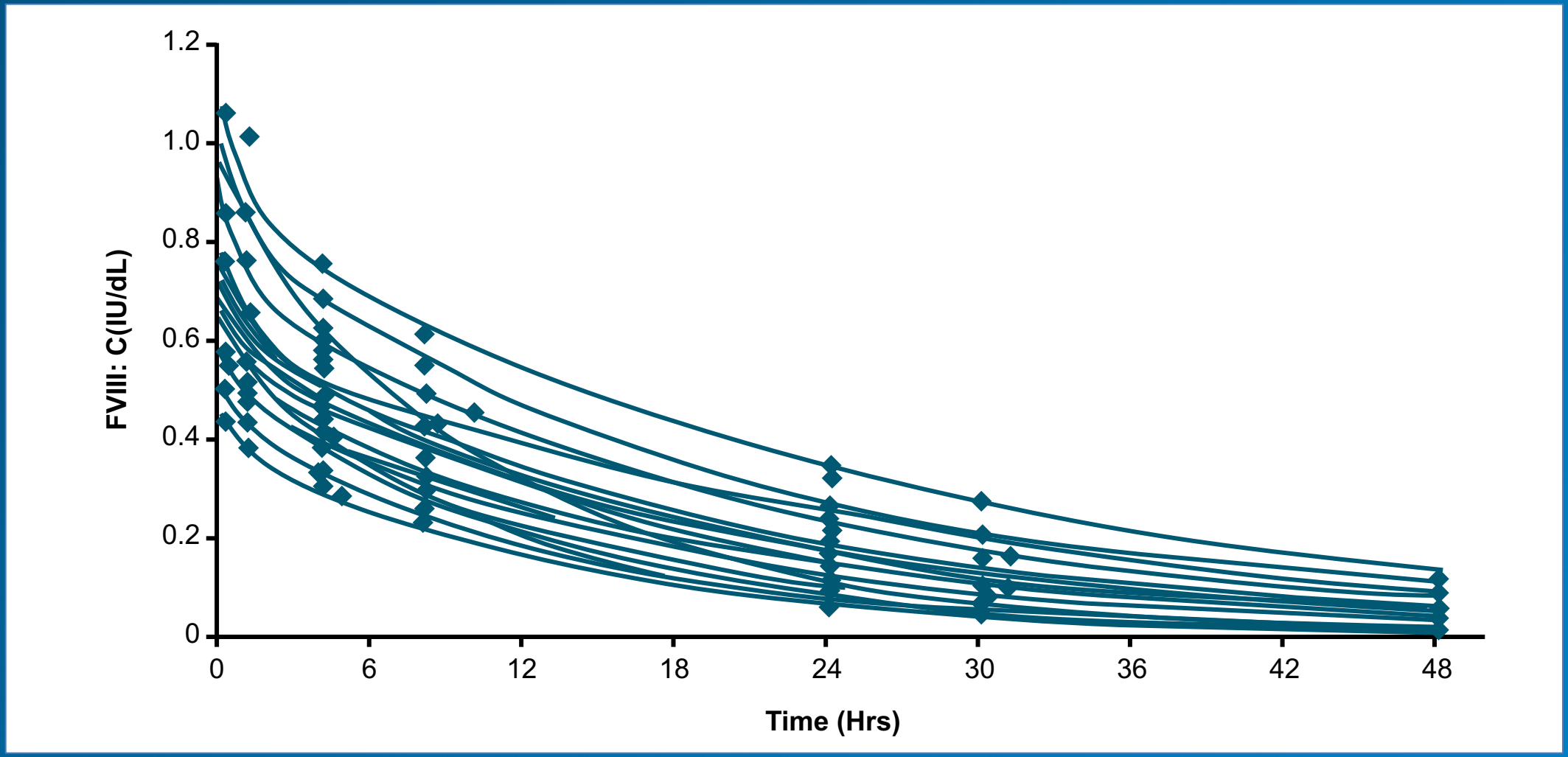
WFH, World Federation of Hemophilia.
Srivastava et al. *Haemophilia* 2020:26(suppl 6);1-158.

WFH Recommendation for Adolescents & Adults

"For **adolescents** and **adults** with haemophilia
who show **evidence of joint damage** and have not as yet been on prophylaxis,
the WFH recommends **commencing tertiary prophylaxis**
in order to **reduce** the number of hemarthroses, spontaneous and breakthrough bleeding,
and **slow down** the progression of hemophilic **arthropathy**."

WFH, World Federation of Hemophilia.
Srivastava et al. *Haemophilia* 2020:26(suppl 6);1-158.

