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Hemophilia A:

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

This transcript has been edited for style and clarity and includes all slides from the presentation.

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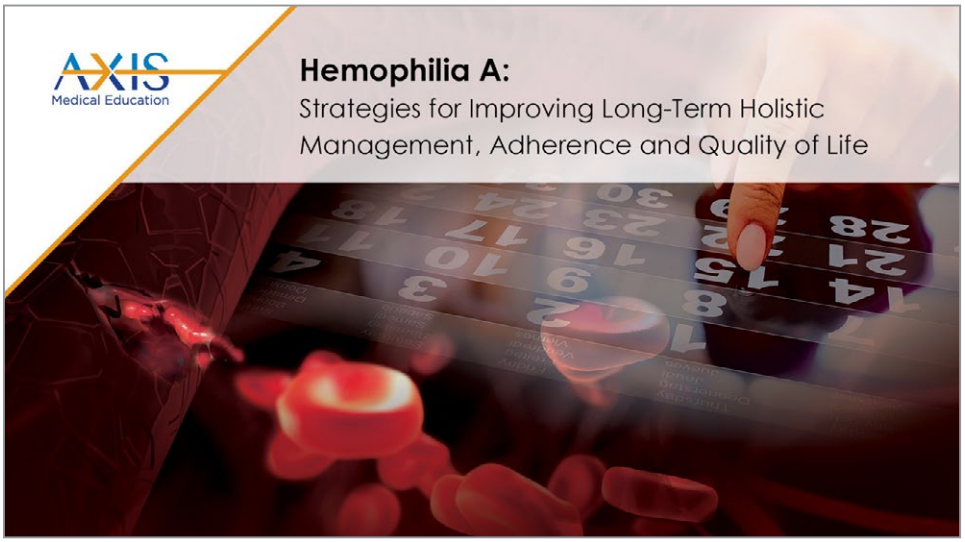
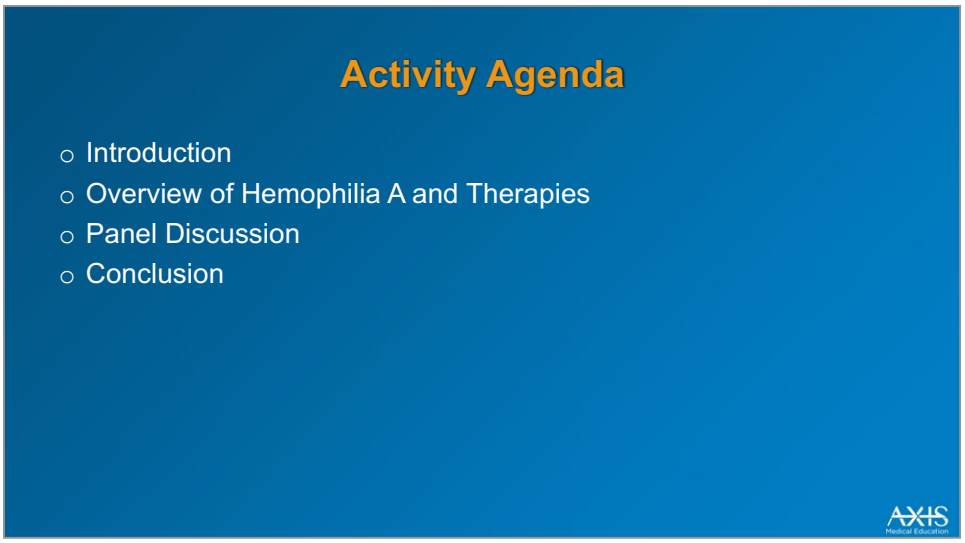
Hemophilia A: Strategies for Improving Long-Term Holistic Management, Adherence and Quality of Life

Miguel Escobar, MD, Cindy Leissinger, MD and Guy Young, MD

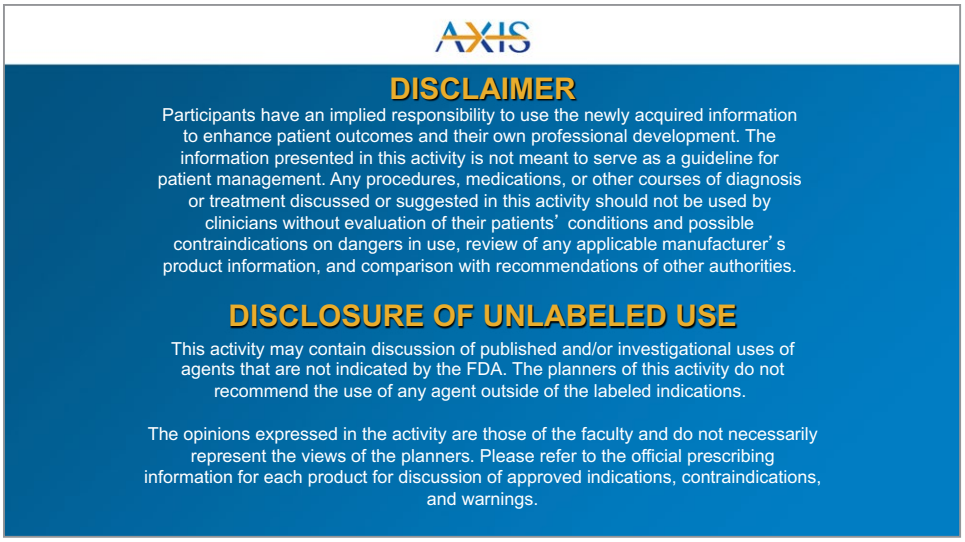


Miguel Escobar, MD:
Hello, and welcome to this educational activity entitled *Hemophilia A: Strategies for Improving Long-Term Holistic Management, Adherence, and Quality of Life*.

My name is Miguel Escobar, and I'm a hematologist at the University of Texas in Houston. I am joined today by two other hematologists, Dr. Cindy Leissinger, Professor of Medicine at the Tulane University School of Medicine and Director of the Louisiana Center for Bleeding and Clotting Disorders, and Dr. Guy Young, who is Professor of Pediatrics and the Director of the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles, at the University of Southern California.



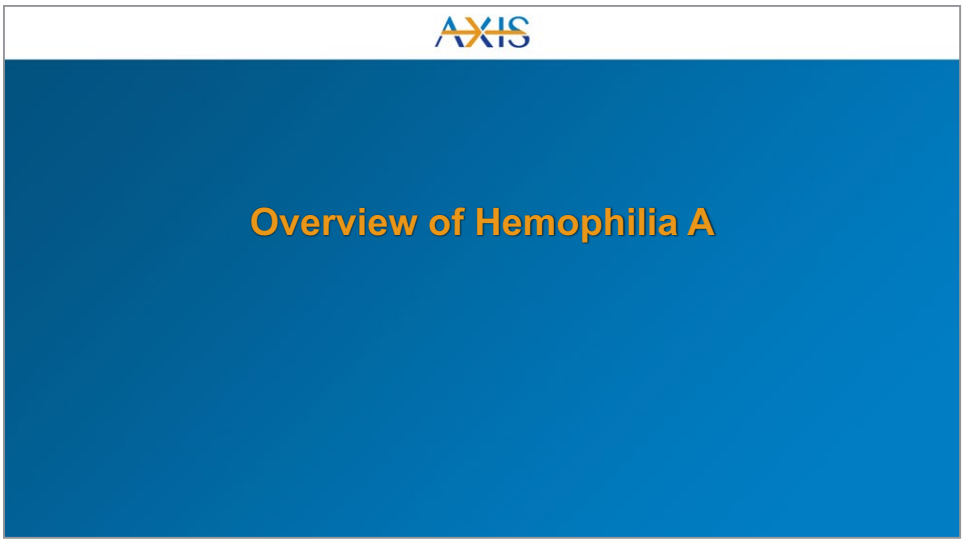
- Today we'll be reviewing the role and evolution of currently approved prophylaxis therapy in hemophilia A, as well as consider clinical value, real-world experience, and patient quality of life factors when advising care management options for these patients.



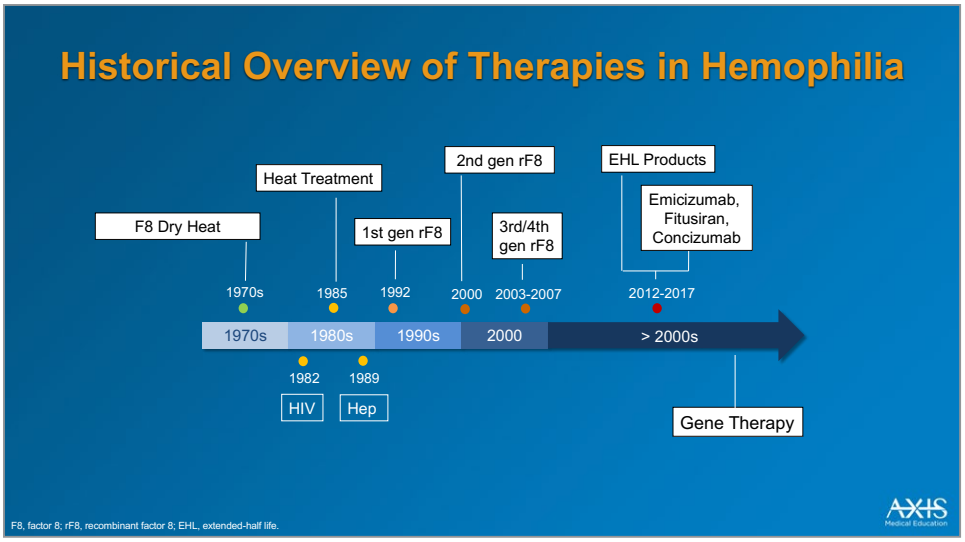
- First, a disclaimer and disclosure indicating that we might be discussing off-label use of approved agents or agents that are in development.

- Our financial disclosure information.

- And the learning objectives for this activity.



- In the first part of this presentation, I will be giving an overview of hemophilia A.



- Hemophilia A and B are rare inherited bleeding disorders that are characterized by the deficiency of either factor VIII or factor IX. Although the history of hemophilia dates back probably to the second century, a description of hemophilia appeared probably at the beginning of the 19th century.

