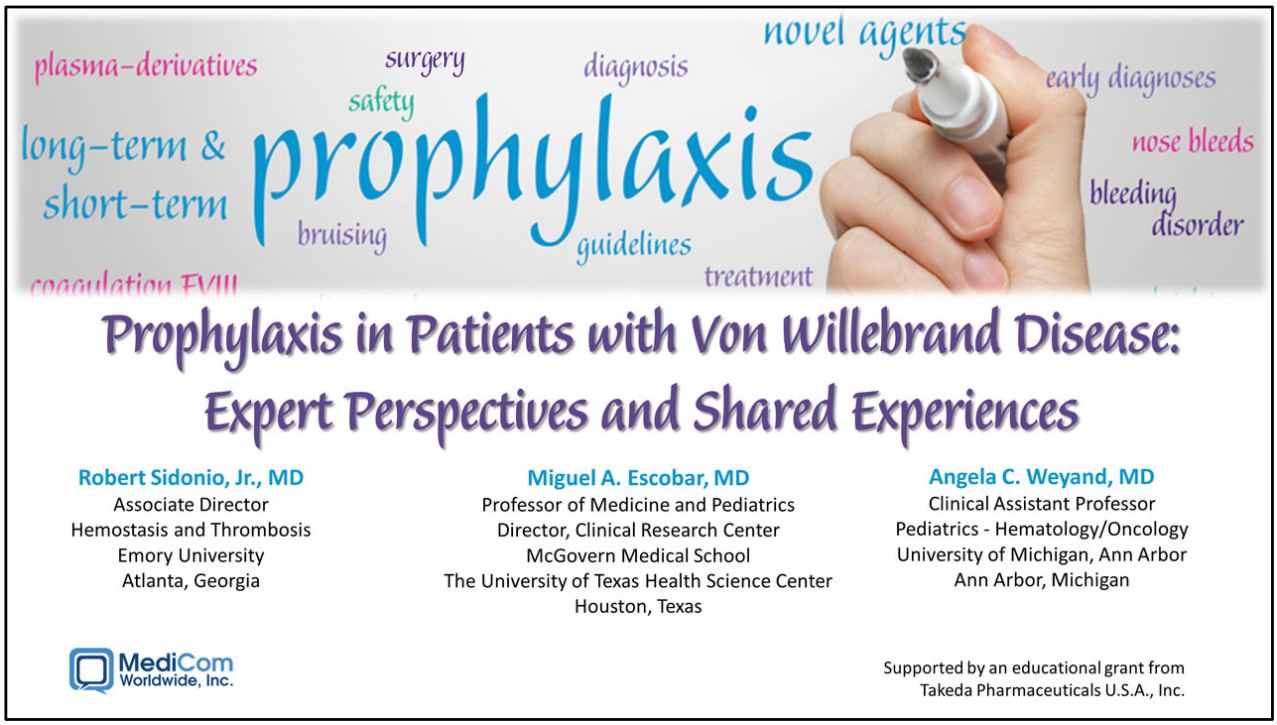
Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



Let's go ahead and get started. You can see the word cloud here, so on behalf of Dr. Miguel Escobar and Dr. Angela Weyand, I'm happy to be chairing this session, *Prophylaxis in Patients with von Willebrand Disease: Expert Perspectives and Shared Experiences*. This is MediCom Worldwide, Inc., and is supported by an educational grant from Takeda Pharmaceuticals in the United States.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

Faculty Disclosures

- **Dr. Robert Sidonio, Jr.** has relevant financial relationships related to consulting from Bayer AG, Genentech, Inc., Grifols S.A., Guardian Therapeutics, Novo Nordisk A/S, Octapharma USA, Inc., Sanofi, Sobi, and Takeda Oncology, as well as investigator sponsored studies from Genentech, Octapharma, and Takeda.
- **Dr. Miguel Escobar** has relevant financial relationships related to advisory activities from CSL Behring, Genentech - A Member of the Roche Group, HEMA Biologics, LLC, LFB Biopharmaceuticals Limited, Novo Nordisk A/S, Pfizer Inc., Sanofi, Takeda Oncology, and uniQure N.V., as well as consulting from HEMA Biologics and LFB. He is on the speakers' bureau for Bayer AG, BioMarin Pharmaceutical Inc., and Kedrion, and has received research grant(s) from Genentech - A Member of the Roche Group, Novo Nordisk A/S, Sanofi, Takeda, and uniQure.
- **Dr. Angela Weyand** has relevant financial relationships related to consulting from Bayer AG, Genentech - A Member of the Roche Group, Sanofi, and Takeda Oncology. She has received research grant(s) from Novo Nordisk A/S, Pfizer Inc., Sanofi, and Takeda.

I'll leave these faculty disclosures for everybody to peruse.

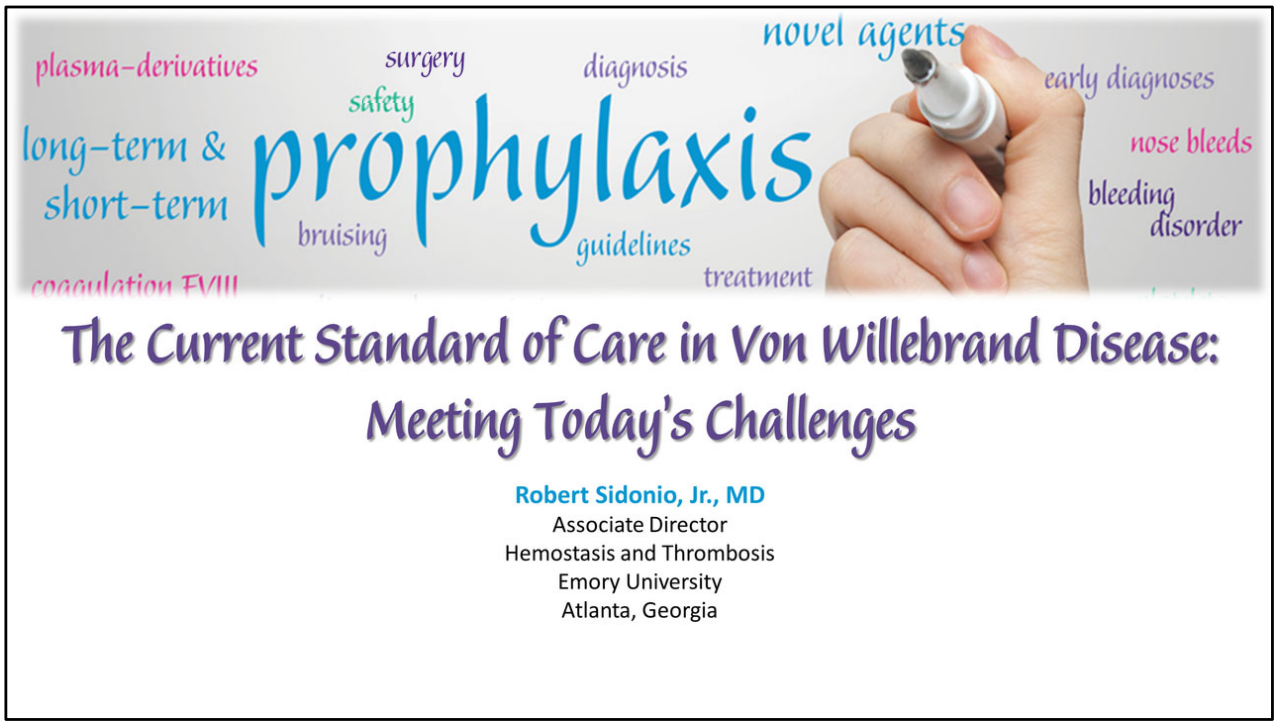
Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

Learning Objectives

- Outline recent guidelines concerning the use of short- and long-term prophylaxis in patients with von Willebrand Disease (VWD)
- Identify patient and disease characteristics that suggests a patient with VWD will benefit from long-term prophylaxis
- Summarize the safety and efficacy data from recent and ongoing trials investigating novel prophylaxis agents for VWD
- Outline factors that must be considered when identifying therapeutic strategies, doses and regimens for prophylaxis in patients with VWD

These are the learning objectives to outline recent guidelines regarding the use of short and long-term prophylaxis. Identify patient and disease characteristics that suggest the patient with VWD will benefit from that long-term prophylaxis. Summarize the safety and efficacy data from recent and ongoing trials. Outline factors that must be considered when identifying therapeutic strategies, doses, and regimens for prophylaxis and patients or persons with von Willebrand disease. We're going to cover a lot in the next hour.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



I'm going to start this out, and we're going to talk about the current standard of care on von Willebrand disease and how we can meet those challenges. It's really exciting to see a number of clinical trials with actually available data. Hopefully, even more data will be seen at the ASH Meeting as well. I'm Robert Sidonio, as mentioned before. I'm at Emory University at Children's Healthcare of Atlanta.

Von Willebrand Disease (VWD)

- Erik von Willebrand reported mucocutaneous bleeding and death among several members of a family living on the Åland islands the Baltic Sea
  - Both males and females were affected
  - Bleeding time was prolonged despite normal platelet counts
- Index case was a 5-year-old girl named Hjørdis
  - Hjørdis died after her 4th menstrual period
- At least 25k cases of VWD (many unrecognized as likely occurs in 1 in 1000 persons)

James PD, et al. *Genet Med*. 2011;13(5).; Soucie JM, et al. *Haemophilia*. 2021;27(3):445-453.