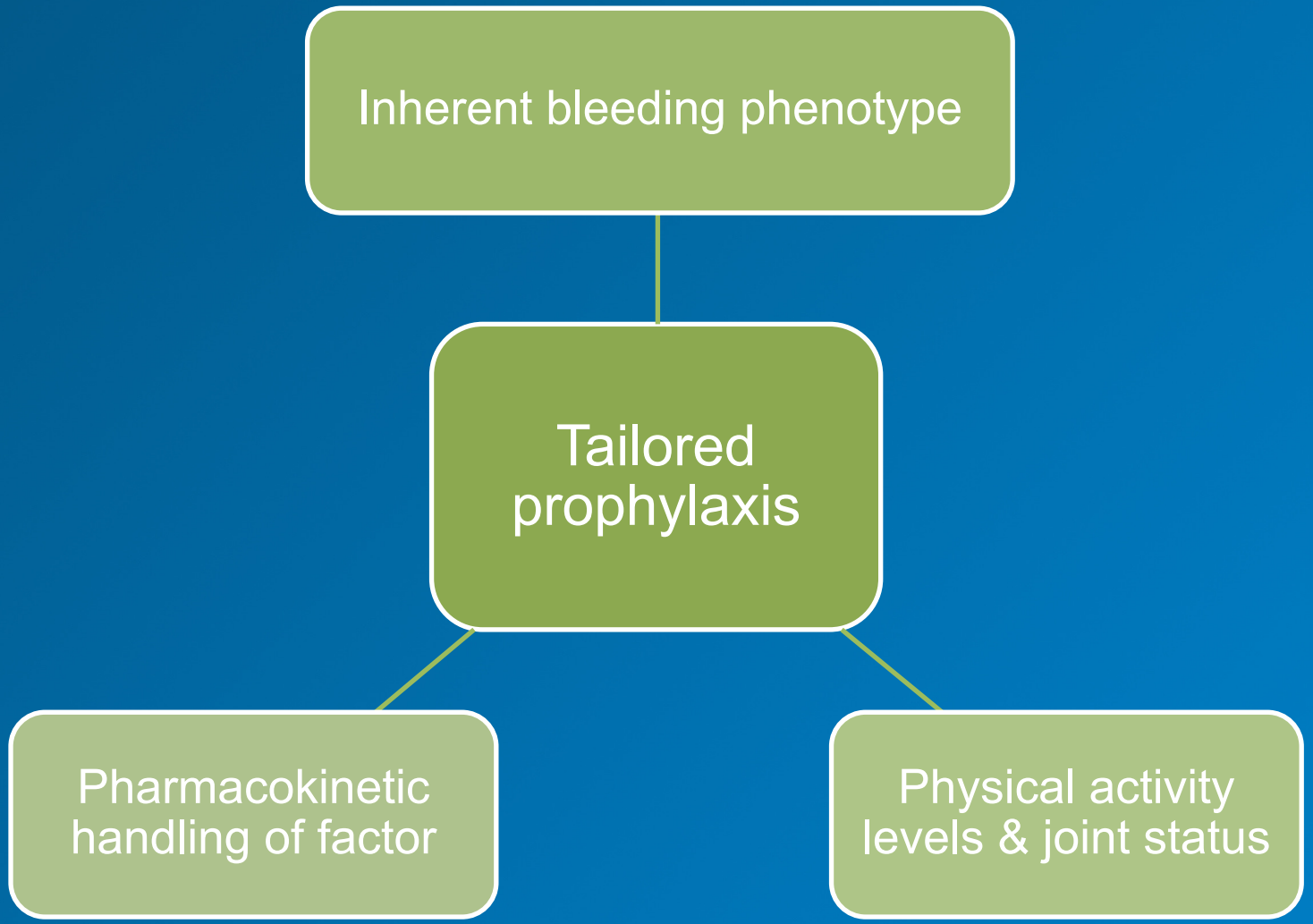
Significant Variability in Clearance of FVIII



Bjorkman. *Haemophilia* 2010;16:597.

AXIS Medical Education

Personalized Prophylaxis



Carcao and Iorio. *Semin Thromb Hemost*. 2015;41:864-871.

AXIS Medical Education

Factors to Consider When Personalizing Prophylaxis in Patients With Hemophilia A

- Adherence
- Age
- Venous access

- Bleeding phenotype
- Peak/trough
- Factor half-life
- Joint status

- Timing of infusions

- Activity type
- Activity pattern

Ar et al. *Expert Rev Hematol*. 2016;9:1203-1208.

AXIS Medical Education

PROPEL Study: Phase 3b/4 PK-Guided Prophylaxis With Antihemophilic Factor (Recombinant), Pegylated FVIII

- Study examined PK-guided prophylaxis with rurioctocog alfa pegol in patients with severe hemophilia A targeting two FVIII trough levels (N = 115):
  - Low trough (1%-3%, reference)
  - High trough (8%-12%, elevated)
- Elevated/high trough cohort had a higher percentage of zero bleeds
- Elevated/high also had a lower mean total ABR, and reduced mean spontaneous joint ABR vs the low trough reference cohort

	Low Trough (1-3%)	High Trough (8-12%)
% of zero bleeds	42%	62%
P	.55	
Total ABR	3.6	1.6
Mean spontaneous joint ABR	2.0	0.5