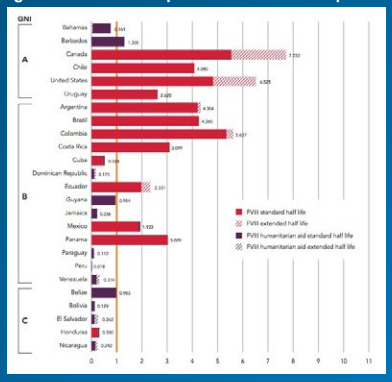
  With the discovery of the anti-hemophilic globulin in the middle of the 20th century, this opened up the development of initially what it was, the cryoprecipitate and then the factor VIII and the factor IX concentrates.

  Unfortunately, in the late 1970s and early 1980s, we had the tragic consequences of HIV and hepatitis, and then after this, the high-purity plasma concentrates and recombinant products were developed and revolutionized the treatment of hemophilia, because we started adopting home therapy as well as prophylaxis, which has dramatically improved the quality of life for our patients, and also the life expectancy of people with hemophilia.

  More recently, with the improvement in technology, we have extended half-life products. In the past few years, we have non-replacement therapy products, and we also have other molecules, including gene therapy that are under investigation for the possible even cure of hemophilia.

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.

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- There is a survey that is done by the World Federation of Hemophilia every 1 or 2 years, and we can see that the mean per-capita use of factor VIII could be quite substantial in some countries like the developed countries, but we can also see that even within the same continent there's a big disparity, a big gap in the utilization of factor, and certainly this is mostly due to financial restraints within some of the countries.

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.

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- In this same survey, some of the information that gets reported here is the percentage of individuals that are on prophylaxis around the world. We can clearly see that the majority of the countries are doing very well in terms of prophylaxis for pediatric population.

  But when we look at the percentage population above the age of 18 that is on prophylaxis, we see that there is a substantial drop in that amount of prophylaxis.

WFH Guidelines for the Management of Hemophilia, 3rd Edition


SUPPLEMENT ARTICLE

WFH Guidelines for the Management of Hemophilia, 3rd edition

- 12 Chapters
- >50 Participants
- 338 Recommendations

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

- The World Federation of Hemophilia guidelines were published in 2020 and include 12 very detailed chapters on the management of hemophilia.

  So I encourage you to go to the World Federation of Hemophilia website, and downloads are in different languages, and take a look at these recommendations. And I'll talk briefly about some of the recommendations that have been done here.

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.

- Now getting more into the topic of prophylaxis, this is the standard of care nowadays for our patients at least with the severe phenotype. And it could be even what we call an old definition of prophylaxis, which was quite vague. More recently there have been some changes to this definition, and now we can say that prophylaxis is the regular administration of therapeutic products. We're not just talking about clotting factor, since we have non-replacement therapy, and it is aimed at maintaining hemostasis to prevent bleeding.

  In addition, it said that prophylaxis should enable people with hemophilia to lead healthy and active lives, including participation in most physical activities similar to the non-hemophilic population. This is very important, because now our patients with hemophilia are being compared to the general population.

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.

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- Their definitions of prophylaxis in regard to the type of prophylaxis—I'm not going to go really into detail, but, for example, primary prophylaxis is that regular continuous prophylaxis that is started before the onset of joint disease, ideally is to start these patients before the age of 3. Then we've got secondary prophylaxis, usually it's initiated after at least two bleeds the patient has had into their joints. And then tertiary prophylaxis, which is again the regular continuous prophylaxis in individuals that already have joint disease.

  It's also important to mention that prophylaxis can be defined according to the intensity. There are different types of prophylaxis that can be administered, anywhere from high-dose, intermediate dose, or the low-dose prophylaxis that we see is used sometimes in many of the developing countries that have financial restraints or that have some limitations on the factor utilization.

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.

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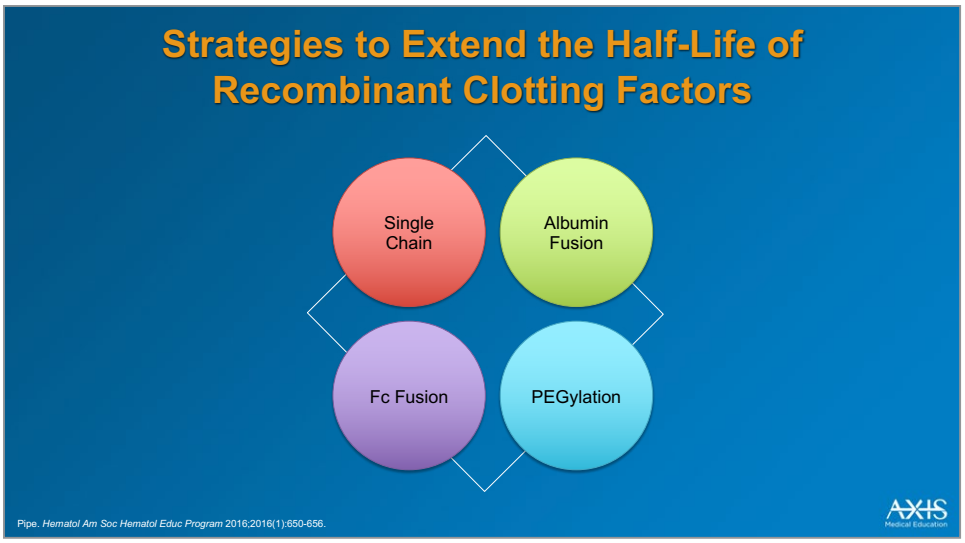
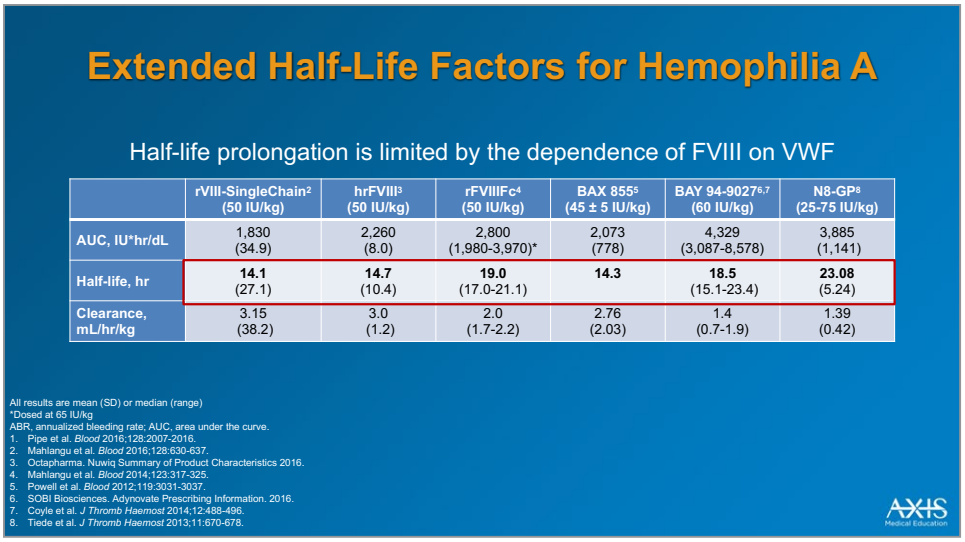
- There are many factor VIII concentrates available. We have the standard half-life products and more recently the extended half-life products. There are different cell lines that are used to develop these concentrates, and different constructs. Most of them are going to be either a full-length or B-domain deleted, and some of them have some different features than others. And the half-life is also going to have some variability that I will discuss further in the talk.



- There are different strategies to extend the half-life of the recombinant clotting factors. There's the single-chain products, there's the albumin fusion, and there is also the Fc fusion through the immunoglobulin, or also the utilization of a PEG molecule that is attached to the factor VIII, again, to extend the half-life of these products.



	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)

- Now, it's important to note that the half-life prolongation of factor VIII is going to be limited by the dependence of factor VIII on the von Willebrand. When we look at the different PKs that have been done in all the molecules now that have been approved or have been in clinical trials, we can see that all the different variables, like area under the curve, the half-life, and the clearance is quite variable among the products, and I think this is important to know.

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.

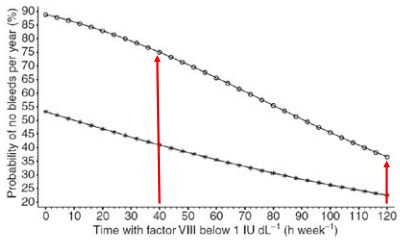
1. Nolan et al. *Haemophilia* 2016;22:72-80.
2. Pasi et al. *Thromb Haemost* 2017;117:508-518.
3. Fischer et al. *Lancet Haematol* 2017;4:e75-82.

- Now, in regards to the efficacy of the extended half-life products, I think they are as effective as the standard half-life products.

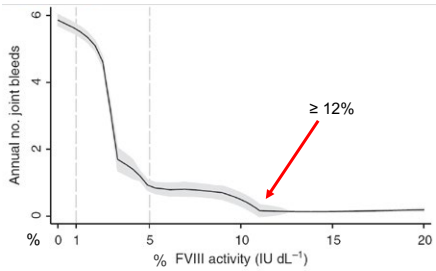
  If we look at some of the molecules that have undergone the clinical trials, both with pediatric for adolescents and for adults, the annualized bleeding rates, the annualized spontaneous bleeding rates are actually quite low; it could be anywhere from 0 to maybe close to 2.0, and again there is going to be some variability because the studies are not equally done.

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.

- Another point of interest is what is that minimal level that is going to be effective for our patients to prevent bleeding, and we've been debating this for many years.

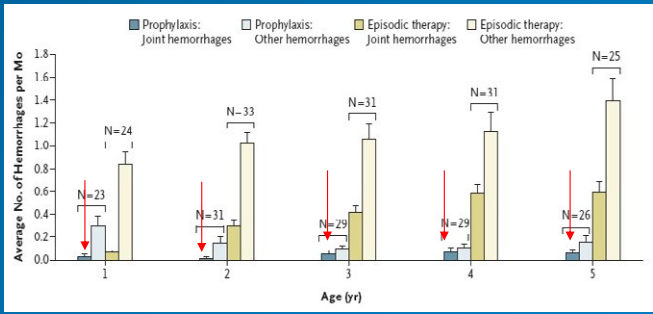
  We should be getting away from maintaining patients with trough levels of 1%, there are plenty of data now supporting that these individuals continue to have spontaneous bleeds, and there are data supporting that. The more time our patients remain with levels below 1%, the higher the risk of bleeding.