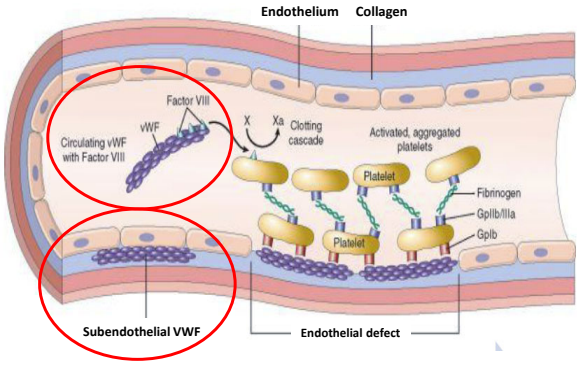
This is a great picture. It's not why I have a mustache, but it's a great mustache that he has. This is Erik von Willebrand, and he reported mucocutaneous bleeding, and unfortunately, death among several families that were living on the Åland Islands in the Baltic Sea. I've circled it for you in case you knew where that was already. The characteristics were pretty straightforward. They're both males and females, so looked different than hemophilia. The bleeding time, which I believe they used on the ear at the time, was quite prolonged. I can't imagine doing those bleeding times and watch it not stop bleeding for 15 to 20 minutes.

The index case was a five-year-old girl named Hjordis. I always want to tell the story in the clinic, in our menstrual bleeding clinic, but then I remember that she died after her fourth menstrual period, which is probably not an appropriate story to tell teenage girls that are just coming to our clinic for the first time. Not only did she have heavy menstrual bleeding, she also had very prolonged issues with musculoskeletal bleeding and didn't have any treatments, so she pretty much had to rest and lay down for multiple weeks.

We know that there are at least 25,000 cases of von Willebrand disease, and many are unrecognized, and likely, the prevalence is somewhere in the one in a thousand range.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

VWF Plays Two Important Roles



1. **VWF tethers the platelet to exposed collagen**
2. **VWF serves as a carrier protein for factor VIII**

VWF=von Willebrand factor
James PD, Goodeve AC. *Genet Med*. 2011;13(5).

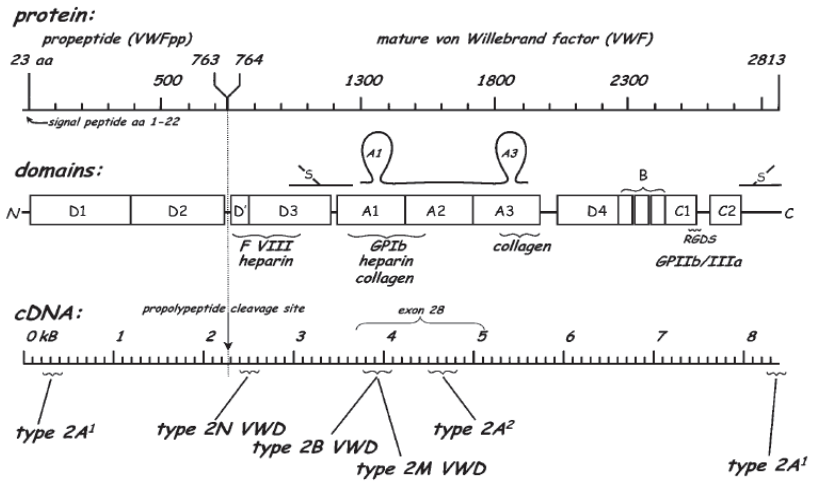
Just for level setting, but everybody probably knows because there's been actually a number of von Willebrand talks, there are two important roles, and there likely are many other roles that we don't know.

We know that von Willebrand's factor tethers the platelet to the exposed collagen as seen in this cartoon, in this paper done by Dr. Paula James.

Then it serves as a carrier protein for Factor VIII, delivering it to the site of damage, and allowing for hemostasis.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

VWF Genetics



The Diagnosis, Evaluation and Management of von Willebrand Disease. NBLI von Willebrand Disease Expert Panel. 2007.

We know that genetics has actually been fairly well described, but if you were at a talk yesterday by Dr. Jill Johnson, there's probably more work that we need to be done in this field, focusing on genotyping, focusing on structural variance. Thankfully, most of it has been mapped out, and I think in the next 5 to 10 years, we'll be elucidating more of this, but it's been a lot of work that's been done by a number of experts including one of them sitting there, Dr. Montgomery.

VWD Classification

	Type 1	Type 2	Type 3
Definition	Below normal levels of VWF	Normal levels of VWF, but VWF fails to work properly	Total or near total quantitative deficiency of VWF
Severity	Mild-to-moderate	Mild-to-moderate	Severe
Prevalence (% of cases)	85%	13%	3%

- Type 2 includes four subtypes:
  1. Type 2A: Typically manifests as mild-to-moderate mucocutaneous bleeding
  2. Type 2B: Typically manifests as mild-to-moderate mucocutaneous bleeding that can include thrombocytopenia that worsens in certain circumstances
  3. Type 2M: Typically manifests as mild-moderate mucocutaneous bleeding
  4. Type 2N: Can manifest as excessive bleeding with surgery and mimics mild hemophilia A

Centers for Disease Control and Prevention (CCD). Von Willebrand Disease (VWD). https://www.cdc.gov/ncbddd/vwd/facts.html#Accessed. July 2022.

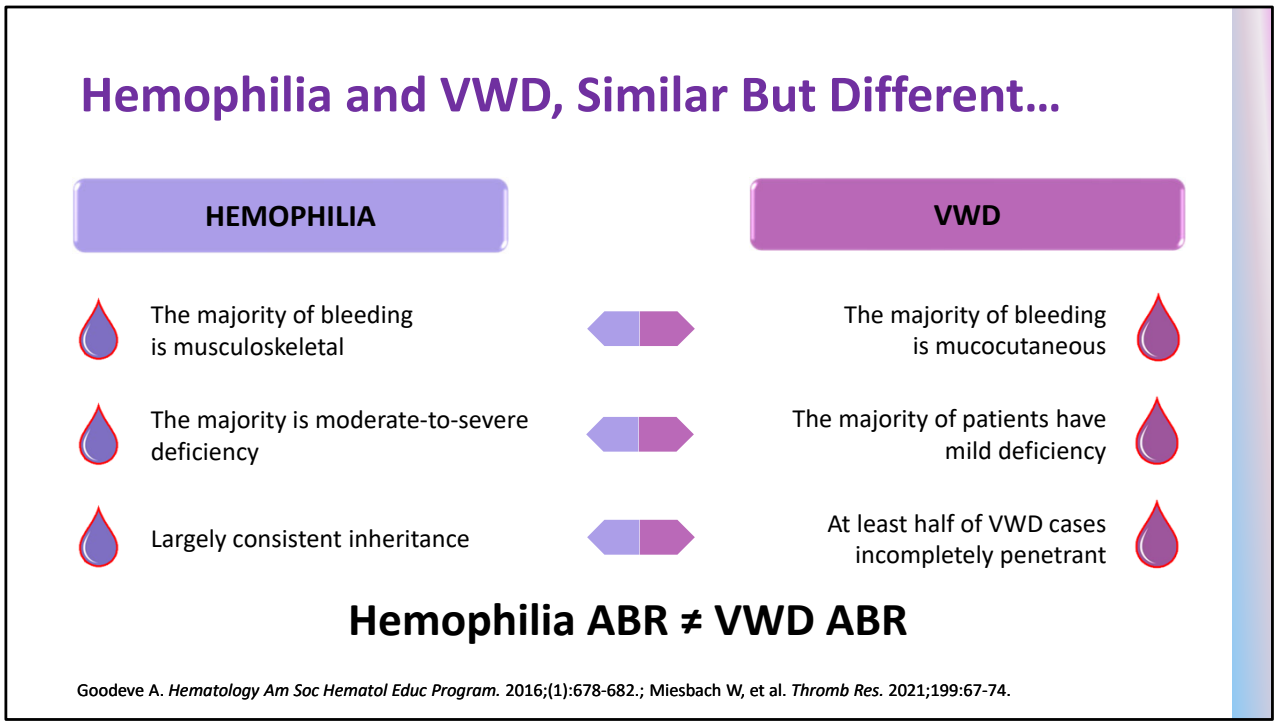
The classification, these are even the ones listed here on the subtypes, they're not all of them, there are going to be more coming, and they're not just doing it just to make it really difficult in your life. It is important, I think, to discern between the different subtypes. I think we all know there's certain types of 2A that bleed quite a lot, and it's nice to be able to predict that for the family and make sure they understand what the bleeding they have.

Generally, Type 1 is where there is an issue with secretion or clearance. They have below-normal levels of VWF, and it can be as mildly deficient as 40% to 50% as you would see in low VWF, or could be as severe as you see, almost as severe as in Type 3. I think that's what makes it very difficult because most of our healthcare providers see mild Type 1 and they associate von Willebrands with that. That makes up most of the cases. I think these numbers will change as we genotype more patients. I think they're likely more Type 2 patients. Type 2 patients may or may not have reduced levels of VWF, but the VWF fails to work properly, and they can have some severity that can be quite severe. It says mild to moderate, but many Type 2A patients have pretty severe disease. Type 3 is one of those ones that's really easy to diagnose, you have absolutely no VWF, and you have an associative Factor VIII level that is quite low and can often be confused with hemophilia.

I think this is going to be really interesting. I was part of a case in which a child had excessive bleeding at birth. They actually did whole exome sequencing, and ultimately, this child was determined to have Type 2N/Type 1 von Willebrand disease with absolutely no functional testing done for at least a year or two after the diagnosis. I think we're going to see a lot more of those kinds of cases in which the

genotype is going to be described even before the functional testing.