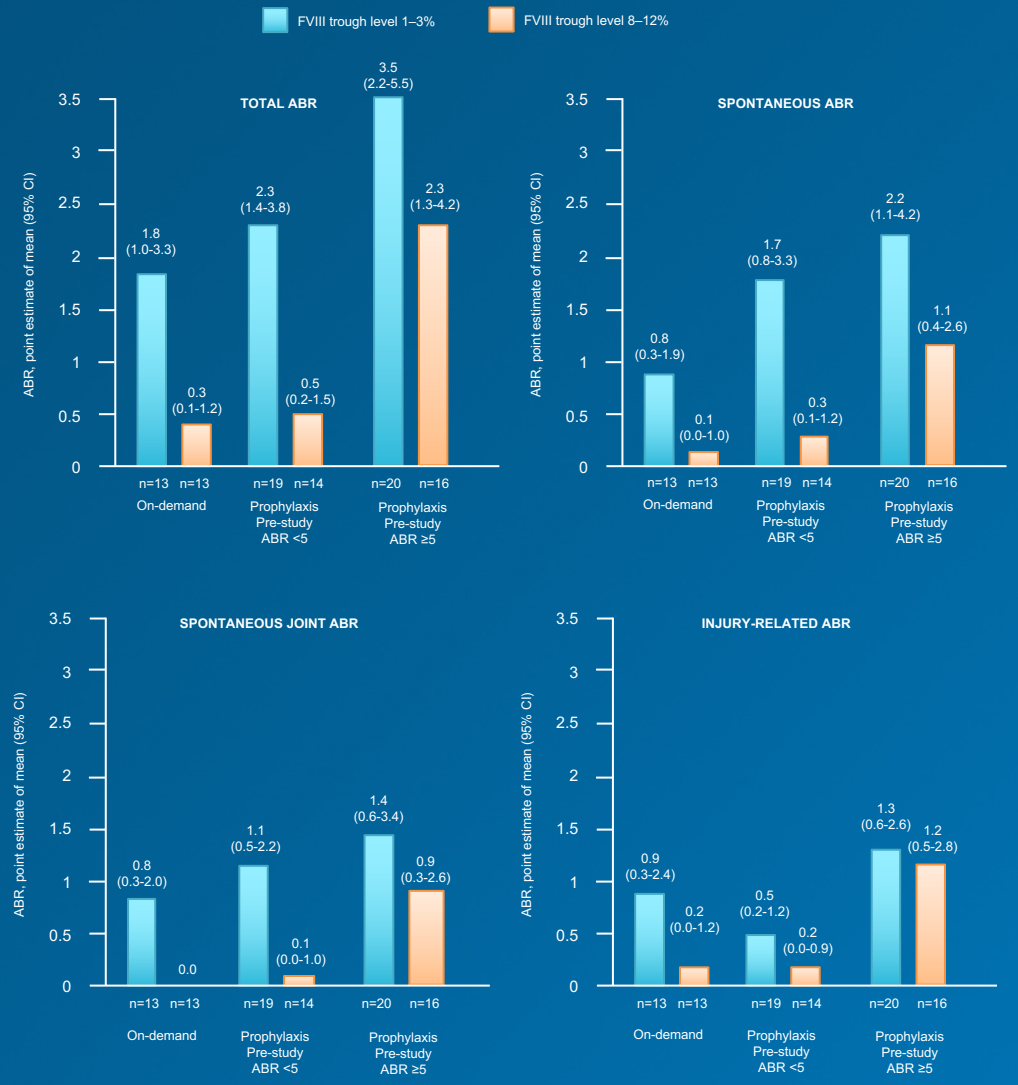
ABR, annual bleed rate; FVIII, factor VIII; PK, pharmacokinetics.
Klamroth et al. *Blood* 2021;137:1818-1827.

AXIS Medical Education

PROPEL Post Hoc Analysis: Rurioctocog Alfa Pegol

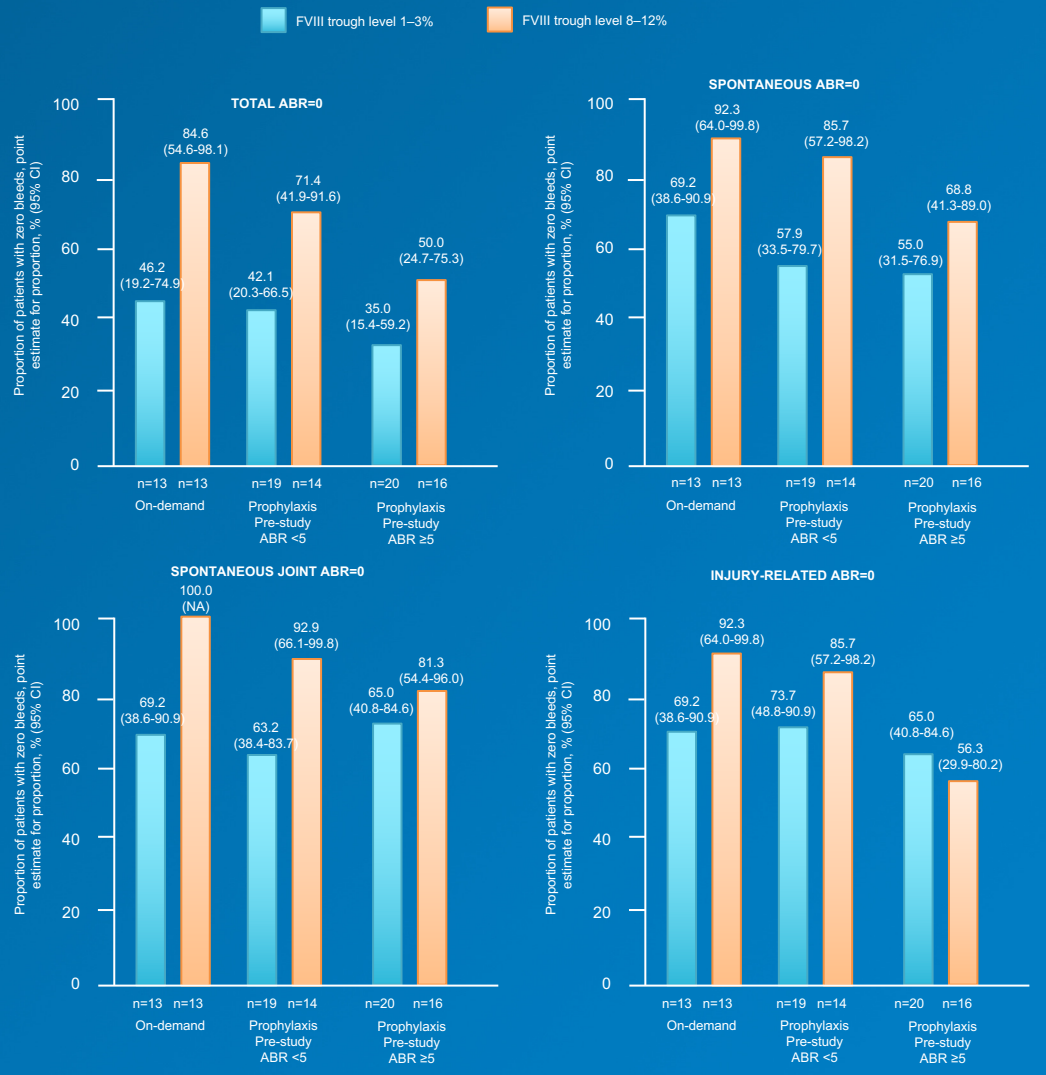
ABRs STRATIFIED BY PRE-STUDY TREATMENT REGIMEN (PPAS)