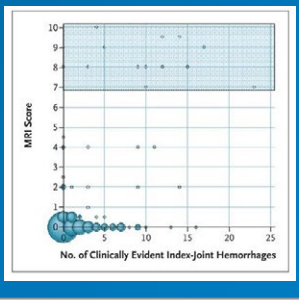
  Now, if we look at the guidelines that just came out from the World Hemophilia, they actually suggest that maintaining levels above 3%, maybe closer to the range of 3% to 5%, should be our goal for prophylaxis.

  Now, there are data even supporting that. Levels above 12% should be the ideal when patients with a severe phenotype stop bleeding. And I will talk briefly about one of the studies that has been recently published where they discuss maintaining much higher trough levels when compared maybe to the 1% to 3%.

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.

Now, you guys are probably all familiar with the Joint Outcome Study. It's a very important study that was done, in the United States where they took very young children with severe hemophilia A, and they put them in prophylaxis 24 U/kg every other day and compare them to episodic or on-demand treatment. This was a randomized, controlled trial, and again they started very early, and they monitored these children both clinically and with MRIs of the joints.

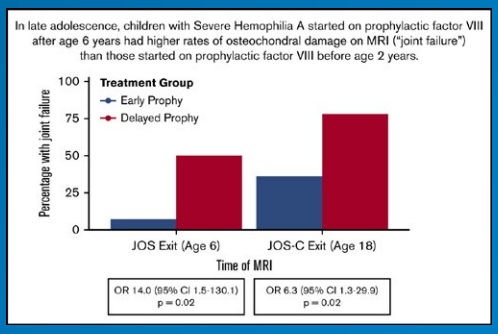
And what they found here was that children with severe hemophilia that initiated prophylaxis prior to the age of 2.5 had much more reduced joint damage at the age of 6, which is when the study ended, compared to those individuals that were treated with episodic treatment.

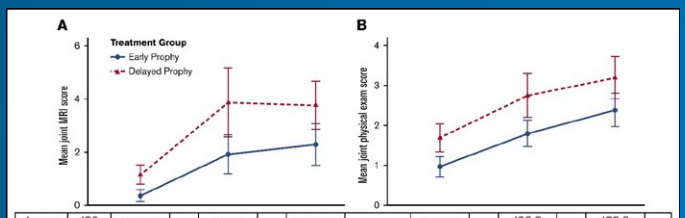
Now, when these kids reached the age of 6, they saw that 93% of those kids that were on the prophylaxis had normal index-joint structure compared to only 55% of those individuals that were on the episodic treatment.

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

Follow-up patients from the JOS





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

JOS, Joint Outcome Study.
Warren et al. *Blood Adv.* 2020;4(11):2451-2459.

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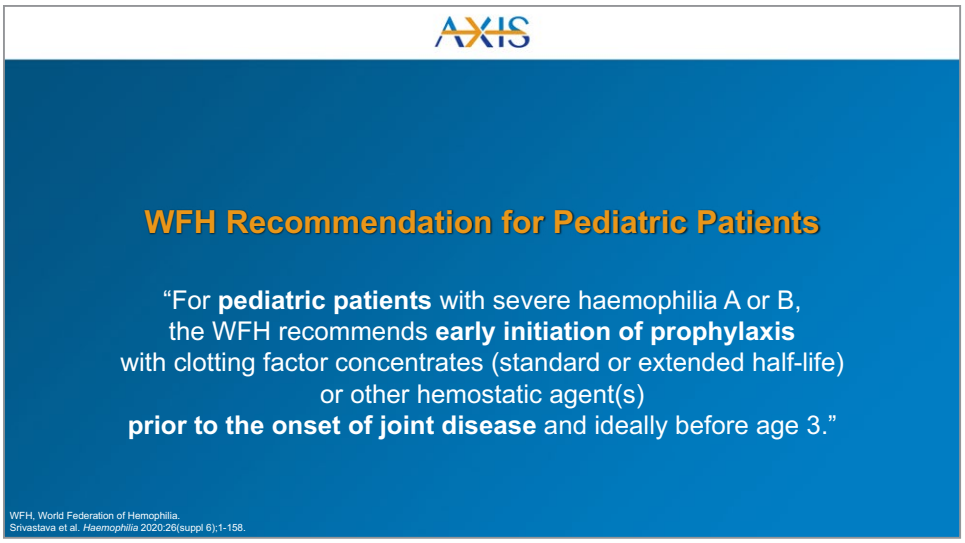
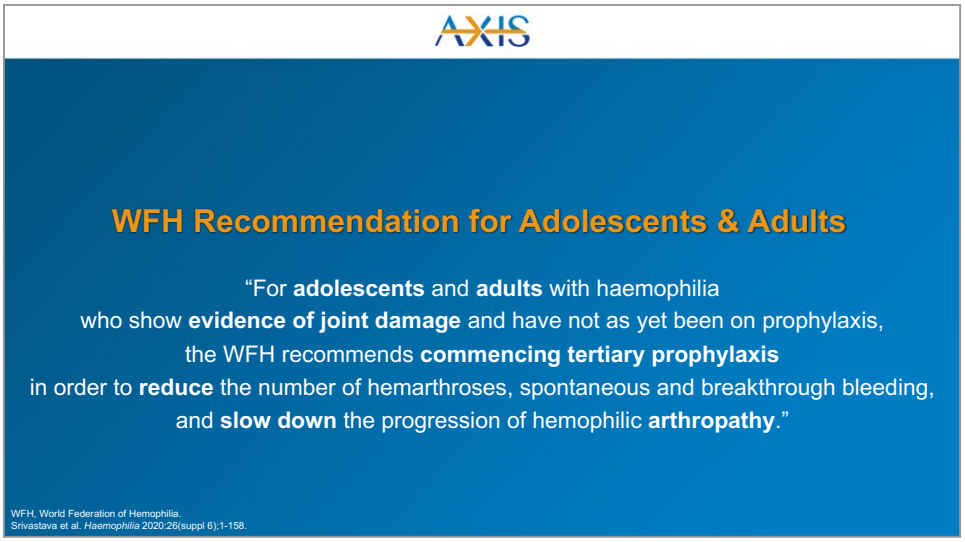
Now, there was a continuation of this study called the Joint Outcome Continuation Study where they took a subgroup of those individuals from the initial study and they evaluated early versus delayed prophylaxis effect on the long-term joint health, and they followed them until the age of 18. This was more observational, and it was a partially retrospective study, as well, and they looked again at MRI and also at the joint physical examination scores and the annualized bleeding rates.

There were 37 of 65 of those patients that were enrolled in this study. Now, at the end of this study, what they found when they looked at the MRI, about 77% of the individuals had osteochondral damage when they compared it, for example, with the patients that started prophylaxis much earlier, that was only 35% of those individuals had osteochondral damage when they looked at the imaging studies.

So again, a conclusion from these studies is pretty much that initiation of prophylaxis prior to the age of 2.5 is critical to protect the joints of patients with a severe phenotype. Now, those who delay initiation of prophylaxis had higher bleeding rates, and definitely ended up with joint damage.

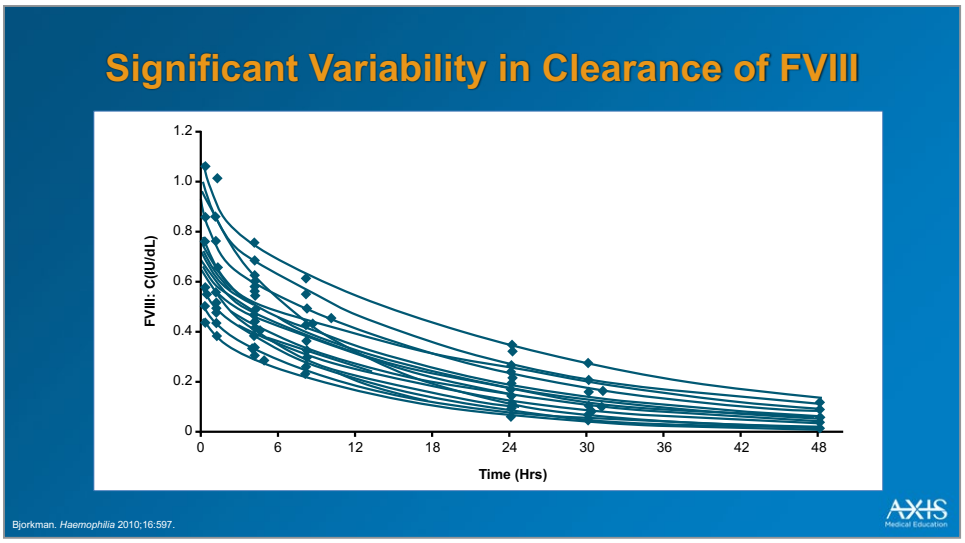


- So going back to the guidelines, one of the recommendations from this publication is that for pediatric patients with severe hemophilia A or B, early initiation with a clotting factor concentrate, either the standard or an extended half-life, or other hemostatic agent or agents prior to the onset of joint disease ideally should be started before the age of 3.