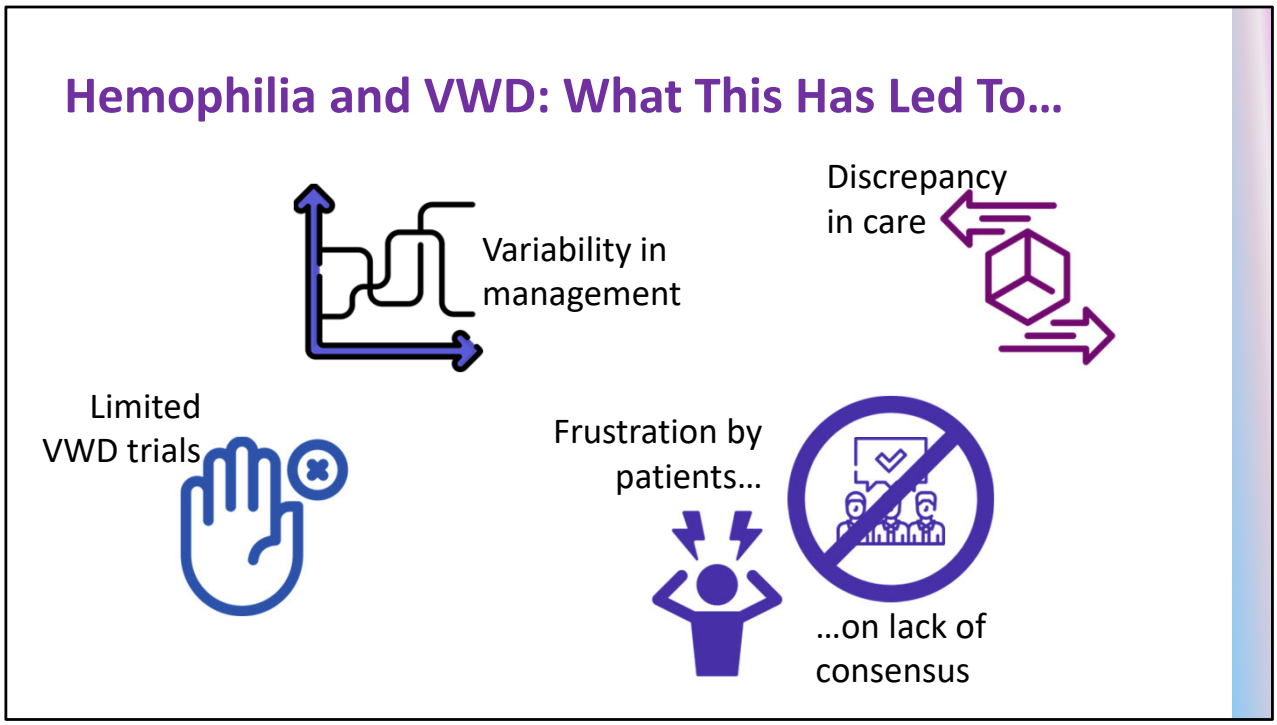
There are many subtypes. I'm not going to go through all of them, but it's important to separate them out, and there's a whole set of guidelines you can utilize to make that diagnosis.



One of the things I really wanted to emphasize, and hopefully, you've heard that from here at this meeting is hemophilia is not von Willebrands. Some of the comments that Dr. Weyand was talking about, about trying to apply the same metrics for one disorder for the other, like, we have to run the trial just like we run the hemophilia trials. Well, we shouldn't have to do that.

I don't think a hemophilia ABR is anywhere near the same thing as a von Willebrand ABR, and I don't want to minimize the ABR in von Willebrands, but it is quite different. We know that von Willebrand's, the majority of bleeding is typically mucocutaneous with higher, with worse severity, it can become more musculoskeletal. A majority have mild deficiency, I think, which colors our opinion of what von Willebrand has, and at least half the cases are incompletely penetrant, makes diagnosis quite challenging, and hopefully, our genotyping efforts are going to improve that.

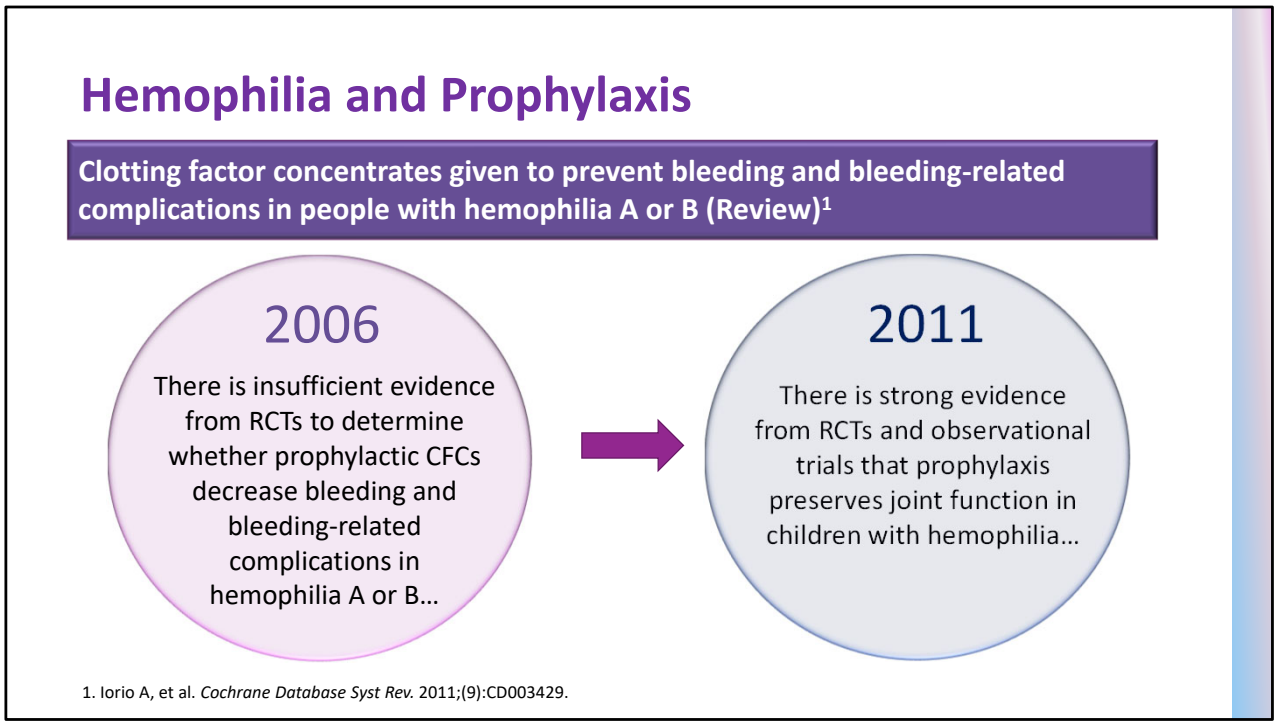
The hemophilia, although there's not perfect correlation, there tends to be fairly consistent inheritance. The majority of the patients have moderate to severe disease, so that really colors our opinion as well of what hemophilia is compared to von Willebrand's. I think we've done a really good job of taking care of hemophilia patients. We have all these wonderful drugs. I think the time for von Willebrands is now, and I think we need the next decade, we need to catch up to hemophilia care and really advocate for this patient population.



I think all of these issues and trying to attribute and trying to say we can do everything just like we did in hemophilia that worked for our hemophilia trials. I think part of the problem is there's been quite a variety in management. I think we see this, we get these referrals where patients are not adequately managed. They're not offered things like prophylaxis when it could be something offered.

I was revising a chapter on von Willebrands, and there's a whole section about how prophylaxis in von Willebrands should be rarely offered and should be only considered in very extreme situations. Of course, I deleted that section when I changed it. A lot of this leads to discrepancy in care. By the time the patient comes to you, they're extremely frustrated. That can make it difficult because you're the first person getting this. The nurses are hearing this, and so you're spending a lot of time deescalating and trying to ensure them that you're not going to be the same.

There have been very few trials in von Willebrands. When we talk about trials, we get super excited when we have 20 to 30 patients in this trial, and it's likely because of the design of these trials. Oftentimes, they don't allow us in these von Willebrands trials to have what we call PTPs. Those are widely accepted in hemophilia to have PTP trials, but they're not as widely accepted in von Willebrands because they want to show the difference, which may be difficult to show a significant improvement.



We know that back in 2006, just as a reminder, technically, there was insufficient evidence from RCTs to determine whether prophylactic clotting factor concentrates would decrease bleeding and bleeding-related complications in hemophilia A or B. It wasn't much longer after that, which those trials were conducted, and that changed that opinion, but we know that there are many countries prior to 2006, particularly in Europe, that were implementing prophylaxis in hemophilia. I know that RCTs are the gold standard, but we don't need to wait for them to do these things, and obviously, we need to advocate for our patients. We're not going to wait five to six years until an RCT comes out and demonstrates that prophylaxis has a role.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

International Effort to Develop the 2021 VWD Guidelines


CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jer
Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[
Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husain

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[17]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta
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Medical Center, Kansas City, KS


CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

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James P, et al. *Blood Adv*. 2021;5(1):280-300.;
Connell N, et al. *Blood Adv.* 2021;5(1):301-325.

As mentioned before in other talks, there's been international effort to develop guidelines. There are a number of people in this room that were integral in this. It had two different papers that came out, one led by Paula James, one led by Nathan Connell. These were pretty rigorous. This took multiple years to develop, and it's probably going to be, I don't know, 10 years before we do another one of these. These are expensive endeavors. Obviously, we put a lot of time and effort in this, and we had patient inclusion, which actually colored a lot of our decision-making as how the patients felt about how we were going to vote on certain topics.