Total, spontaneous, and spontaneous joint ABRs were lower in the 8-12% study arm versus the 1-3% arm, regardless of prophylactic treatment regimen and ABR in the 12 months before the study



PROPORTION OF PATIENTS WITH ZERO BLEEDS STRATIFIED BY PRE-STUDY TREATMENT REGIMEN (PPAS)

The proportion of patients with zero total, spontaneous, and spontaneous joint ABRs was higher in the 8–12% study arm versus the 1–3% arm, regardless of prophylactic treatment regimen and ABR in the 12 months before the study



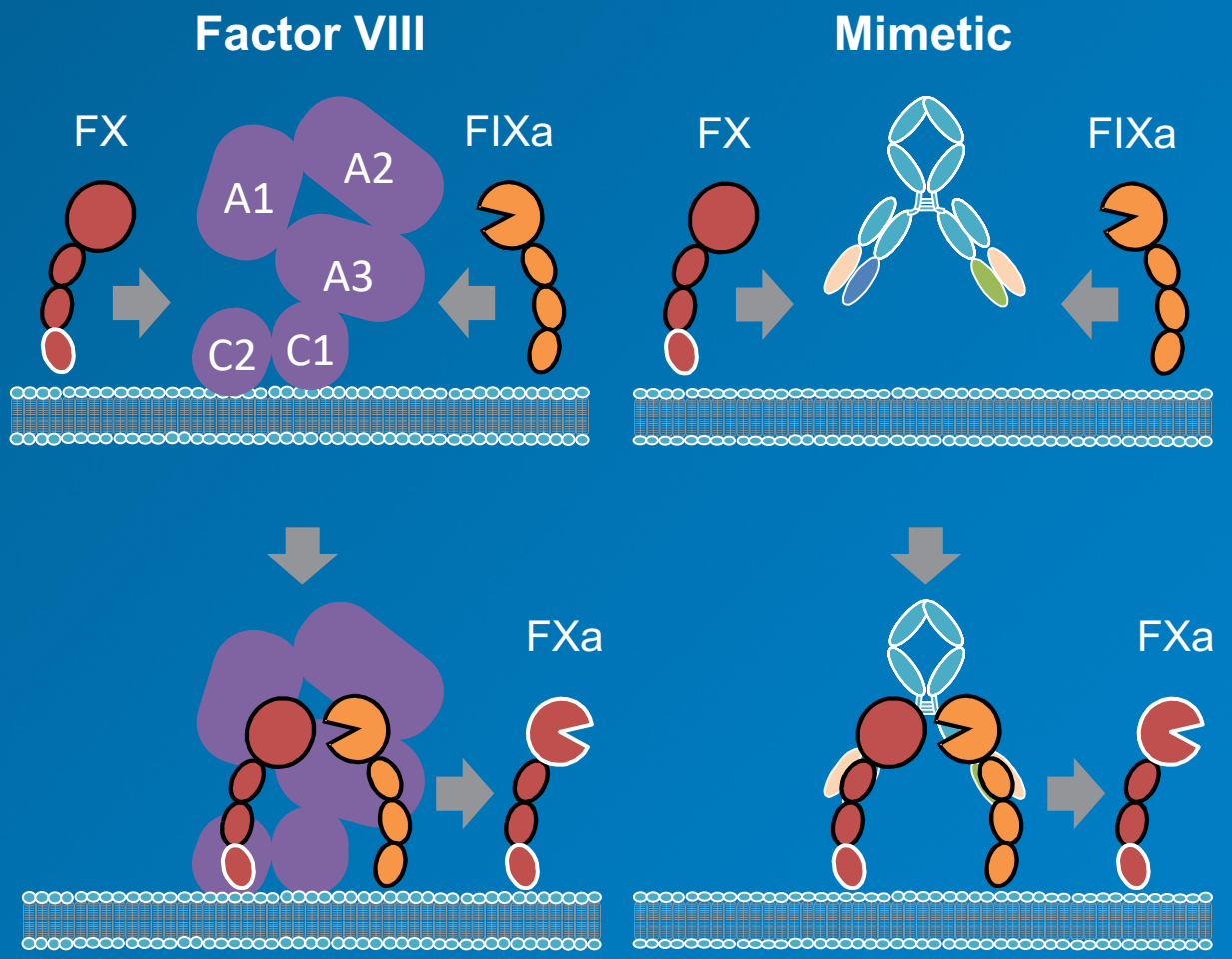
ABR, annualized bleeding rate; PPAS, per-protocol analysis set.
Adapted from Escuriola-Ettingshausen et al. PBO542. ISTH 2021.