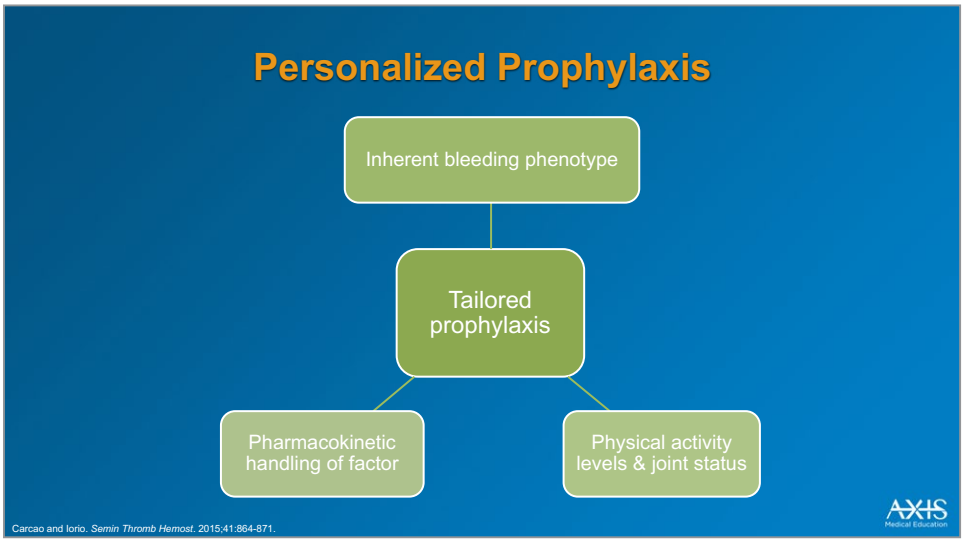
- Now in addition, they also make the recommendation that for adolescents and adults with hemophilia that already show evidence of joint damage and that have not been on prophylaxis, the World Federation of Hemophilia recommendations starting tertiary prophylaxis to reduce the number of hemarthroses, breakthrough bleeding, and to slow down the progression of hemophilic arthropathy.

  This goes back to my initial comment where we see that our adolescents, and especially our adults and our older adults, are probably not getting enough prophylaxis to prevent bleeding.

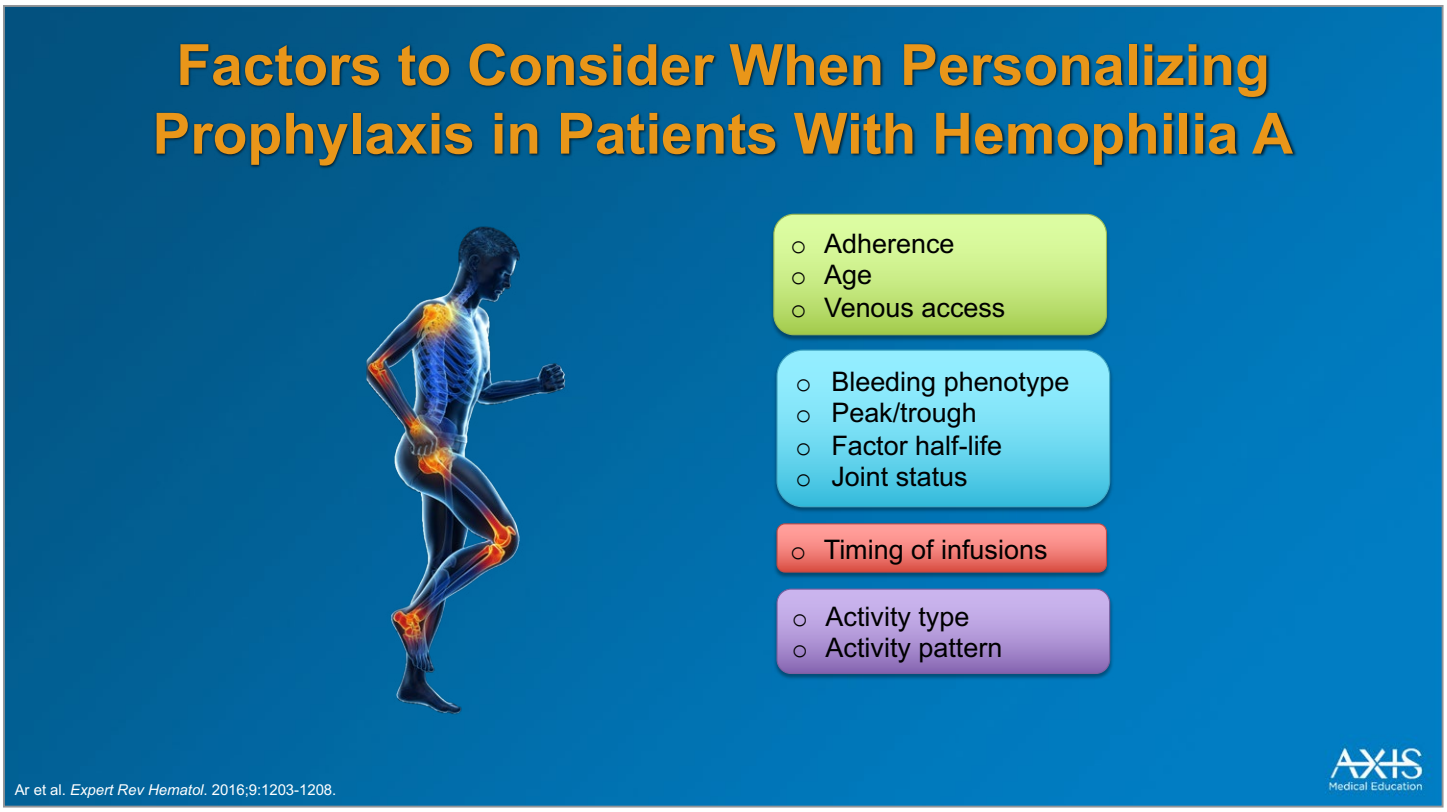


- Now, also it's important to note that there is high interpatient variability when it comes to dosing, and also when we look at the terminal half-life of factor VIII. There are many studies that have shown that even when patients get the same product at the same dose, their pharmacokinetic (PK) studies could differ substantially. This is why it is important to individualize management of patients with hemophilia.

  There was a recent study that shows that the terminal half-life of factor VIII is actually depending on age, it's dependent on the concentrate type, on the blood group, and it's also dependent on inhibitor story; so if that patient had a history of an inhibitor, there is going to be most likely a decrease on the half-life of the factor VIII. So again, here is when those population-based PK modeling studies can be very valuable to be able to estimate the half-life of factor VIII in patients with hemophilia.



- Now, when we talk about personalized prophylaxis, I think there are three big variables that we need to take into account. One certainly is the phenotype of that patient, but we have to look at also the pharmacokinetics of that specific product on that specific individual. So I think that treating as we did in the old days, that maybe one treatment for all, I think that has really changed drastically. And we also have to take into consideration the physical activity of that individual and the joint status.



There are different factors that we need to consider when personalizing prophylaxis in patients with hemophilia. As I mentioned, the bleeding phenotype is very important because I think we have a small proportion of patients that are supposed to be severe patients and they might not have that much bleeding.

The majority of the patients with severe phenotype do have spontaneous bleeds. We need to take into consideration certainly the pharmacokinetics of that specific product, so look at the area under the curve, the peak, the trough, the half-life.

And then when it comes to the patient, we need to see their joint status because it might be very different to treat an individual that has normal joints or an individual that already has advanced arthropathy. We need to take into consideration the activity type of this individual, the pattern of activities that they have.

Also, the age and the adherence, as well, that we're going to be discussing in more detail at the end of this presentation. Venous access certainly is an issue, and also the timing of the infusions is also very important to take into account.

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.

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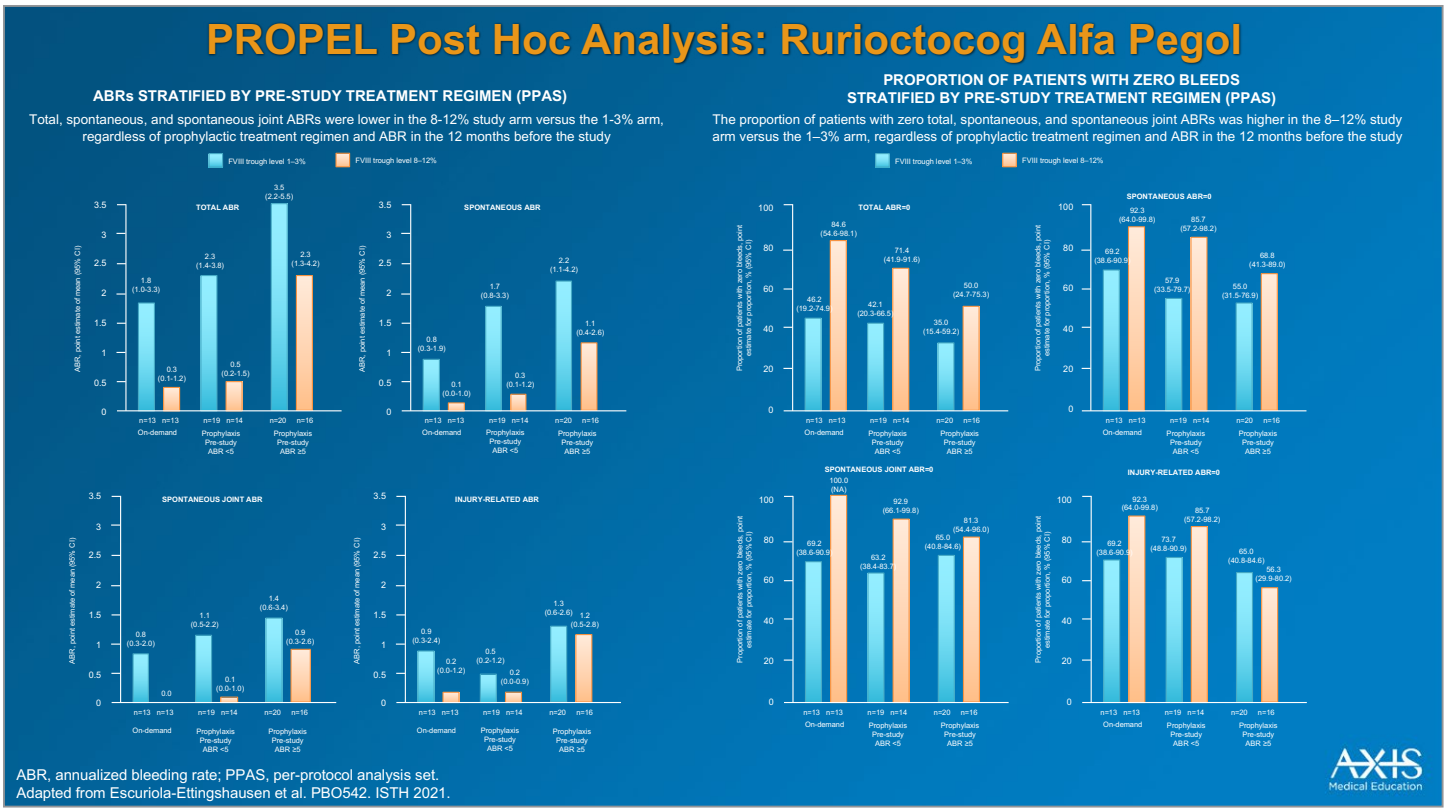
Now, I'd like to briefly mention some data that got recently published, and it's called the PROPEL study. This study examined PK-guided prophylaxis with an extended half-life product in patients that had severe hemophilia A, and they were actually targeting two different factor VIII trough levels.