Prophylaxis

Definition in Hemophilia

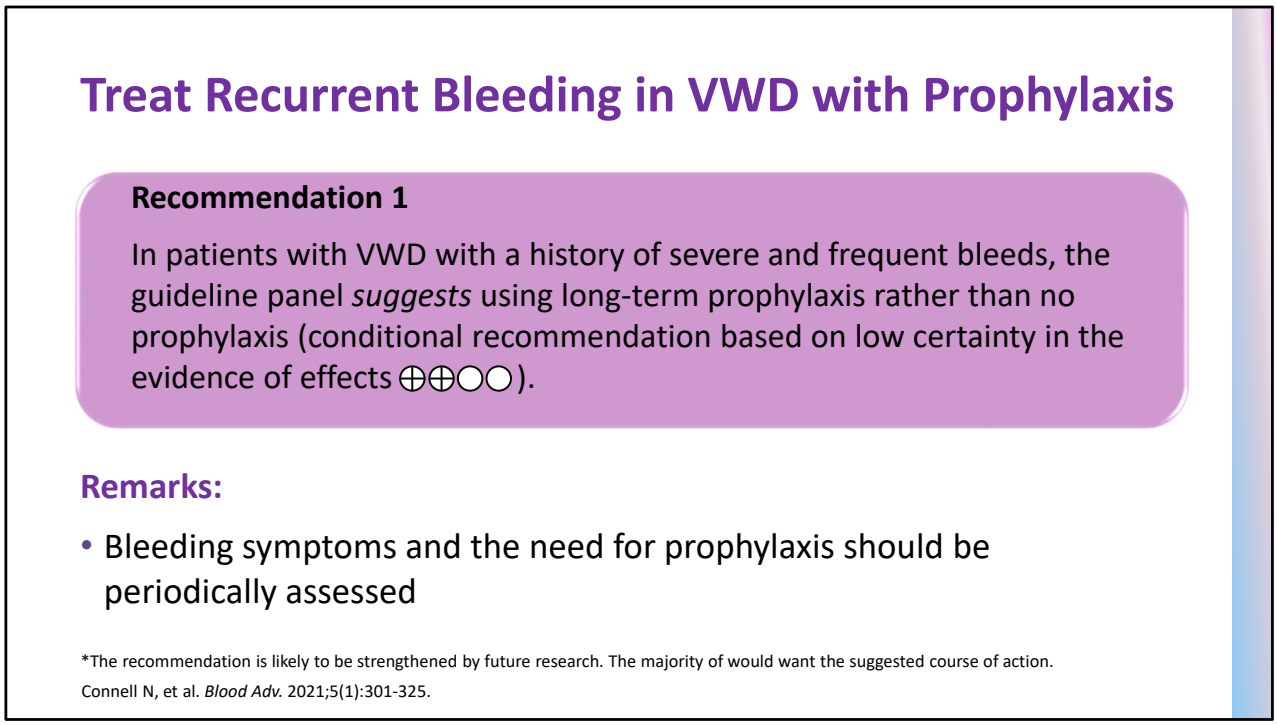
- *Primary:* Before the second clinically evident large joint bleed
- *Secondary:* After the second joint bleeding and before initiation of joint disease
- *Tertiary:* Treatment started after the onset of joint disease

Proposed Definition in VWD

- A period of at least 3 to 6 months of treatment consisting of VWF concentrate administered at least once weekly, or for women with HMB, use of VWF concentrate administered at lease once per menstrual cycle

Connell N, et al. *Blood Adv.* 2021;5(1):301-325.

I think the definition of hemophilia has been illustrated. It's been slowly refined, primary prophylaxis before the second bleed or before a large evident joint bleed. Certainly, we've defined secondary and tertiary when we come to hemophilia. It hasn't been perfectly described. Nathan Connell attempted to come up with a consensus of what prophylaxis should be, a period of at least three to six months of treatment consisting of VWF concentrate administered at least once weekly, and for women with heavy menstrual bleeding, use of concentrate administered at least once per menstrual cycle. We attempted to come up with some definition, and it's not going to be the same as hemophilia, and it doesn't need to be the same as hemophilia. I think we don't need to measure everything through the lens of hemophilia just because that's what we know.



One of the recommendations that was really integral in this was really probably the most important thing that came out of the management part was recommendation one here in patients with von Willebrands and a history of severe and frequent bleeds. The guideline panel suggests long-term prophy rather than no prophylaxis. There's a caveat there.

Obviously, this is a conditional recommendation based on the low certainty of evidence, but it's clear based on expert opinion, and it's likely to be strengthened by future research. It was deemed as the majority would want this course of action. I think it's really important to notice that the severity of von Willebrands is not listed in the subtype, isn't specifically listed there as well, so it's really focusing on the bleeding symptoms and the outcomes of achieving hemostatic control and limiting anemia.

Available VWF Concentrates

Product Name	Ratio of VWF:RCo to FVIII:C	Half-life (h)	Regulatory Approval
Alphanate (antihemophilic factor/VWF complex [human])	1.3:1	VWF:RCo 7.67 ± 3.32 FVIII:C 17.9 ± 9.6	Yes: surgery and/or invasive procedures; except Type 3 (not indicated for severe type 3 undergoing major surgery) No: prophylaxis
Humate-P (antihemophilic factor/VWF complex [human])	1.8-2.4:1	VWF:RCo 10.5 (2.8-33.6) FVIII:C 12.2 (8.4-17.4)	Yes: bleeding and surgery prophylaxis No: prophylaxis
Wilate (VWF/coagulation factor VIII complex [human])	1:1	VWF:RCo 15.8 ± 11 FVIII:C 19.6 ± 6.9	Yes: bleeding and surgery prophylaxis No: prophylaxis
Vonvendi [VWF (recombinant)]	N/A	VWF:RCo 19.1 ± 5 (No FVIII content)	Yes: on-demand bleeding, perioperative management of bleeding Yes: prophylaxis for severe Type 3 VWD receiving on-demand therapy

ALPHANATE® (antihemophilic factor/VSF complex [human]). Los Angeles, CA: Grifols Biologicals LLC. Revised June 2018. Alphanate Prescribing Information Patient.pdf. Accessed August 8, 2022, 2022.; HUMATE-P® (antihemophilic factor/von Willebrand factor complex [human]). Marburg, Germany: CSL Behring GmbH. Revised June 2020. Package-Insert---Humate-P-1.pdf. Accessed August 8, 2022.; WILATE® (von Willebrand factor/coagulation factor VIII complex [human]). Vienna, Austria: Octapharma Pharmazeutika Produktionsges.m.b.H. Revised March 2020. Package Insert - Wilate.pdf. Accessed August 8, 2022.; VONVENDI® (von Willebrand factor [recombinant]). Lexington, MA: Baxalta US Inc. Revised 1/2022. Package-Insert---VONVENDI.pdf. Accessed August 8, 2022.

There are a number of concentrates that are available. Not going to spend a lot of time on this. I know Dr. Escobar and Dr. Weyand are going to go more into this. It's really important mainly just to show this chart is that they have different ratios, they have different half-lives, and certainly, now they have different indications. We're hopeful that in the next few years, a couple of these products will have expansion of their labels because I think that's really important.

Oftentimes, we see that it's not indicative for prophylaxis, and I know that I haven't been practicing that long, but there have been a number of us in this room that prescribed factor for prophylaxis for hemophilia before there was a label as well. I don't think we always need to wait on that. Hopefully, everybody will advocate and consider participation in these trials, because it's really important for this patient population.

Prophylaxis in VWD

Dose escalation prospective study design part of the VWD prophylaxis network

- n=105 (90 retrospective; 10 prospective)
  - Type 1 VWD(<20 VWF levels) (13)
  - Type 2A/2M/2B VWD (38)
  - Type 3 VWD (54)

Indication	N	Prior to prophylaxis, median (IQR) prophylaxis	During prophylaxis, median (IQR)	Median rate change (IQR)	Median percentage change (IQR)
Epistaxis	28	11.1 (6.0 to 48.0)	3.8 (0.21 to 16.8)	-6.1 (-42.0 to -1.5)	-86.7 (-95.5 to -49.8)
GI bleeding	18	9.3 (6.0 to 21.6)	6.0 (3.6 to 7.1)	-3.0 (-6.0 to 0.0)	-44.3 (-72.2 to 0)
Joint bleeding	25	11.9 (6.0 to 18.0)	0.8 (0.0 to 3.2)	-8.5 (-12.0 to -4.2)	-86.9 (-100.0 to -52.5)
Menorrhagia	9	9.6 (8.4 to 12.0)	0.0 (0.0 to 0.4)	-9 (-9.3 to -6.0)	-100.0 (-100.0 to -95.8)

IQR=in quartile range
Holm E, et el. *Blood Coagul Fibrinolysis.* 2015;26(4):383-388(6).

When you look at prophy in von Willebrands, we'll go through this quickly. The von Willebrand prophy network was set up almost a decade ago and they were able to demonstrate, this was part of the dose escalation prospective study after they did a retrospective study, you can see the levels there. You had to have less than 20% for Type 1, and you had to have a diagnosis by your local provider, but you can see clearly here, prior to prophylaxis in the first here, the number of patients listed by symptoms, the number of bleeds prior to that, during prophylaxis, and the change. You can see a lot of negative numbers, meaning there was an improvement in bleeding.

One of the things that probably wasn't as improved as GI bleeding, and we all know that that's a difficult measurement and it certainly doesn't mean that we shouldn't use a concentrate, but it's more complex than just replacing with concentrate.