AXIS Medical Education

Non-Factor Therapies

Emicizumab-kxwh

- Humanized modified IgG4 bi-specific antibody
- Subcutaneous administration once weekly, every 2 weeks, or every 4 weeks[1-5]
- Mimics FVIII function irrespective of the presence of FVIII inhibitors[1,4]
- Not expected to induce FVIII inhibitors[1,6]



FVIII, factor VIII; FIXa, activated factor IX; FX, factor X; FXa, activated factor X.

1. Kitazawa et al. *Nat Med*. 2012;18:1570. 2. Mahlangu et al. N Engl J Med. 2018;379:811. 3. Pipe et al. *Lancet Haematol*. 2019;6:e295.
4. Muto et al. *J Thromb Haemost*. 2014;12:206. 5. Shima et al. N Engl J Med. 2016;374:2044. 6. Sampei et al. *PLoS One* 2013;8:e57479.

AXIS Medical Education

Emicizumab Clinical Development Program

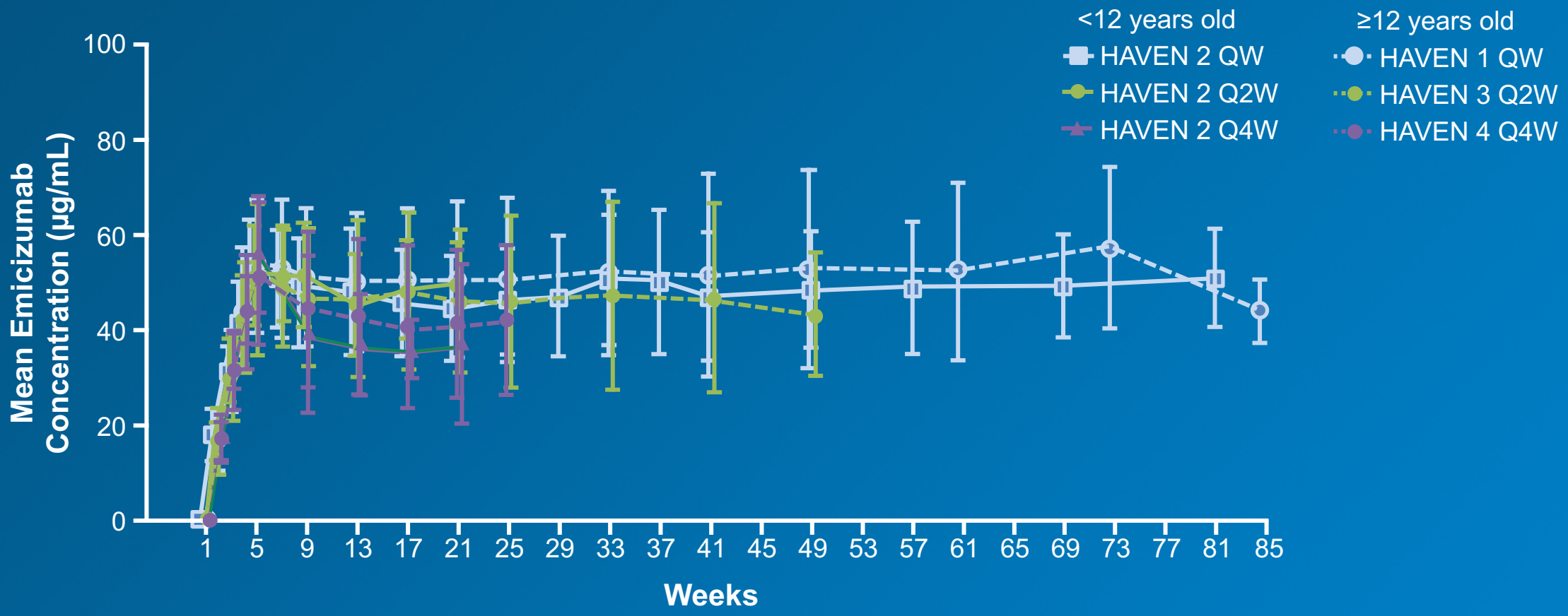
Phase	Study	Patient Age, y	Inhibitors	Dosing	Duration, wk	Endpoints
N/A	NIS[1]	≥12	With and without	Standard of care	≤47.7	Bleeding rate, safety, real-world data
3	HAVEN 1[2]	≥12	With	QW*	≥24	Bleeding rate, safety, QoL, PK/PD
3	HAVEN 2[3]	<12	With	QW*	52	Safety, QoL, PK/PD
3	HAVEN 3[4]	≥12	Without	QW* Q2W†	≥24	Safety, QoL, PK/PD
3	HAVEN 4[5]	≥12	With and without	Q4W‡	≥24	Safety, QoL, PK/PD

*Loading dose: 3 mg/kg/wk for 4 wk; maintenance dose: 1.5 mg/kg/wk QW starting Wk 5.
†Loading dose: 3 mg/kg/wk for 4 wk; maintenance dose: 3 mg/kg/wk Q2W starting Wk 5.
‡Loading dose: 3 mg/kg/wk for 4 wk; maintenance dose: 6 mg/kg/wk Q4W starting Wk 5.
NIS, noninterventional study; PD, pharmacodynamics; PK, pharmacokinetics; QoL, quality of life; Q, every; W, week.