One level was what they called a low trough level, keeping levels between 1% and 3%, and the high trough level, keeping levels between 8% and 12%. There was a total of 115 patients that were included in this study.

What did they find? Well, they found that those individuals, that cohort group of individuals that had high trough levels between 8% and 12%, had a much higher percentage of zero bleeds when they compare it to the lower trough levels; it was 62% versus 42%, so there was a big difference.

Now, they also found that the individuals that had a high trough level, again between 8% and 12%, had a lower mean total annualized bleeding rate (ABR), 1.6 compared to 3.6, with the lower trough levels, and they also have a reduced mean spontaneous joint ABR.

This is probably expected, right, because as I already mentioned probably the higher the trough level that we maintain in our patients, the less likelihood of them having especially spontaneous bleeding.



- Now, there was an additional study that was done, a post hoc analysis from this same study and here they looked at the ABR, but stratified by pre-study treatment regimen.

  What they found was that total spontaneous joint ABRs were lower again in the 8% to 12% arm versus the 1% to 3% arm, regardless of the prophylactic treatment regimen and the ABR that they had before starting this study.

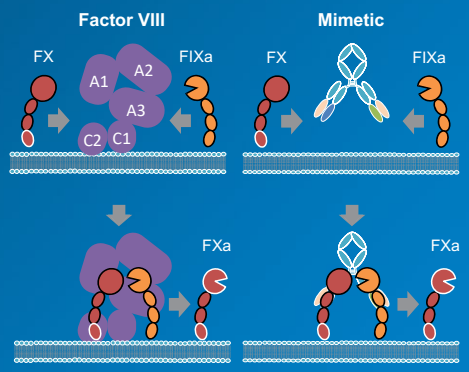
  Now, they also looked at the proportion of patients with zero bleeds. And they found exactly the same, that the group of individuals that were in the high trough level had more patients with zero bleeds.

Non-Factor Therapies

- Now, I'm going to briefly describe the non-factor therapies, and I'm only going to talk about one product that has been approved so far.

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]



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.

- You are probably familiar with emicizumab. This is a monoclonal antibody that mimics the function of factor VIII irrespective if the patient has or not has an inhibitor. This is a molecule that is specifically used for hemophilia A only.

  This antibody, what it does, it binds factor X with IXa, and again it kind of mimics the function of factor VIII. It can be administered subcutaneously, and it can be given once a week, every 2 weeks, or every 4 weeks.

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.

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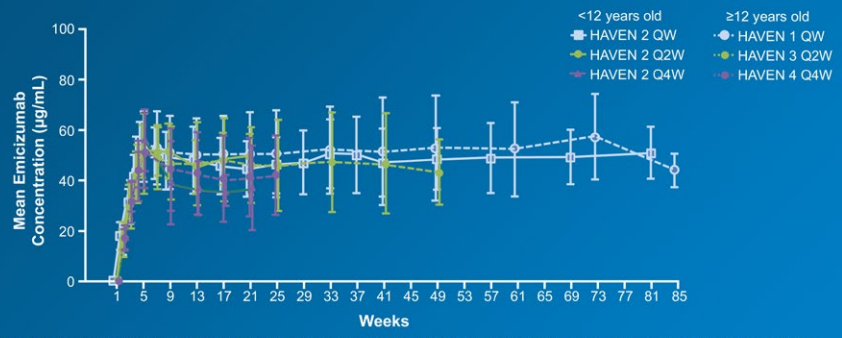
- Now, there were four different studies that were performed and were called the HAVEN studies, and these were done in all ages; they were done in the pediatric population up to the age of 1, and in the adult population up to the age I believe it was 77. And they took patients with and without inhibitors, there were some patients that underwent surgical procedures, but in general the entire population was tested.

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.

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- When they did the PK profiles, again both for the pediatric group and for the adolescents and the older individuals, we see that the trough emicizumab concentrations certainly increase with loading doses until about Week 5, we could easily do a loading dose for the first 4 weeks, and then the levels were maintained pretty similar among the different studies, with levels anywhere between 38 and 50 Qg/mL in these individuals that were treated either once a week, every 2 weeks, or every 4 weeks.

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 Asian Black Other or unknown	 75 (66.4) 21 (18.6) 11 (9.7) 6 (5.3)	 54 (61.4) 13 (14.8) 12 (13.6) 9 (10.2)	 102 (67.1) 32 (21.1) 8 (5.3) 10 (6.6)	 36 (75.0) 10 (20.8) 1 (2.1) 1 (2.1)	 267 (66.6) 76 (19.0) 32 (8.0) 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.

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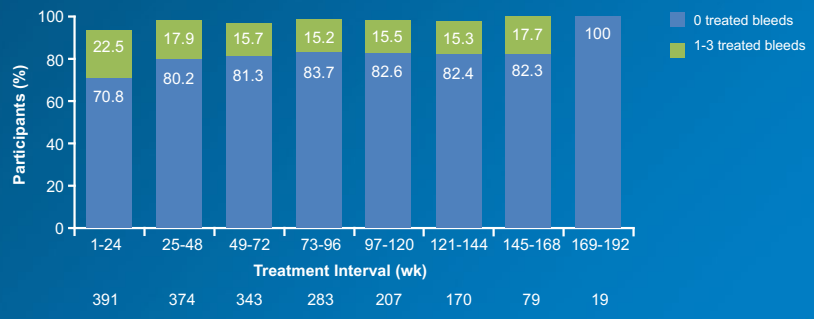
- There was a total of 399 patients that were exposed to or treated with emicizumab. The median age was about 28. And there was a large proportion of individuals in these studies that had target joints, 61% of those individuals had target joints.

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.

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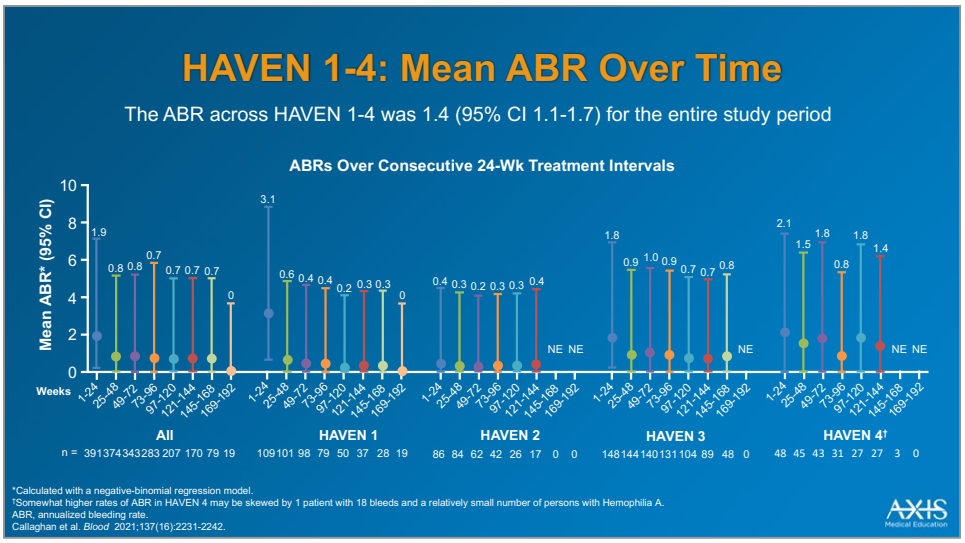
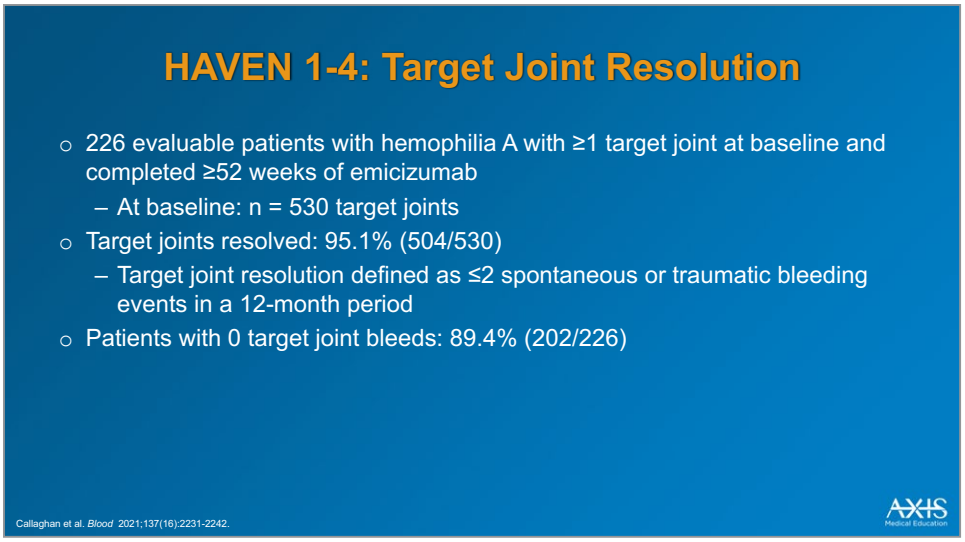
- Now, in regards to the number of treated bleeds after Week 24, more than 97% of the patients had 3 or less bleeds per treatment interval.