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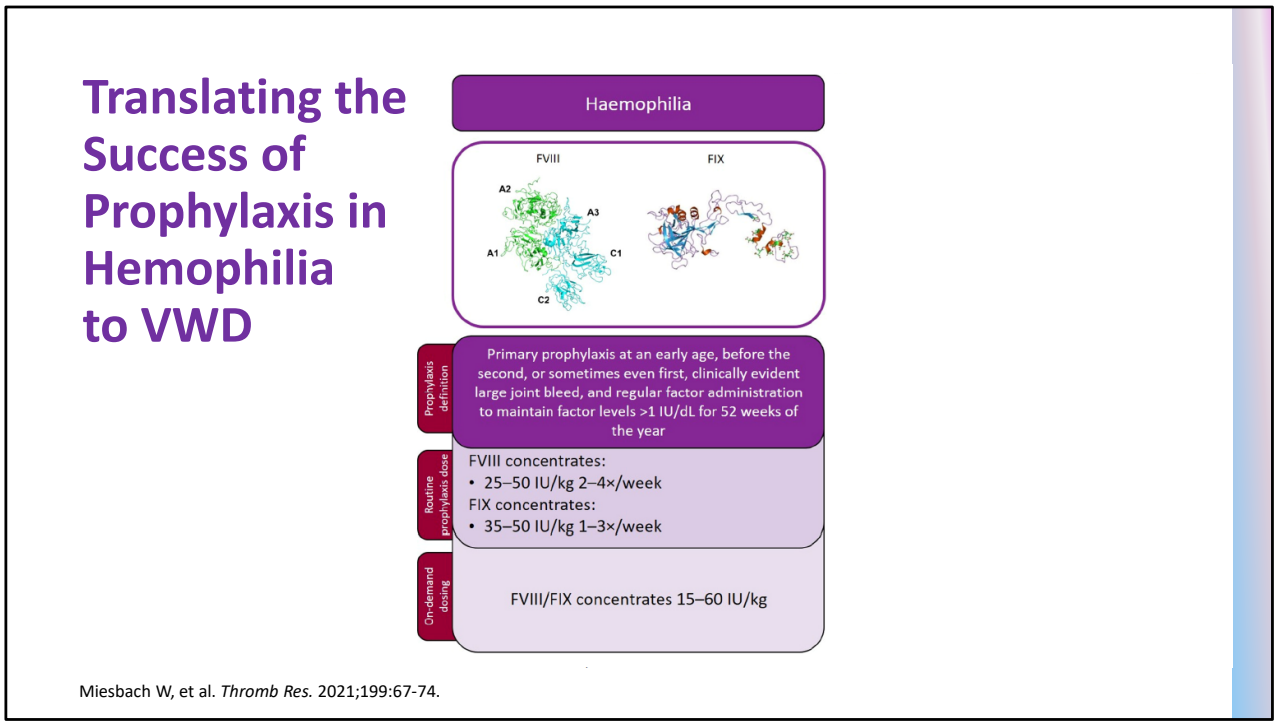

Last couple slides here. I know I keep talking about, I don't want to talk about hemophilia, but then I keep talking about it. Translating the success of prophylaxis in hemophilia, I think there's some lessons we learned.

This is a great paper by Wolfgang Miesbach who talks about the differences there. We have hemophilia. We've defined what prophylaxis is. We generally know what the doses are, and these are doses of prior to some label changes here, of standard half-life products. We know generally what we should be doing for on-demand doses.

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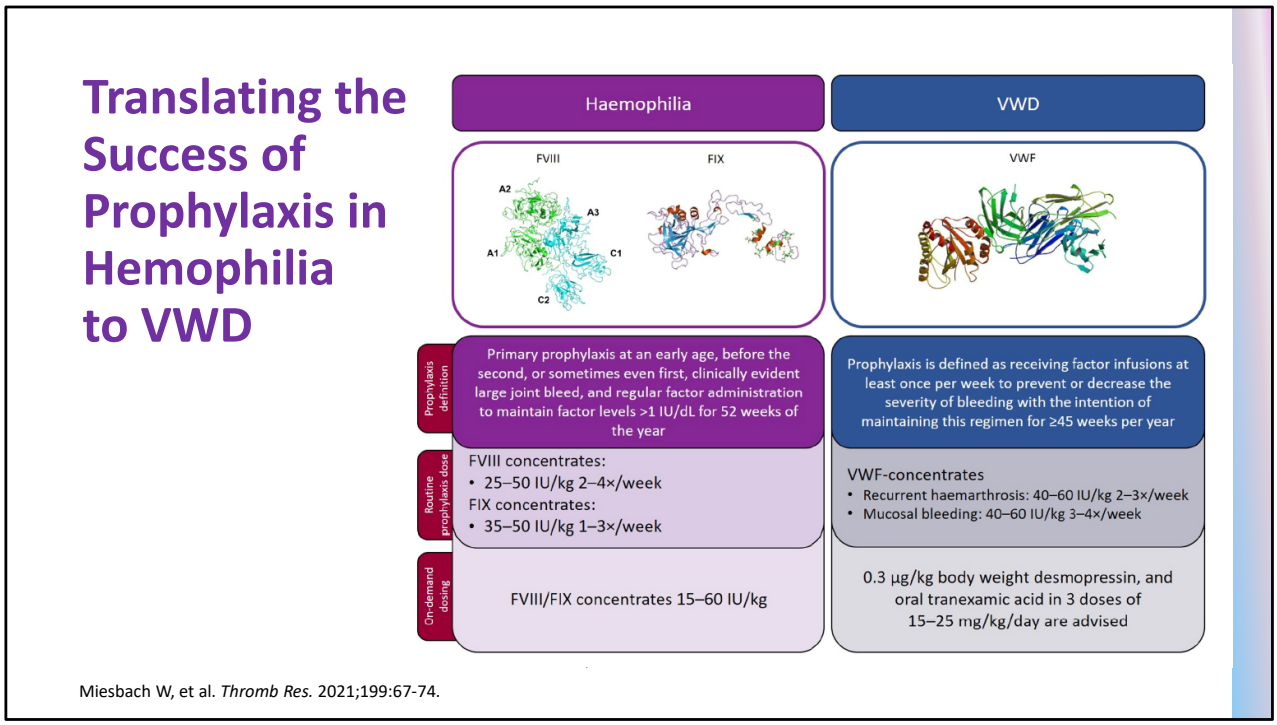
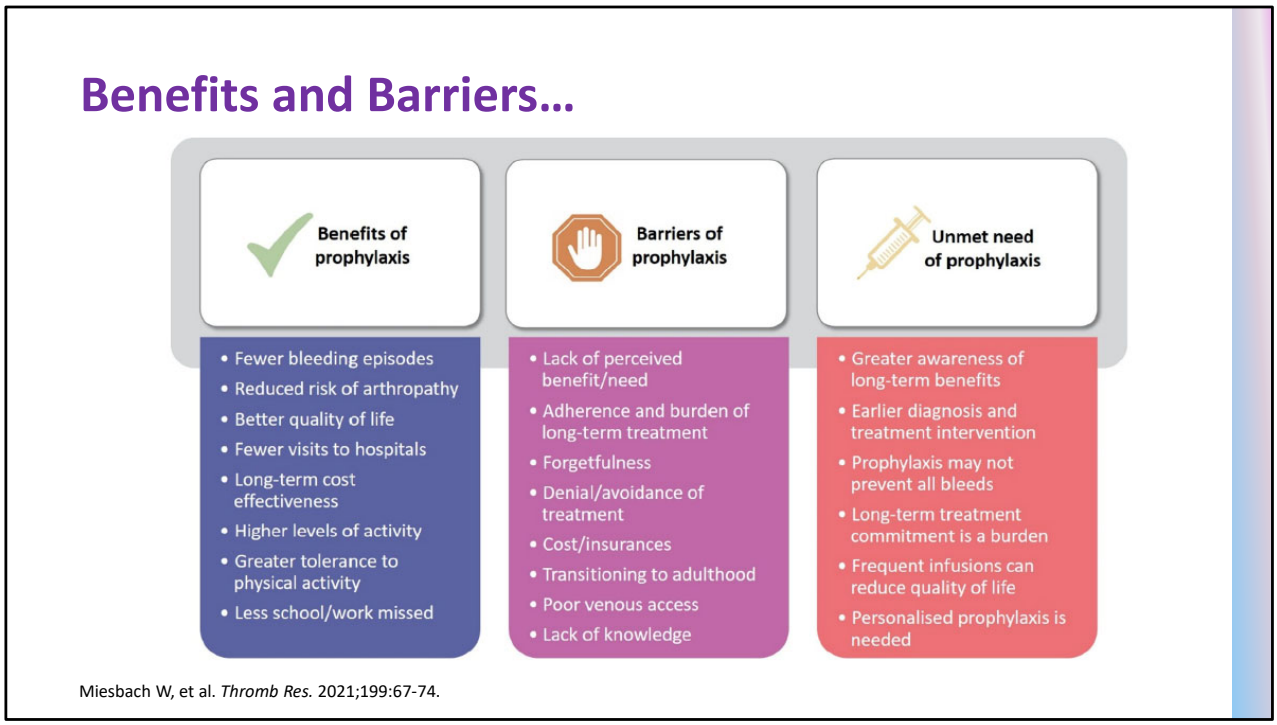


Miesbach W, et al. *Thromb Res.* 2021;199:67-74.

For von Willebrand disease, and this is going to change because this paper was in 2021, we're still trying to define it. He attempted to define it with this data of over 45 weeks per year.

I think we're still trying to nail down what's the exact definition of von Willebrand prophylaxis, and likely, there is tailored dosing based on the bleeding symptom. At least that's my belief is that prophy dosing should be based on what bleeding kind of symptom occurs, and likely that's going to be how we conduct trials in the future when we talk about Von Willebrand disease.



There are a number of benefits and barriers. Obviously, lots of benefits of prophylaxis, higher activity levels, physical activities, a greater participation, less school and work missed, better quality of life, hopefully, reduction of hema arthropathy that we may see in the future.

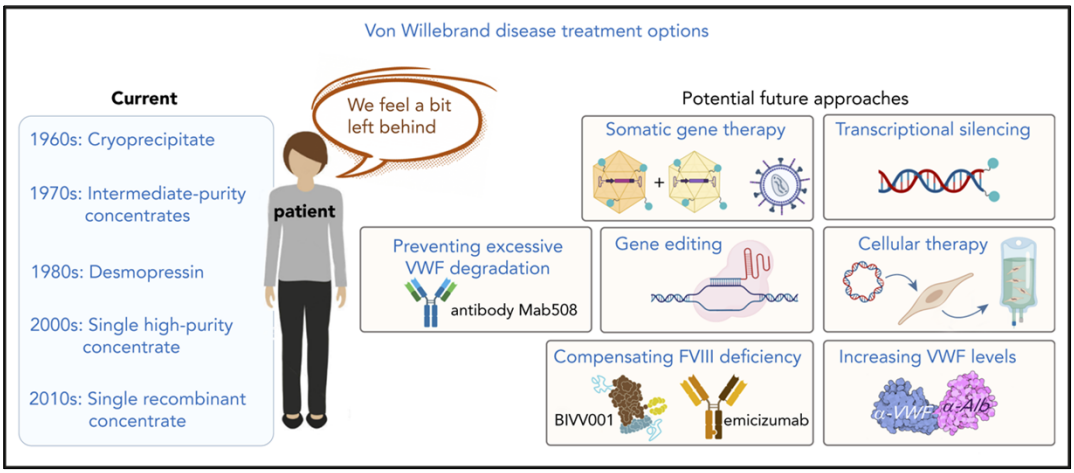
There are a lot of barriers. A lot of providers, even at this meeting, don't see the benefit of prophylaxis for their patients. Certainly, not for all your patients, but some of them. These are IV drugs that there's going to be some adherence issues, and there's going to be definitely some issues related to our patients to accepting it.