1. Kruse-Jarres et al. *Haemophilia* 2019;25:213; 2. Oldenburg et al. *N Engl J Med*. 2017;377:809; 3. Young et al. *Blood* 2019;134:2127;
4. Mahlangu et al. *N Engl J Med*. 2018;379; 5. Pipe et al. *Lancet Haematol*. 2019;6:e295.

AXIS Medical Education

HAVEN 1-4: Emicizumab PK Profiles



Trough emicizumab plasma concentrations increased with loading doses until week 5, then were maintained with QW, Q2W, and Q4W dosing at approximately 50 µg/mL, 45-50 µg/mL, and 38 µg/mL, respectively

PK, pharmacokinetics; Q, every; W, week.

Young et al. *Blood* 2018;132:632.

AXIS Medical Education

HAVEN 1-4: Participant Characteristics

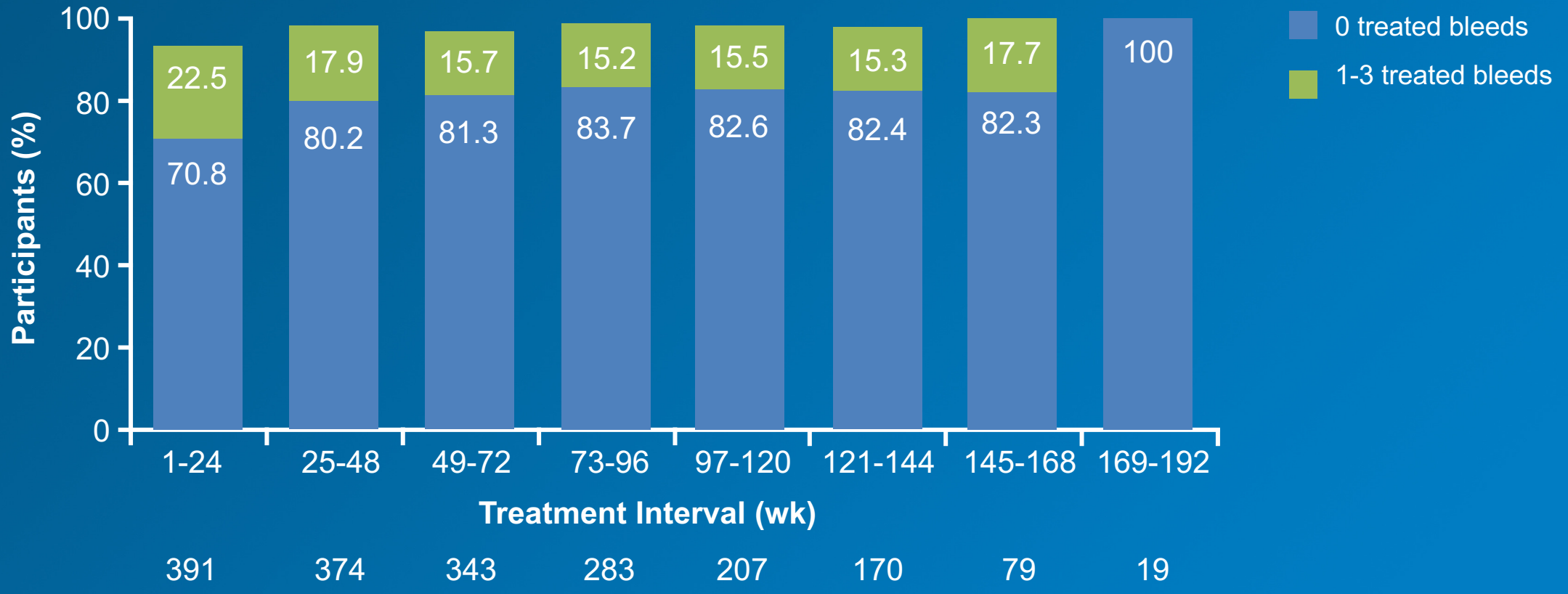
Characteristic*	HAVEN 1†	HAVEN 2	HAVEN 3	HAVEN 4	Total
Patients enrolled, N	113	88	152	48	**401**
Patients treated with emicizumab, n	112	88	151‡	48	**399**
Median duration of exposure, wk (IQR)	109.3 (92.1-167.1)	92.1 (68.3-124.4)	163.4 (108.1-170.4)	150.6 (84.4-153.0)	**120.4 (89.0-164.4)**
Total patient-years of emicizumab exposure	270.5	166.1	417.5	116.2	**970.3**
Median age, y (range)	29.0 (12-75)	7.0 (1-15)	38.0 (13-77)	38.0 (14-68)	**28.0 (1-77)**
Race, n (%)					
White	75 (66.4)	54 (61.4)	102 (67.1)	36 (75.0)	**267 (66.6)**
Asian	21 (18.6)	13 (14.8)	32 (21.1)	10 (20.8)	**76 (19.0)**
Black	11 (9.7)	12 (13.6)	8 (5.3)	1 (2.1)	**32 (8.0)**
Other or unknown	6 (5.3)	9 (10.2)	10 (6.6)	1 (2.1)	**26 (6.5)**
Median no. of bleeds in 24 wk prior to study entry (IQR)	10.0 (6.0-17.0)	6.0 (3.5-9.0)	9.0 (3.0-17.0)	5.0 (2.0-10.5)	**8.0 (5.0-15.0)**
Presence of target joints, n (%)	77 (68.8)	34 (38.6)	102 (67.1)	31 (64.6)	**244 (61.0)**