- If we look at the ABR across all the HAVEN studies, it was quite low; it was 1.4 for the entire study period, and the ABRs were over consecutive 24-week treatment intervals. Even the patients that had inhibitors, as we know these are individuals that usually have many target joints, they have advanced joint disease, the overall ABR was quite low for these patients. So it was a quite effective treatment.



- Now, in terms of the target joint resolution. There were a total of 226 evaluable patients that had more than 1 target joint at baseline and completed at least 52 weeks of treatment with emicizumab.

  At baseline there were a total of 530 target joints in 61% of the patients, and at the end of the study the target joints resolved in 95% of those patients, and target joint resolution was defined as less than 2 spontaneous or traumatic bleeding events in a 12-month period. Now, the patients with 0 target joint bleeds was equal to 89.4%, so again a very efficacious treatment for this group of individuals.

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.

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- Now, to finish here in regards to safety in the studies HAVEN 1 to 4. I think our main concern was those individuals that developed thromboembolic events that were seen at the initiation of the studies.

  There were a few patients that developed thrombotic microangiopathy, and this was very early recognized; it was related to the use of activated prothrombic complex when it was used for more than 24 hours and at high doses.

  After some changes were made to the protocols and the patients did not receive any more activate prothrombic complexes, there were really no further thromboembolic events throughout the rest of the studies.

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

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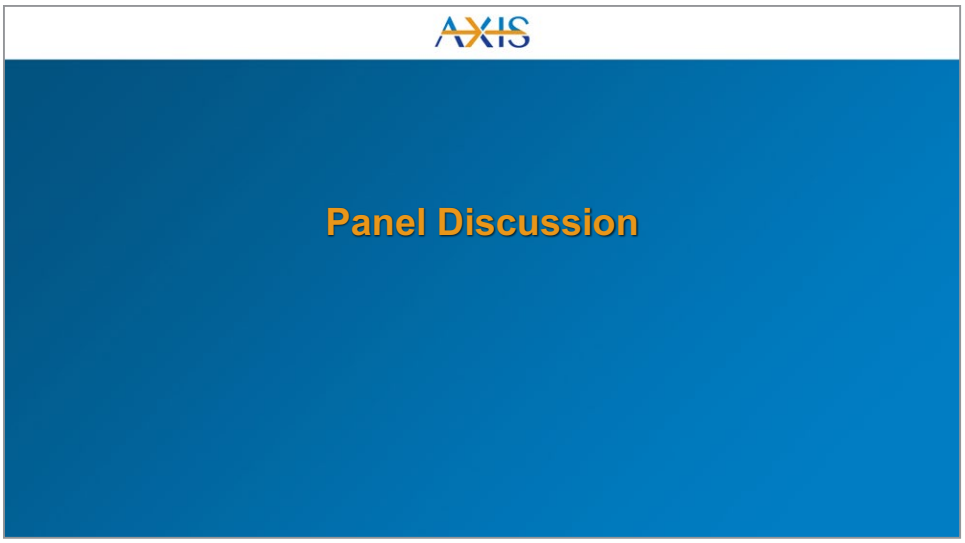
- So with this, I'd like to finalize the introduction to hemophilia. I talked about the importance of prophylaxis that at this point should be the standard of care for patients with a severe phenotype. I discussed the extended half-life factor VIII products and non-replacement products that are as effective as the standard half-life products.

  I also discussed the variability that there is among the patients when it comes to dosing and when it comes to the half-life of factor VIII, and my recommendations on trying to do more of a personalized type treatment for our patients with hemophilia A.



So with this, I'd like now to invite Dr. Young and Dr. Leissinger to join me to discuss how we can optimize prophylaxis, to talk about quality of life, and long-term therapy compliance with our patients with hemophilia A.

Escobar: So, Dr. Young and Dr. Leissinger, I'd like to know in your clinical practice, how do you currently differentiate among available agents and create treatment plans that certainly include the patient and the caregiver. So, for example, Guy, let's say you get in your clinic a brand new 3-year-old that comes with severe hemophilia A, is on a standard half-life factor VIII let's say 2 times a week, but still have, let's say, 3 bleeds in the last 6 months. How will you assess that patient, and what will you look at to make a decision going forward certainly in that discussion with the parents?

Guy Young, MD: Yes sure, Miguel, that's a really important question. Any time I see a new patient, whether it's a brand-new outpatient who a patient who has transferred to my center like this 3 year old that you're speaking about, I think it's always important to have a refresh about what treatment is the patient on, the actual drug, the regimen, and how is it working. And then to discuss with the parents. I like to use shared decision-making even if I'm not completely dogmatic about each aspect, but the whole process of shared decision-making is speaking to the parents about what options are there.

Obviously, one option is always to stay on what you're on, if it's working you can stay on what you're on, but it's important to review that. And then to discuss other options, even if it's working to discuss other options with the family to say well, you know, there is

this new drug, or there's this other different drug. Here are the benefits of this one, here are the benefits of that one, here are the risks, here are the risks. So discussing the pros and cons of the treatment the patient is currently on in comparison to the other options that the patient has. And this way the patients and the parents of those patients have the breadth of the different choices, and they can make the best choice for their patient.

And the best choice for somebody who's on twice a week extended half-life factor VIII if they're not bleeding very much could be just to stay on that. In the scenario you gave, the patient had 3 bleeds in the past 6 months, I think you said, or even if it was 3 bleeds in the past year, that's too many. We really don't accept more than maybe 1 bleed a year is acceptable to say we don't need to change anything, but anything more than that we would want to consider some other options.

Escobar: Yes, I think you bring an important point there is how much are we willing to tolerate in terms of bleeding, because I think it might be different from an adult, let's say, that has a lot of arthropathy versus maybe a child, how much are you really tolerating. And it seems like you're telling me that probably your goal is to have zero bleeds, I assume, or as close to that.

Young: Yes. I think absolutely there's going to be a difference between children and adults, and while I treat children and adults I'm going to defer to Cindy to talk about the adults. Certainly with young children like a 3-year-old, yes, our goal really is zero bleeds, because I think the obvious bleeds are really just the tip of the iceberg. Subclinical bleeding, or some people might call it micro-bleeding, truly that must happen. If a patient has 1 bleed in a year, I imagine they probably have had at least 1 or 2 or more, it's hard to know really, subclinical bleeds too.

So the goal really is 0, and if the patient has zero bleeds a year then they didn't necessarily have subclinical bleeding either. And I think what we saw in the Joint Outcome Continuation study is that even for those patients on really effective prophylaxis, there was a deterioration in their joint disease, even those who started early. So we know that we have to really have a very low threshold for tolerance of any kind of bleed from a young age.

Escobar: Now, Cindy, let's say you have a 22 year old comes to your center with severe hemophilia A, has some mild arthropathy, let's say, of 2 joints, and is on prophylaxis with an extended half-life factor VIII that he takes intermittently, and he bleeds also, let's say, 3 times in the last 6 months. How would you approach this type of patient?

Cindy Leissinger, MD: The way we would approach the patient's going to be similar to what Guy said. I mean, obviously we want to sit down, first of all, and listen and hear what they're on, how they've been doing, and walk through with them what the different options are.

And then I think especially with a 22 year old who's just beginning to fully make decisions on their own, make their own treatment decisions, especially important in that age group because in that late teen or early twenty group we sometimes see patients who veer off of prophylaxis for various reasons, especially maybe they get to college, they get busy doing other things, and they're not at home with their mom and dad.

And so there we have to really sit and listen and figure out what's most important to them, and here's where that, as Guy said, that shared decision-making where their personal goals, their beliefs, kind of what they want really comes into play, and we really try to sit and have that conversation.

Obviously, I will lay out the options, and I will also lay out what I think might be my recommendation or prioritize those recommendations I think would be the most beneficial for the patient. But at the end of the day, they need to buy into this; they need to agree, they need to feel like this is something that matches what they want for their lifestyle.

And activity level comes into play. Are you just starting college and perhaps for the first time you've got access to a regular gym, and you want to start working out? Or for some guys, they go to college and they're like well, you know, now I'm doing less sports than I did in high school, and so now I'm much more centered, I spend more time in the library. And so again we look at where they are in their life journey and what's going to be most appropriate, and then review these options.

Certainly, if they've had 3 bleeds in the last 6 months even in a young adult, that's too many, and especially if these are joint bleeds. And so, again, if these are joint bleeds, we're going to talk very seriously about what we can

do better. And it may be an adherence problem. Maybe as we review their infusion logs or their records, we'll see where these bleeds are happening because perhaps they missed a dose, or maybe not; maybe these breakthrough bleeds are occurring despite good adherence. And so that's going to play a role, too, into what we recommend. If their adherence has not been very good, we're going to talk about what strategy might help improve their adherence.

Escobar: Okay. Yes, those are very important points. And I think you brought the adherence point, but I want you to hold onto it because we're going to discuss it further. But I'd like to know is how do you include, let's say, quality of life into your decision-making, because sometimes I don't know if we do include this part or not. Maybe for the adult it might be a little bit different than for the pediatric population. I just want to hear your opinion in terms of the quality of life, including when you make that decision. So, Cindy, if you can give us your input.

Leissinger: I think this has become extremely important. And I really like that the new World Federation guidelines incorporate this concept into the recommendations regarding prophylaxis, that really quality of life is one of the goals now with prophylaxis. And so it's really a team event, we all discuss with patients—a social worker, nurse, physician, even our physical therapist—we talk about what are your goals, what are you doing now?

Just as I said, maybe there is a desire to go now start in a soccer league on the weekends. So these are all important issues for quality of life. What is it that's important to you now at this point in your life, and whether it's a young patient or an older patient who may be developing—and I know we'll get to this—but may be developing comorbidities where they need other medications and therapies, and we have to consider that?

So really again, I just kind of come back to this listening aspect of what we do, where we ask what's important, where are you going, and we listen to what our patients are telling us. I think that's the key.