We always talk about this IV culture has been widely accepted in hemophilia. Everybody expects this. Patients always tell me they don't like needles. I said, "I don't like needles, nobody likes needles." It's a culture that's accepted. You have all the women that know how to stick all the men in the family for hemophilia, and in families with von Willebrand's, most people don't have any venipuncture skills, and it hasn't been deemed as something that we should teach them and really try to implement those things that we taught about hemophilia in the early days of the HTC development.

I hope that there's an unmet need there, obviously. I believe there's personalized prophylaxis that should be considered. We all just give doses for von Willebrand factor. I

think we typically use the doses and the guidelines. Most of us probably don't look at incremental recovery. We don't check levels, and we don't do the calculations. I think we need to do better by our patients when it comes to that, and try to do a better job of implementing what we've learned in hemophilia.

The Future of VWD?



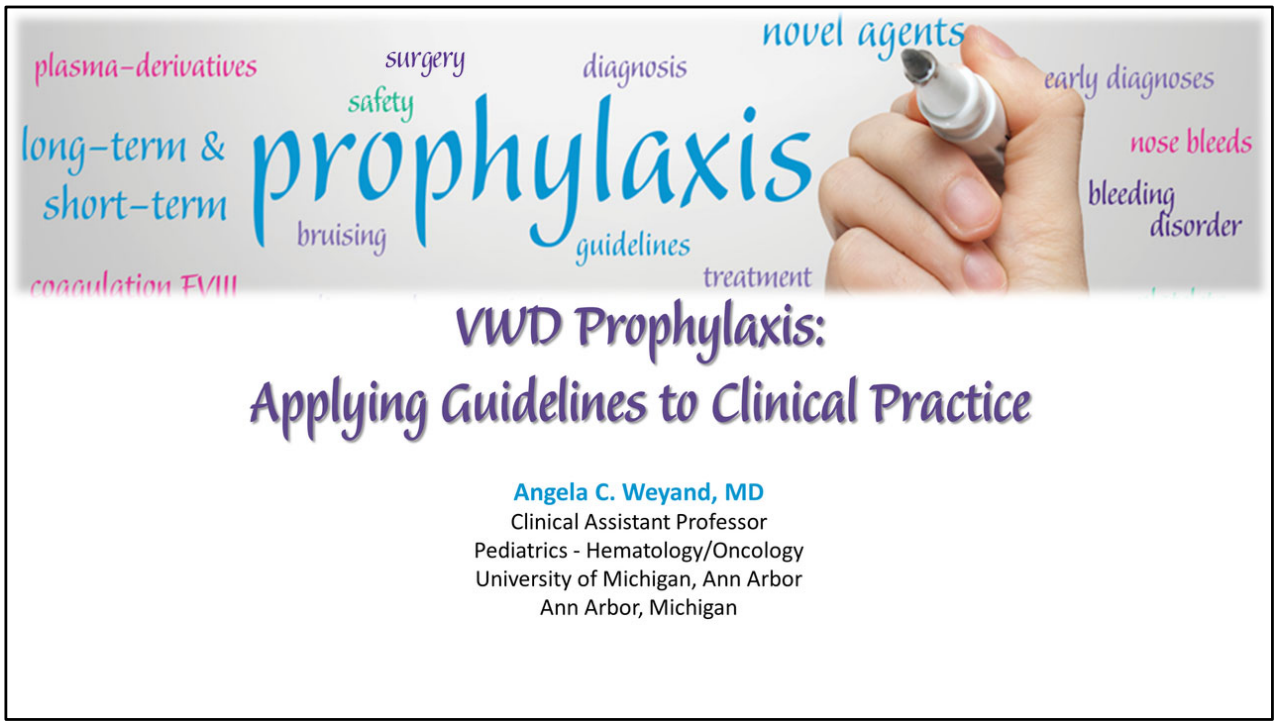
Denis CV, et al. *Blood.* 2021;137(17):2299-2306.

This is the last slide here. Cecil made a nice paper here about the future of von Willebrands. You can see all of the improvements there. It's a really short timeline for von Willebrands. Starts with cryoprecipitate, intermediate purity, concentrates, Desmopressin, single high purity concentrate. The only thing that's changed in the last few decades is the advent of a single recombinant concentrate.

I often wonder, we've advocated for our patients with von Willebrands for hemophilia to be mostly on recombinant products, and we haven't applied that same metric into von Willebrands. There are a number of things being investigated. Certain drugs that may have a benefit are listed here, including investigational drugs, monoclonal antibodies created by Benny Sorensen in Hemab, and BT200 may have actually a role in this as well. There is some excitement of new drugs, non-factor therapies that may actually be really beneficial for this patient population.

With that, I'm going to turn it over to Dr. Angela Weyand, who hails from University of Michigan, who is a native of Kansas City that I learned last session. Angela, I ask you to take it from there.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



Dr. Angela Weyand: Thank you. I'm going to be speaking a little bit more about applying the guidelines. I was able to be a member of the ASH, ISTH, NHF, WFH guideline panel on the management of von Willebrand disease. We'll be talking a little bit about that, recommendation number one.

Management: Prophylaxis

In patients with VWD with a history of severe and frequent bleeds, should routine prophylaxis with VWF concentrate or no routine prophylaxis (ie, treatment on demand) be used?

Recommendation 1. In patients with VWD with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis.

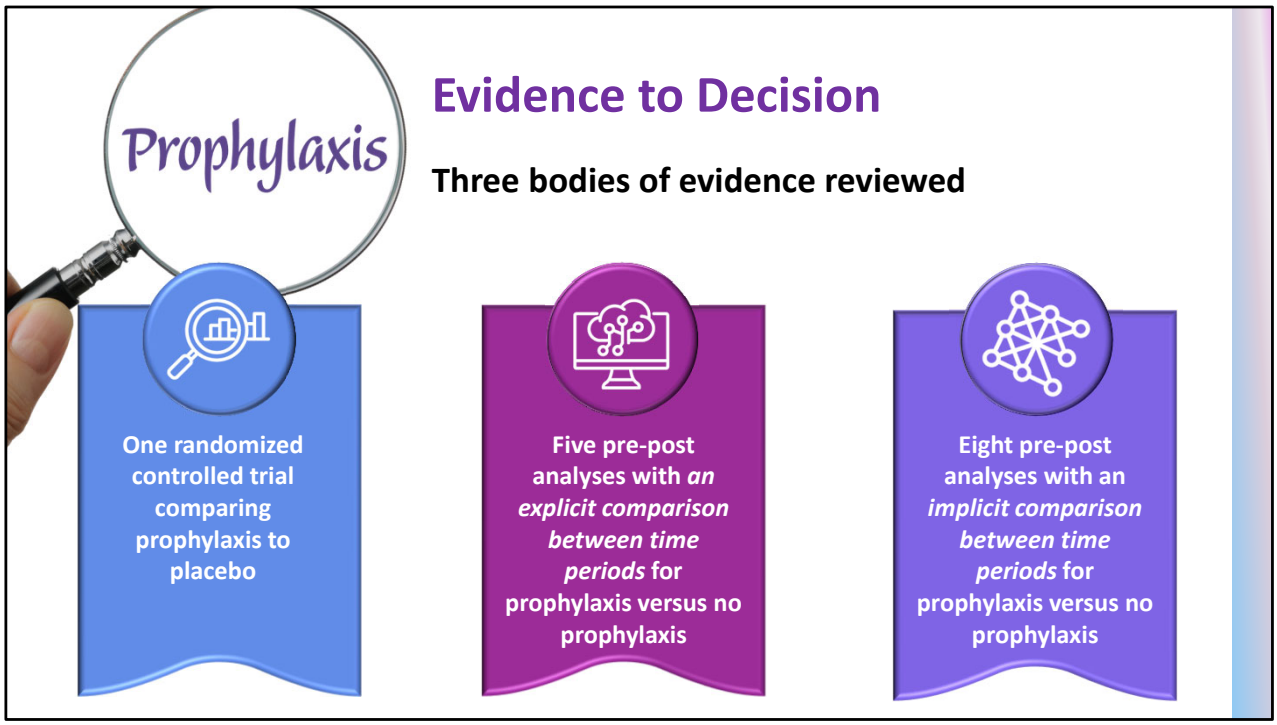
Conditional recommendation based on low certainty in the evidence of effects

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.

This was when we prioritized the topics that we wanted to discuss in the management guidelines. This was universally accepted as something that we should discuss. I think it is unfortunate that within hemophilia is just accepted, we put all of our severe patients on prophylaxis more and more, moderate patients as well. This, I think, even in people who do von Willebrand disease a lot is not our way of approaching it yet.