*Values based on total enrolled population of N = 401. †One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analyses.
‡One participant in HAVEN 3 was assigned to no prophylaxis and was lost to follow-up and not treated, thus excluded from the efficacy and safety analyses.
IQR, interquartile range.
Callaghan et al. *Blood* 2021;137(16):2231-2242.

AXIS Medical Education

HAVEN 1-4: Number of Treated Bleeds

After Week 24, ≥97% patients had ≤3 bleeds per treatment interval

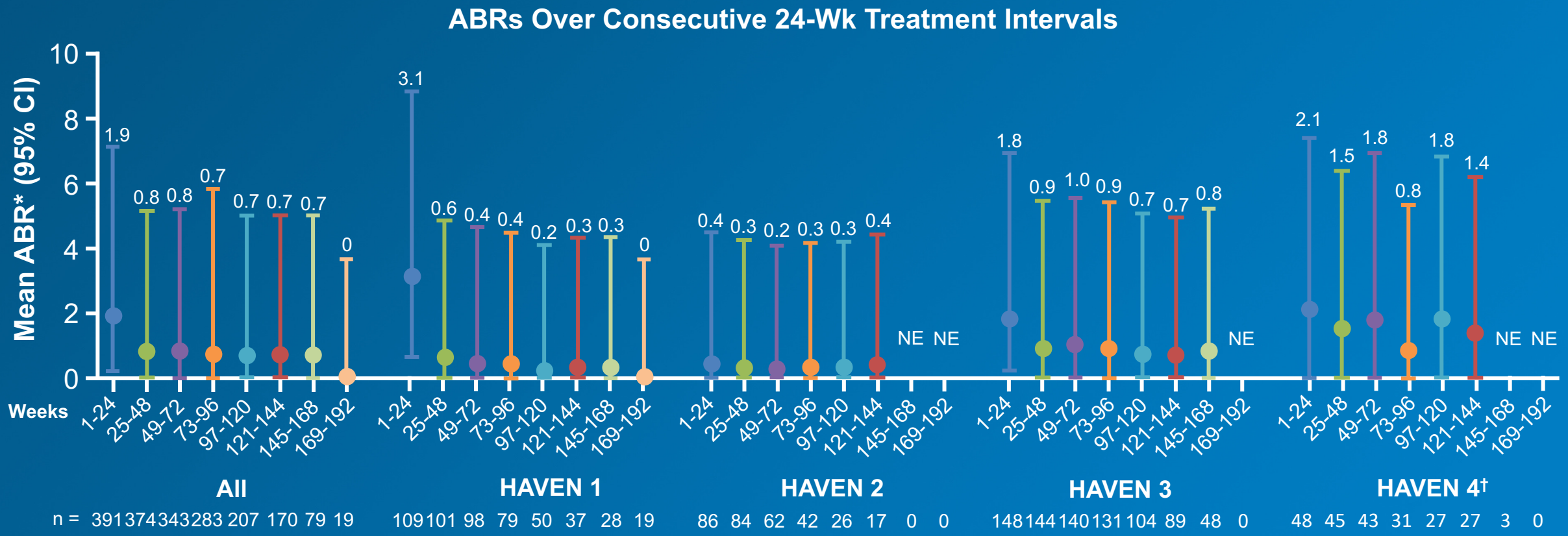


Callaghan et al. *Blood* 2021;137(16):2231-2242.

AXIS Medical Education

HAVEN 1-4: Mean ABR Over Time

The ABR across HAVEN 1-4 was 1.4 (95% CI 1.1-1.7) for the entire study period



*Calculated with a negative-binomial regression model.
†Somewhat higher rates of ABR in HAVEN 4 may be skewed by 1 patient with 18 bleeds and a relatively small number of persons with Hemophilia A.
ABR, annualized bleeding rate.
Callaghan et al. *Blood* 2021;137(16):2231-2242.

AXIS Medical Education

HAVEN 1-4: Target Joint Resolution

- 226 evaluable patients with hemophilia A with ≥1 target joint at baseline and completed ≥52 weeks of emicizumab
  - At baseline: n = 530 target joints
- Target joints resolved: 95.1% (504/530)
  - Target joint resolution defined as ≤2 spontaneous or traumatic bleeding events in a 12-month period
- Patients with 0 target joint bleeds: 89.4% (202/226)

Callaghan et al. *Blood* 2021;137(16):2231-2242.