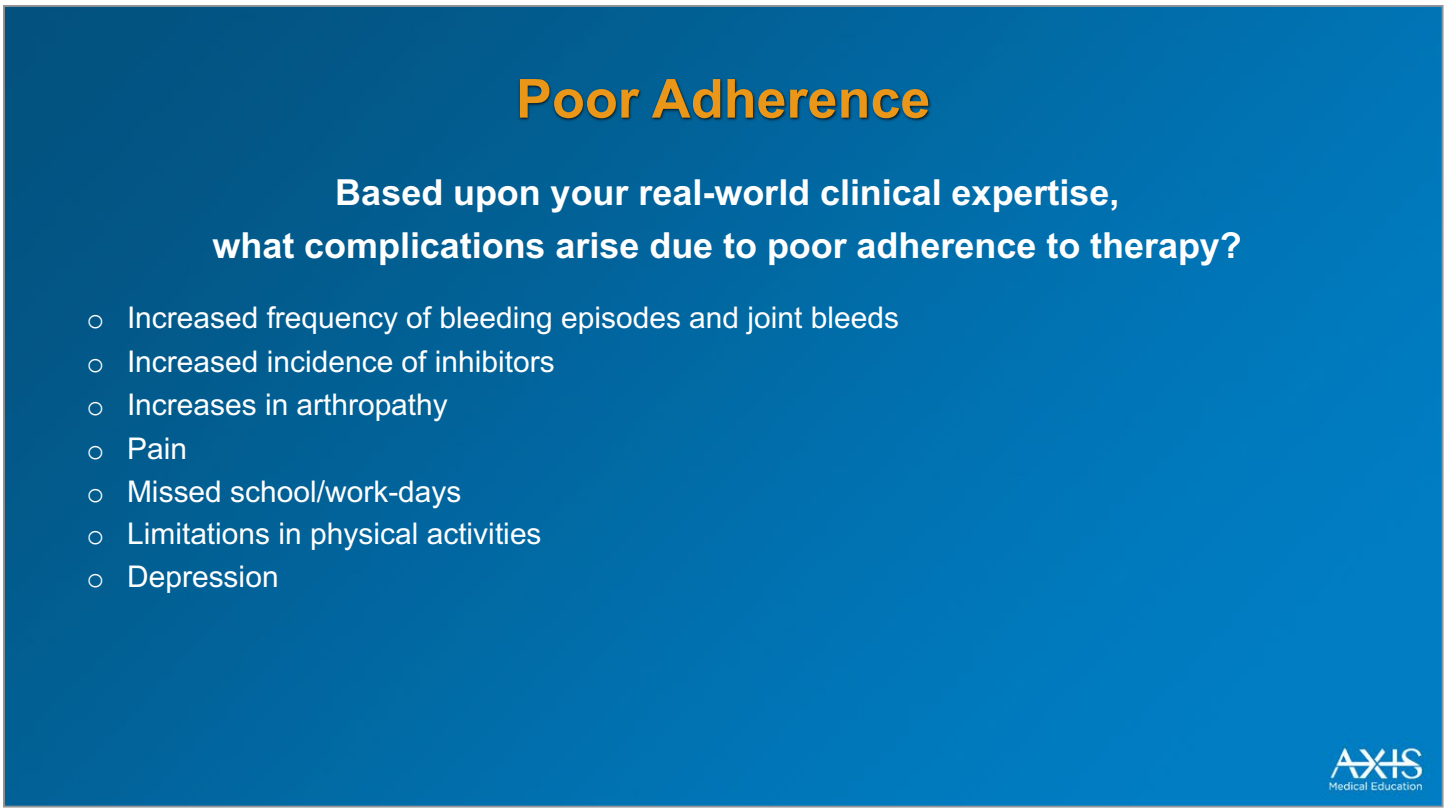
Escobar: Great. How about you, Guy, how do you use the quality of life into your practice?

Young: Yes, I think similar to Cindy, we rely upon our multidisciplinary colleagues. Physical therapists are really good at telling us how their physical quality of life is, mobility and activity. Our social workers are really good at looking into school, which is obviously a big thing for children, but also how the household is functioning.

We have families that both kids have hemophilia, we have families where one kid does, and one doesn't or two do and one doesn't. Both situations are challenging. And so we have our social workers work with the families. We also have a psychologist on our team, as well, who can delve into areas in a deeper way than the social worker can into psychological issues. So we definitely take a look at sort of the whole patient, and really in pediatrics the whole family, too, so it's part of the whole group.

I think an interesting thing is there's so much now about quality of life tools, and we see in clinical trials quality of life as part of the secondary outcome measures, and lots of quality of life papers are being published from drug trials and other things. And I guess the question is do we want to incorporate these tools into our practice?

Escobar: Yes, I think these are very important points, because as you both mentioned, I think quality of life certainly has become more part of our standard of care.



Escobar: So now I'd like to get into a topic that I think touches every single one of our patients, I have to say, and it's adherence. We know hemophilia is a chronic disease, and like any chronic disease like diabetes, like asthma, it is a burden for patients to have to treat all their lives.

So how do you approach this problem that we're still facing. If you want to start, Guy?

Young: Yes, sure. So definitely in the pediatric age group; of course, when we say pediatrics we're talking about infants up to teenagers, and things do change a lot. My experience is that the issues of adherence do follow what has been published, which is that in the younger years adherence is very good; I mean, most parents are very diligent about ensuring that whatever treatment we prescribe, that they get those treatments.

As kids get to school age and they can start to resist things, as time becomes really crunched because we want to do prophylaxis in the morning, at least with factor we want to do it in the morning, it gets more challenging. And then once we get to the teenage years where we expect the patients to assume independence and responsibility for their own care, it drops off even further. And then in young adulthood it gets even more difficult, especially during the transitional time when kids are moving out of the house, going to college, or getting jobs, and they're very transient.

The way we approach it is that there are patients who are exceptionally adherent, including teenagers, so we don't spend a lot of energy on those. Oh, you're doing your factor or you're doing your emicizumab, great, yes, no problem, and you kind of know they're doing it.

Where we focus our energy is on that 20% in the younger age group perhaps, 50% to 60% in the teenagers and young adults, where we have between nursing, social work, and psychology, we focus a lot of energy there. And essentially you've already said it, you want to identify what is the barrier.

Is the barrier venous access, is the barrier time, is the barrier forgetfulness? Really dig in and find out what for that patient is the barrier. Because we say teenagers don't adhere, which is true, but the barrier for one is different than the barrier for the other. If you can identify the barrier, you can then put a strategy together to try to improve that.

It's challenging no matter

what. We've had some successes. Oftentimes even if you identify the barrier and a strategy to improve it, things don't necessarily get better. But I think that's the best you can do is focus your energy on those patients who really are having trouble with adherence, identify the barrier, use that to identify strategy to overcome it.

Escobar: Okay, great. So, Cindy, what do you think?

Leissinger: Completely agree with Guy. It's perhaps the most challenging aspect of what we do in comprehensive care, because we can go through all the strategies of laying out the best therapy, making decisions with our patients and patients accepting those decisions, and write out and prescribe what we believe will be the very best prophylaxis regimen for our patients, but if they don't adhere then it's all pretty much for not.

Because as we know, 1 or 2 joint bleeds can set off that progressive joint disease pattern that our patients have with irreversible joint disease being the result. As I said, it doesn't take many failures of prophylaxis to lead to a significant undesired result particularly with joint disease. And, of course, this is all part of the education of our patients and what we tell our patients.

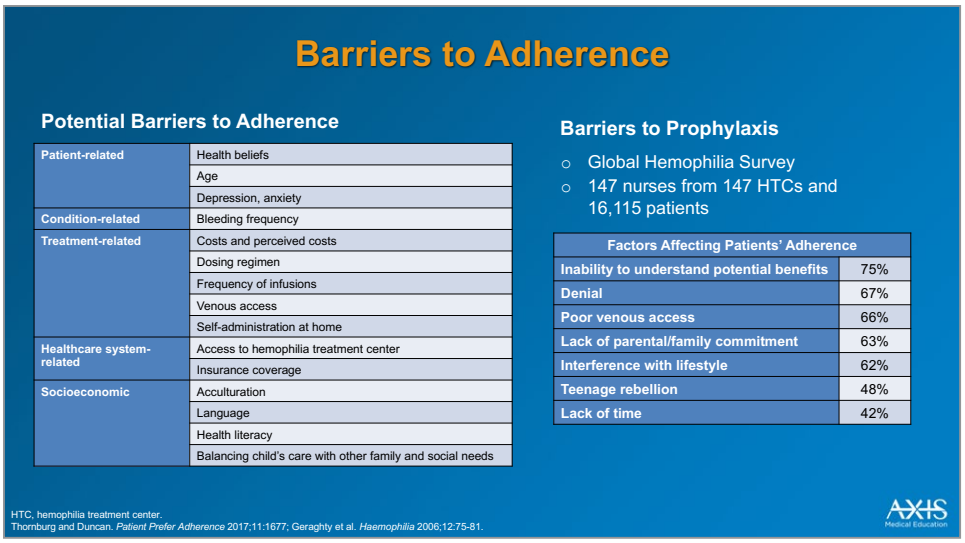
But I think Guy is absolutely right, that when we see patients who are having lapses in adherence, so there are different ways to not… You know, some patients will just have lapses where they'll go for a period of time where they just get tired or whatever and they stop. Others who have periodically missed doses for one reason or another, and I think trying to get to the bottom of what the challenges are for that given individual, and whether it is venous access, or whether it's time, or they've taken a new job and they have to be at work at 6 in the morning. It's really trying to find ways to help to make it easier for patients to adhere.

I will add one somber note, and that is that studies in adherence in chronic illness show that the best predictor of future adherence is past adherence.

When we have those patients, like Guy says, we don't have to spend a whole lot of time motivating them, they are self-motivated. I think the larger challenges are with the other patients who maybe lack a little bit of that; lack a little of that self-confidence, or maybe have some mental health issues. We do know—and it doesn't have to be clinical depression per se, but patients who maybe struggle with being overwhelmed, or anxiety and other things that can be a barrier, and those are perhaps the hardest to help our patients with.

As Guy said, having a psychologist involved, social workers, it's really key. This is a theme, again, for our team, and even our physical therapist is often asking about adherence. And one of the things, too, that's helped us; I mean, we've also incorporated a clinical pharmacologist who can kind of sit with patients and help them. We show them PK modeling, like what happens with their factor and why it's important, and then our physical therapist does ultrasound of their joints and says look, this is what a joint looks like when you have a bleed, and this is the difference. And actually we found that that has helped motivate some of our patients to be a bit more adherent when they see what joint disease starts to look like with the bedside ultrasound.