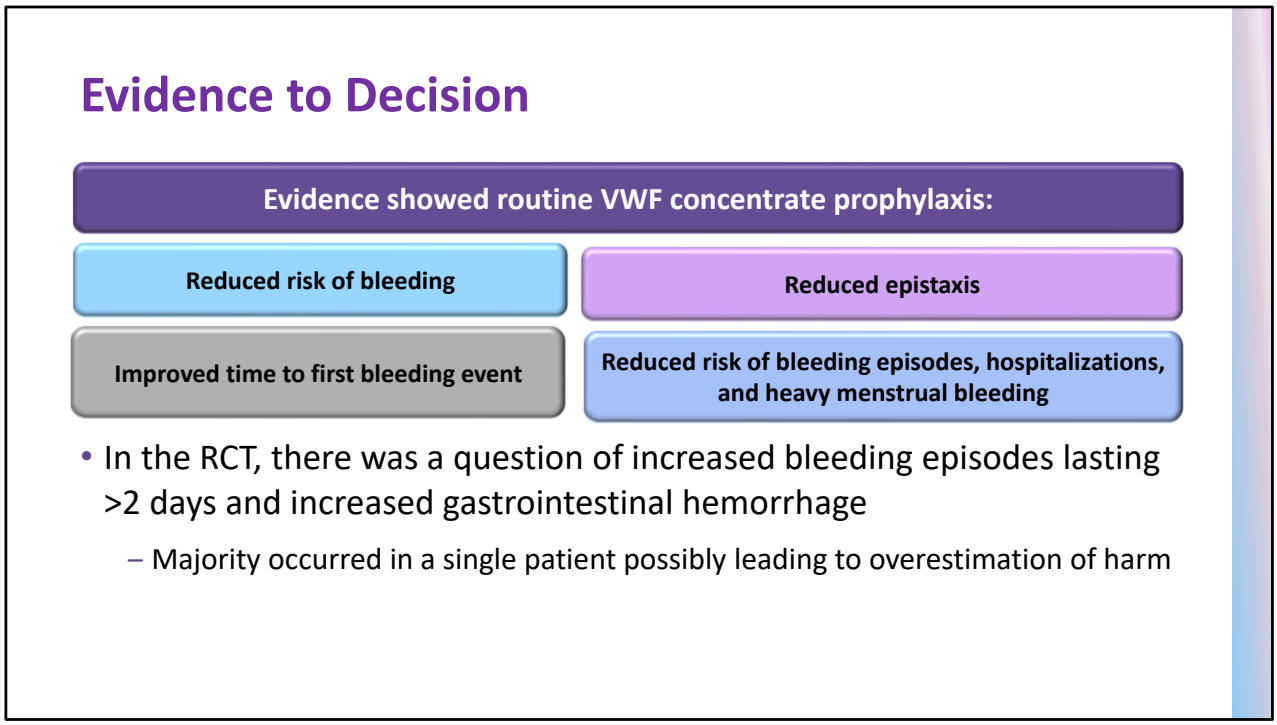
I think even though I was on the guideline panel, and we talked about this, I still find myself trying a lot of different other things before thinking about prophylaxis, which I think is unfortunate, and I'm hoping that will change over time. The question that we wanted to cover was in patients with von Willebrand disease with a history of severe and frequent bleeds, should routine prophylaxis or no routine prophylaxis be used?

I think Robert mentioned, this is vague, severe, and frequent. This is obviously going to be left to the discretion of the treating physician and the patient together, but we did, after looking at all of the data out there, decide a conditional recommendation with low certainty that we would recommend use of prophylaxis.



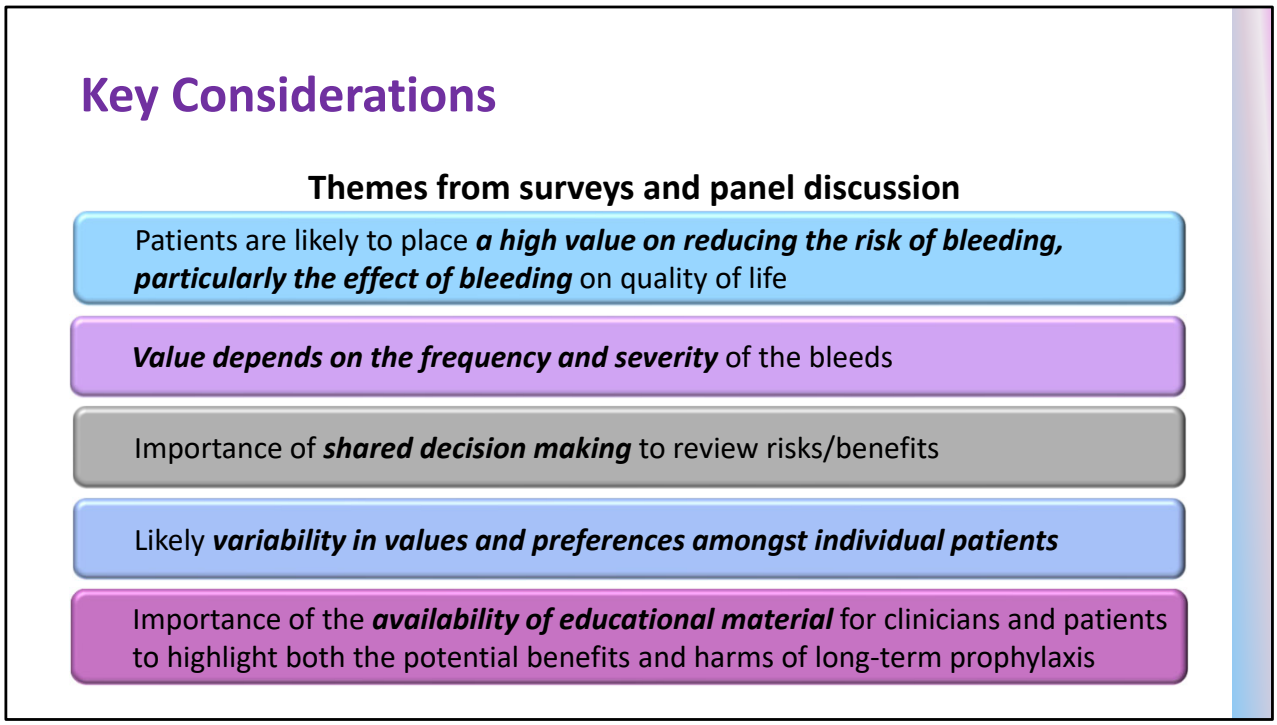
I was surprised, I think, when we were reviewing all the evidence, these guideline panels are pretty intense and you have specific person on the guideline panel that that's all they do is help people with guidelines.

They're very adept at assessing evidence and going through it and assessing it for bias and telling you what is wrong with every single study that's ever been done. There's a lot wrong with every single study that's ever been done, especially with von Willebrand disease, unfortunately, it's what they told us. Basically, the evidence that we reviewed to come to this recommendation was one randomized controlled trial comparing prophylaxis to placebo, five pre and post-analyses that had an explicit comparison between the time periods, and then eight pre and post-analyses that had an implicit comparison between the time periods.



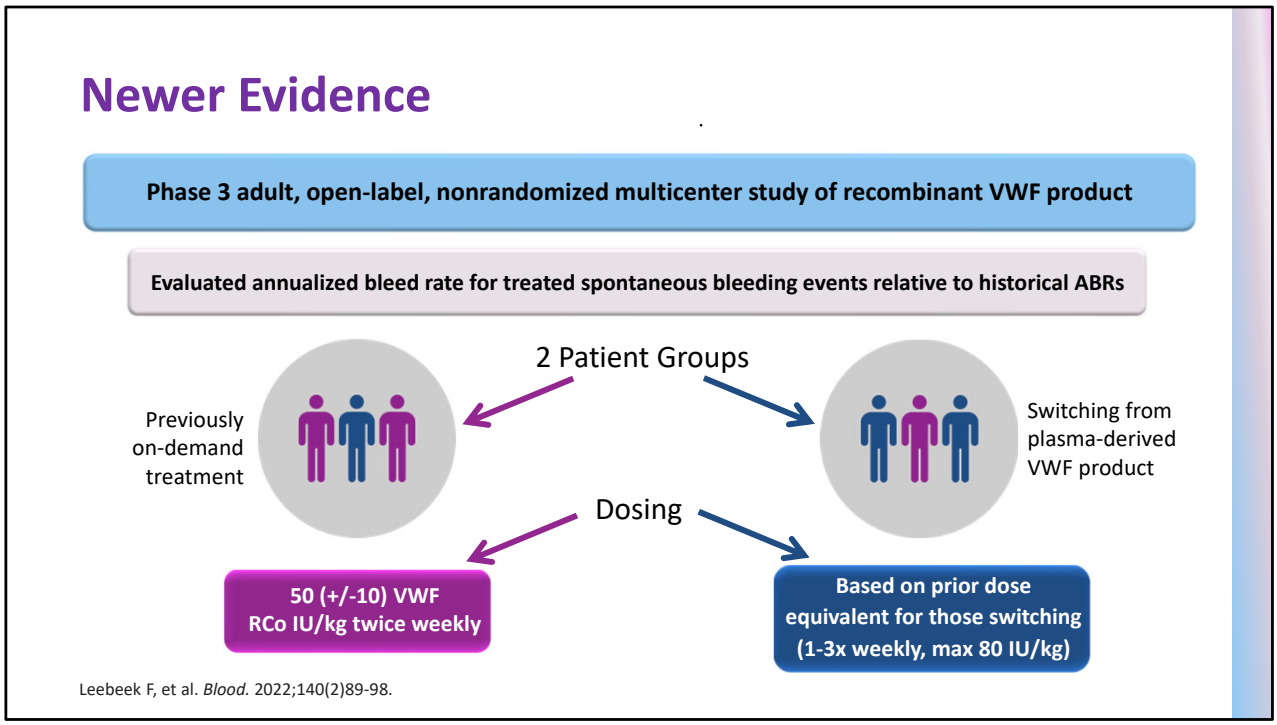
Basically, what that body of evidence showed was that the use of routine VWF concentrate prophylaxis reduced the risk of bleeding, reduced epistaxis, improved or increased the time to first bleeding event, and also reduced the risk of bleeding episodes, hospitalizations, and heavy menstrual bleeding. When we were assessing all the evidence, we did find that in the randomized control trial, there was a question of possibly increased bleeding episodes lasting longer than two days, as well as increased gastrointestinal hemorrhage.