AXIS Medical Education

HAVEN 1-4: Safety

Characteristic, n (%)	Safety Population (N = 399)
Participants with ≥1 AE	381 (95.5)
Treatment-related AE	139 (34.8)
Injection site reaction	111 (27.8)
AE leading to withdrawal from treatment	5 (1.3)
AE leading to dose modification or interruption	9 (2.3)
Grade ≥3 AE	87 (21.8)
Serious AE	93 (23.3)
AE with fatal outcome*	1 (0.3)
Thrombotic microangiopathy events	3 (0.8)*

AEs of Special Interest, n (%)	Safety Population (N = 399)
Systemic hypersensitivity/ anaphylactic reaction	1 (0.3)
Thromboembolic events	4 (1.0)
▪ Associated with concomitant aPCC use	2 (0.5)
▪ Other TE	2 (0.5)
Thrombotic microangiopathy events†	3 (0.8)*

*Death of 1 participant in HAVEN 1 due to rectal hemorrhage. †All associated with concomitant aPCC use.
AE, adverse event; aPPC, activated prothrombin complex concentrate; TE, thromboembolic event.
Callaghan et al. *Blood* 2021;137(16):2231-2242.

AXIS Medical Education

Key Takeaways

- Prophylaxis should be the standard of care for patients with severe phenotype
- Extended half-life FVIII (EHL) products and non-replacement products are as effective as standard half-life (SHL) products
- There is a high interpatient variability in dosing and half-life of factor VIII
- Personalized prophylaxis can optimize treatment and improve outcomes

AXIS Medical Education

Discussion

Treatment Planning

How do you currently differentiate among available agents and create treatment plans that include patient/caregiver input?

- Factors to consider:
  - Dosing
  - Route of administration
  - Efficacy
  - Annualized bleeding rates
  - Rates of inhibitor development with plasma-derived vs recombinant factor replacement
  - Prophylactic treatment vs treatment for acute bleeding
  - Quality of life
  - Lifestyle
- Shared decision-making is critical when creating long-term treatment plans with patients and caregivers

AXIS Medical Education

Poor Adherence

Based upon your real-world clinical expertise,
what complications arise due to poor adherence to therapy?

- Increased frequency of bleeding episodes and joint bleeds
- Increased incidence of inhibitors
- Increases in arthropathy
- Pain
- Missed school/work-days
- Limitations in physical activities
- Depression

AXIS Medical Education

Barriers to Adherence

Potential Barriers to Adherence

Patient-related	Health beliefs
	Age
	Depression, anxiety
Condition-related	Bleeding frequency
Treatment-related	Costs and perceived costs
	Dosing regimen
	Frequency of infusions
	Venous access
	Self-administration at home
Healthcare system-related	Access to hemophilia treatment center
	Insurance coverage
Socioeconomic	Acculturation
	Language
	Health literacy
	Balancing child's care with other family and social needs

Barriers to Prophylaxis

- Global Hemophilia Survey
- 147 nurses from 147 HTCs and 16,115 patients

Factors Affecting Patients' Adherence	
Inability to understand potential benefits	75%
Denial	67%
Poor venous access	66%
Lack of parental/family commitment	63%
Interference with lifestyle	62%
Teenage rebellion	48%
Lack of time	42%

HTC, hemophilia treatment center.

Thornburg and Duncan. *Patient Prefer Adherence* 2017;11:1677; Geraghty et al. *Haemophilia* 2006;12:75-81.

AXIS Medical Education

EHL Factor Concentrates vs Non-Factor Treatments

Can you share your expert opinions on the pros and cons of extended half-life factor concentrates vs non-factor treatments such as emicizumab?

- Convenience
- Impacts on quality of life
- Bleeding risks
- Adherence
- Dosing
- Trough levels
- Side effects of treatment
- Cost differences
- Discrepancies in laboratory monitoring
- Agent-specific potential for developing immunogenicity

EHL, extended half-life.

AXIS Medical Education

Case Study

Case Study

- 17-year-old man with severe hemophilia A
- Has been on prophylaxis with standard half-life FVIII since age of 5, given 3X per week with minimal breakthrough bleeding
- He has right ankle arthropathy from playing soccer in middle school
- In preparation to start college, his parents recently let him manage his own prophylaxis but he has missed an average of 2-4 doses per month and has had 2 spontaneous joint bleeds in the previous 6 months

Discussion:

1. What approaches can be used to improve adherence in this patient?
2. Can the use of an extended half-life factor be an option for the patient?
3. Can emicizumab be an option for prophylaxis?

AXIS Medical Education

Case Study (cont)

- He will start college in 1 year and would like to start playing soccer again (intramurals)

Discussion:

1. If he is still on standard half-life FVIII, how will you manage the patient?
2. If an extended half-life FVIII is used, how will you manage the patient?
3. Is emicizumab an option for prophylaxis in this case?

AXIS Medical Education

Case Study (cont)

- His dentist recommends wisdom teeth extraction (4) and the patient is currently using prophylactic emicizumab at 1.5 mg/kg subcutaneous once a week

Discussion:

1. Can wisdom teeth extraction be done while on emicizumab?
2. Will he need FVIII for surgery?
3. Can an antifibrinolytic be used with emicizumab?
4. Is there a need to monitor any coagulation assays?

AXIS Medical Education

AXIS Medical Education

Hemophilia A:

Strategies for Improving Long-Term Holistic Management, Adherence and Quality of Life