So there's just a whole variety of approaches that we have to bring to bear, it's no one thing, it's everything; it's a 360 with our patients.



Escobar: Those are very important points. This certainly needs to be addressed very early, because many of the times we end up in a bargain with our patients, and we have to do whatever it takes to get them. The adherence probably goes in hand with the quality of life, like you were saying. Sometimes we have to ask them what is really your goal, what do you want, and how are you going to get there; what is that quality of life that you're aiming for, but to be able to get there you need to be adherent.

Now, there's another point here that was brought up and it was the mental health; I think that is something that at least in my opinion I think we might not be addressing fully. And actually in our practice now, we have one tool to look for depression. We have found a couple of our individuals, a couple of our patients, that were not adherent, and when we investigated further we found they were severely depressed.

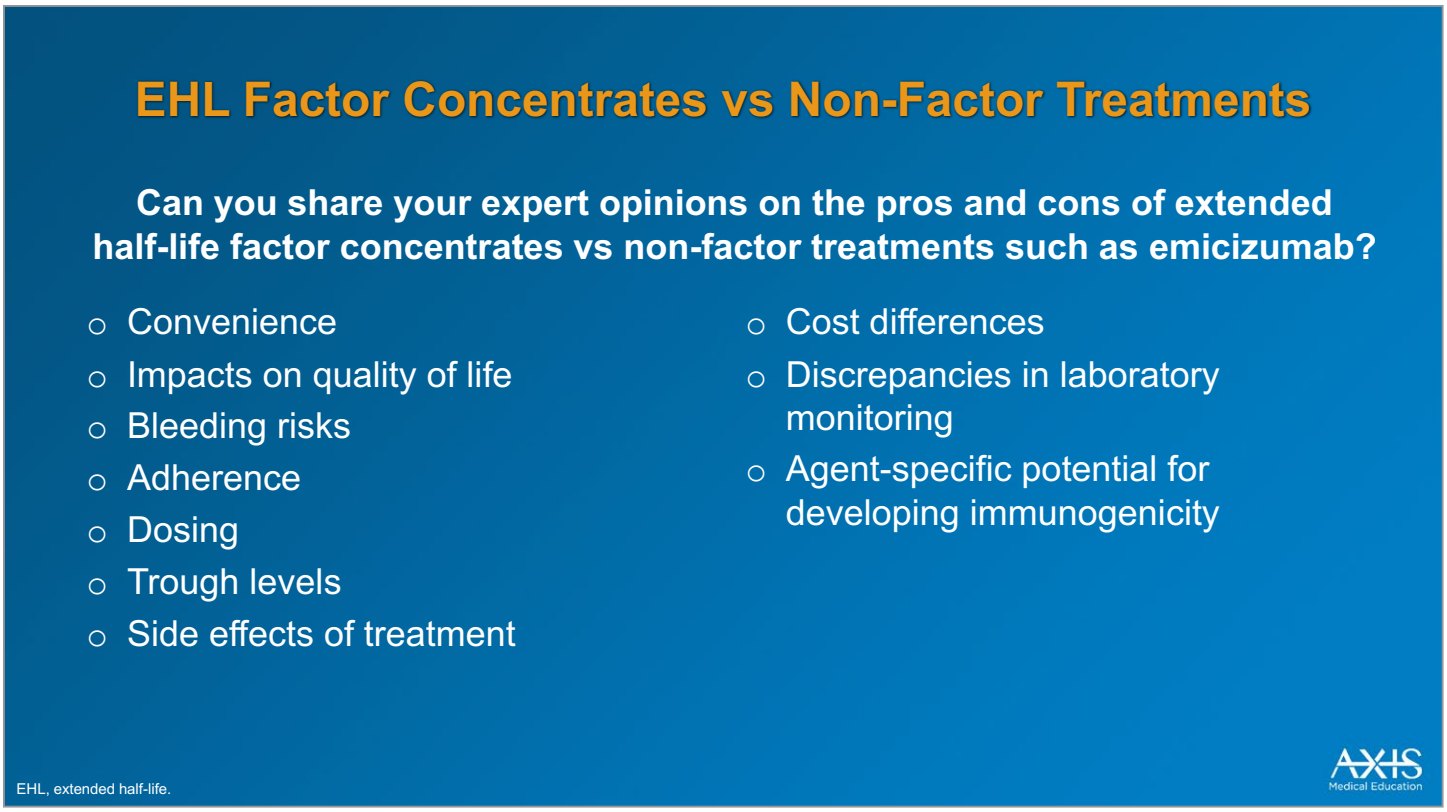
So we are now using one of these scoring systems as part of our clinical history, and every patient we will do this assessment, and depending on the score they have we will then do further investigation, and whatever management needs to be done. Because I think that part of the mental health also could have a lot of impact on how our patients behave in regards to the treatment.

Young: Wrapping it into your discussion earlier about newer treatments, non-factor therapies, the one that we mentioned, emicizumab that's on the market, and then eventually other ones and gene therapy. This is where I think we have to start thinking about those therapies and how they link to adherence.

So I had one case where venous access was the barrier. It was a teenager, he's like I just don't like poking my veins, I don't let my mom poke my veins, I don't want to do that; it's painful, we miss the veins half the time. His barrier was that. He could hit his veins, it just was painful and difficult, he just didn't like to do it.

And so when emicizumab became available, we said look, what about trying something a little bit different. There's no vein to hit; there's still a needle, but there's no vein to hit. And they wanted to try that. And, interestingly, when he got on it he did great and was doing really well for a while, and then, of course, to Cindy's point about what predicts adherence, he was doing so well that, of course, he stopped giving his emicizumab, and then he showed up with his target joint bleed.

But that was in a way a good lesson for him, because he just didn't click that he needed to do the emicizumab every week like he did. And so we had a long discussion with him, and since then, it's about almost a year now that he actually has been adherent.



Escobar: We've talked a little bit about the extended half-life now with the non-replacement therapy with the emicizumab. So briefly I'd like to maybe know if you can share your opinion on how will you decide maybe between one and the other if you have a patient that comes to your clinic. I know that we usually will give them options of what's available, but how do you envision that individual is maybe an extended half-life better for him, or maybe the use of emicizumab? Cindy, how will you maybe make that decision?

Leissinger: I'll let Guy speak about doing this with children and infants and so forth, but in adults they're all coming with some therapy that they've already been on, and probably a lot of set ideas about what they like and what they don't like, etc. But nevertheless, for every adult we see, we go over what new options are there, what new treatments, we even go over what's in the pipeline, so they've heard about it. And so now we've got non-factor therapy, and we have emicizumab. And so we review.

I go over advantages and disadvantages with both factor replacement and with emicizumab, and then I listen to what the patients are saying, and it's across the spectrum. So many of them are very eager to try a non-factor therapy to avoid the IV infusions and the IV sticks; they like the convenience aspect of it, they like the fact that they have kind of a steady state, some with a protective level, right? It's not a normal hemostatic level of protection, but it is much better than certainly severe or moderate baseline that the patient has.

And so some really like that, and they want to try it. Others are very happy with factor replacement, skittish about something new, some want to wait a while and consider it later. So there's just as many individuals as we take care of, that's about how many different tones in those discussions based on the individual.

And so I don't think these decisions have been all that difficult for patients, it's once they know the information and we have a discussion, many of them are pretty clear about their decisions, and for the most part I agree with those.

Escobar: Thank you, Cindy. Guy?

Young: Where I have seen a lot of change in my practice is in those very youngest patients, pups, or maybe not pure pups, but patients who've had very limited exposure to factor, so we're talking about 1 and 2 year olds when we're really going to start prophylaxis for real if it hasn't been started earlier. That could be another

discussion, but typically prophylaxis is started at an early age, as you pointed out, by the World Federation of Hemophilia guidelines typically around the age of 1, let's say, 1, 1.5.

So now you've got a patient who you're going to now initiate prophylaxis, and you have the choices of factor therapy, extended half-life or standard half-life, both given IV and both given multiple times a week—at least 2 in these young children if not 3 certainly for the extended half-life—or we now have the option of a non-factor therapy.

And so I will tell you, the conversation basically is like well, you have the choice of an IV therapy. Most likely we'll need to put in a central venous catheter called a port, because it would be otherwise very, very difficult to do it. The surgeon will place that, your son will be under anesthesia, and then we'll do the factor which you'll do 2 or 3 times a week, and you'll still have to use a needle to access the port. We explain all of these things that I'm sure the audience is familiar with in dosing pediatric patients with factor.

And then you say, well, then there's this newer treatment. We don't have that much data on children as young as your child, which is true and all the HAVEN trials not many kids are less than 2. There are trials going on right now in that age group, but so far we don't have data. So I say we don't have the data, although the indication does include children from newborn and older, so you're not going off-label either.

And you say, well, it's subcutaneous so we don't have to do the port, we don't have to do all the IVs, and it could be done pretty much every 2 weeks after the first 4 doses, that's our typical dosing regimen.

So think about it. If you're a parent or you're thinking about children and you're given those options, I have parents look at me like Dr. Young, I don't understand, what do you mean, this is not really an option. Obviously, we're going to choose the one where our son doesn't need to have surgery, we don't have to access needles through this thing that has a risk for infection. It almost becomes like a false choice, like how can you even compare the two.

So it's an interesting discussion, and I will tell you that 80%, 90% of the parents are choosing to go straight on to emicizumab even if they needed a dose or 2 of factor for bleeding with circumcision, or something like that earlier in life.

So, yes, the shift I've seen is now that we have this other option, one is so much easier, so much more convenient, doesn't involve surgery, doesn't involve the risk of having a port, or if you're not going to put a port in frequent venous access, yes, most parents are choosing to go to emicizumab, and I think it's very understandable.

▶ **Escobar:** Well, I think we've come to the end of this activity. And I really would like to thank Dr. Young and Dr. Leissinger for their input, and I would like to thank the audience for their participation.

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