As Robert mentioned, all of these trials are pretty low enrollment overall, there are not a lot of patients involved. The majority of the gastrointestinal bleeding and the episodes that lasted over two days were within one patient who happen to be in the prophylaxis arm, which likely led to some overestimation of the harm there.



The panels are composed of physicians, and they try to make them very multidisciplinary and include patients, and a lot of coming to the guideline recommendation is putting a lot of thought into like how this is going to increase equity and how this is going to help patients get the very best care that they can get. A lot of the discussion around coming to the recommendation for prophylaxis was that patients really place a very high value on reducing the risk of bleeding, especially if that bleeding is causing impairments in their overall quality of life.

Clearly, the value, because there are the barriers of intravenous infusion and having to do that, that the value depends on the frequency and the severity of the bleeding, that this should really be a shared decision-making process between the healthcare provider and the patient, and that there is likely to be pretty significant variability in the values of the specific patients. Really, we also wanted to make sure there was a lot of educational materials available both for the patients as well as the healthcare providers that are treating these patients.



Since the publication of the guidelines, so as Robert mentioned, it was a multi-year process. At some point, they have to cut off the literature that they're going to consider for the guidelines, even if a brand new study comes out in the middle of that process. Since the guidelines were published, there's been a little bit of more evidence coming out for prophylaxis. This was a phase three open-label study in adults. It was not randomized, but estimated did use a similar ABR to what is used in hemophilia.

There were two patient groups. One were patients that had previously just been on on-demand therapy, and another were patients that had been on a plasma-derived VWF product. This study was looking at the recombinant product. Patients who had previously been on on-demand were started on twice weekly recombinant VWF at a dose of 50 international units per kilo. The patients were switching from plasma-derived, their doses actually based on their prior dose because they wanted to be able to compare the two and range anywhere from one to three times weekly, with a maximum dose of 80 international units per kilo.

Phase 3 Open-label Study Results

Patient demographics and baseline characteristics

	Prior on-demand group* (n = 13)	Switch group† (n = 10)
Age, y		
Mean (SD) Median (range)	38.0 (17.6) 30.0 (20-67)	43.9 (21.8) 34.0 (18-77)
Sex, n (%)		
Male Female	5 (38.5) 8 (61.5)	7 (70.0) 3 (30.0)
Body mass index, kg/m²		
Mean (SD) Median (range)	23.3 (3.1) 23.6 (17.8-29.3)	23.3 (3.5) 23.7 (17.7-28.6)
VWD type, n (%)		
Type 1 Type 2A Type 2B Type 3	2 (15.4) 0 1 (7.7) 10 (76.9)	1 (10.0) 1 (10.0) 0 8 (80.0)
VWF:RCo, IU/dL		
Mean (SD) Median (range)	5.6 (10.7) 0 (0-27.8)	0.8 (2.6) 0 (0-8.3)
FVIII:C, IU/dL		
Mean (SD) Median (range)	25.9 (40.6) 3.0 (2-111)	10.3 (12.5) 3.5 (1-40)

Primary efficacy analysis: comparison of on-study sABRs with historical estimates

	Prior on-demand group (n = 13)	Switch group (n = 10)
Historical		
No. of treated spontaneous BEs	201	50
sABR mean (95% CI)**	6.54 (2.52 to 17.00)	0.51 (0.04 to 6.31)
rVWF prophylaxis (on-study treatment)		
No. of treated spontaneous BEs	9	18
sABR mean (95% CI)**	0.56 (0.15 to 2.05)	0.28 (0.02 to 3.85)
Comparison (rVWF prophylaxis vs historical sABR)		
sABR rVWF prophylaxis: historical ratio (95% CI)	0.085 (0.021 to 0.346)	0.550 (0.086 to 3.523)
sABR percentage change from historical (95% CI)††	−91.5% (−97.9% to −65.4%)	−45.0% (−91.4% to 252.3%)

Leebeek F, et al. *Blood.* 2022;140(2)89-98.

You can see on the left the demographics of the patients as you would expect, a majority of the patients had Type 3 disease, there was a pretty equivalent mix of males and females. Although, there was a predominance of males in the switch group and a predominance of females in the prior on-demand group.

The historical spontaneous annualized bleed rate was pretty high at six and a half. Not too bad in the group that had previously been on plasma-derived at 0.51. Both of those actually improved. I think, no surprise at all that the ABR decreased when he went from on-demand to prophylaxis, but there was also a 45% decrease when they went from the plasma-derived to the recombinant product.

AEs in Patients Who Received rVWF Prophylaxis (Safety Analysis Set)*

	Prior on-demand group (n = 13) n (%)/events	Switch group (n = 10) n (%)/events	Total (n = 23) n (%)/events
AE†	10 (76.9)/26	7 (70.0)/15	17 (73.9)/41
Mild	7 (53.8)/18	4 (40.0)/12	11 (47.8)/30
Moderate	1 (7.7)/5	2 (20.0)/2	3 (13.0)/7‡
Severe	2 (15.4)/3	1 (10.0)/1	3 (13.0)/4§
Serious AE	1 (7.7)/1	2 (20.0)/2	3 (13.0)/3
AE considered related to rVWF	1 (7.7)/1	0	1 (4.3)/1
Serious AE considered related to rVWF	0	0	0
AE considered related to study procedures	0	0	0
Serious AE considered related to study procedures	0	0	0
AE leading to discontinuation of rVWF	1 (7.7)/1	0	1 (4.3)/1
Fatal AE	0	0	0
Life-threatening AE	0	0	0
AE of special interest‖	1 (7.7)/1¶	1 (10.0)/1**	2 (8.7)/2

Leebeek F, et al. *Blood.* 2022;140(2)89-98.

Overall, the recombinant VWF factor product was considered to be safe. There was only one adverse event that actually led to discontinuation of the product that was a non-serious headache that occurred with the infusion, and so they decided to stop the product. There were some serious adverse events like falls and I think a dental problem that clearly weren't related to the product.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

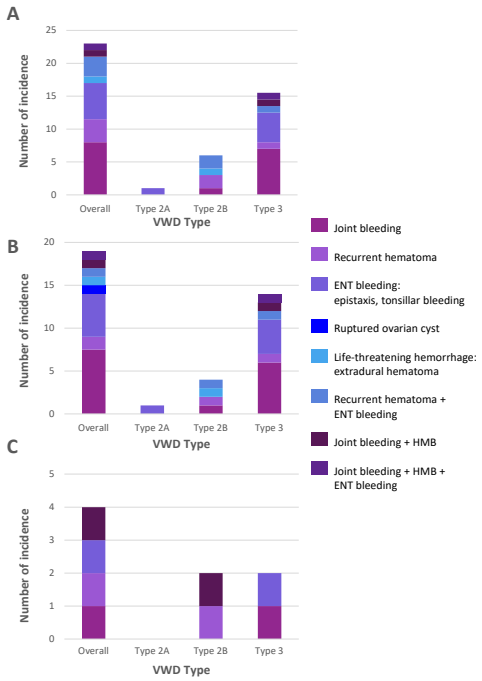
Newer Evidence

Demographic characteristics of patients with VWD receiving LTP

	Total *n* = 23	Type 2A *n* = 1	Type 2B *n* = 6	Type 3 *n* = 16
Sex, *n* (%)				
Male	11 (47.8)	0 (0)	5	6
Female	12 (52.2)	1 (100)	1	10
Blood group O, *n* (%)	11 (47.8)	0 (0)	2 (33.3)	9 (56.2)
Age, years, median (range)[a]	16 (1–85)	4	7 (1–29)	20.5 (3–85)
Body weight, kg, median (range)	58 (15–84)	17	48 (15–72)	58 (21–84)

[a]Median age at the initiation of prophylaxis by Voncento®

Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.



This is another study that actually looked at patients that were receiving long-term prophylaxis with Voncento (human coagulation factor VIII / human von Willebrand factor). As you can see, it's pretty small. There were a varied number of reasons that patients were started on prophylaxis, ranging from joint bleeding, recurrent hematomas, ENT bleeding. Again, in this study, there were the majority of patients were Type 3 disease, and there was a pretty good distribution between male and female patients. I was impressed with the age range of 1 to 85 included, so pretty much all ages of our patients.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

Dose, frequency, duration of follow-up, and bleeding episodes in all patients receiving LTP with Voncento®

	Total *n* = 23	Type 2A *n* = 1	Type 2B *n* = 6	Type 3 *n* = 16
Dose, IU/kg	45 (33–109)	109	54.5 (33–100)	44 (35–62)
Weekly dose, IU/kg/week	96 (44–222)	109	100.5 (67–200)	90 (44–222)
Number of infusions per week	2 (1–3)	1	2 (1–3)	2 (1–3)
Duration of follow-up, months*	19 (5–48)	48	21 (17–27)	17.5 (5–46)
ABR	0.5 (0–7.2)	0.8	0.7 (0–2.9)	0 (0–7.2)
Effectiveness (Excellent/Good)[+]	9/10	0/1	3/3	6/6

Comparison in terms of dose and bleeding episodes between initial prophylaxis and the prophylaxis by Voncento® (LTP group)

	Total *n* = 19	Type 2A *n* = 1	Type 2B *n* = 4	Type 3 *n* = 14
pdVWF**				
Dose IU/kg	42.5 (35–62)	46	44.5 (42–60)	40 (35–62)
Number of infusions per week	2 (1–3)	1	2 (2–3)	2 (1–3)
ABR	1 (0–6)	5	0 (0–6)	1 (0–4)
hFVIII/VWF concentrate (Voncento®)				
Dose, IU/kg	43.5 (33–109)	109	38.5 (33–50)	44 (33–96)
Number of infusions per week	2 (1–3)	1	2.5 (1.5–3)	2 (1–3)
ABR	0.3 (0–2)	0.8	0.6 (0–1.9)	0 (0–2)

Four patients switched from on-demand to LTP, ABR dropped from 0.5 to 0
Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.

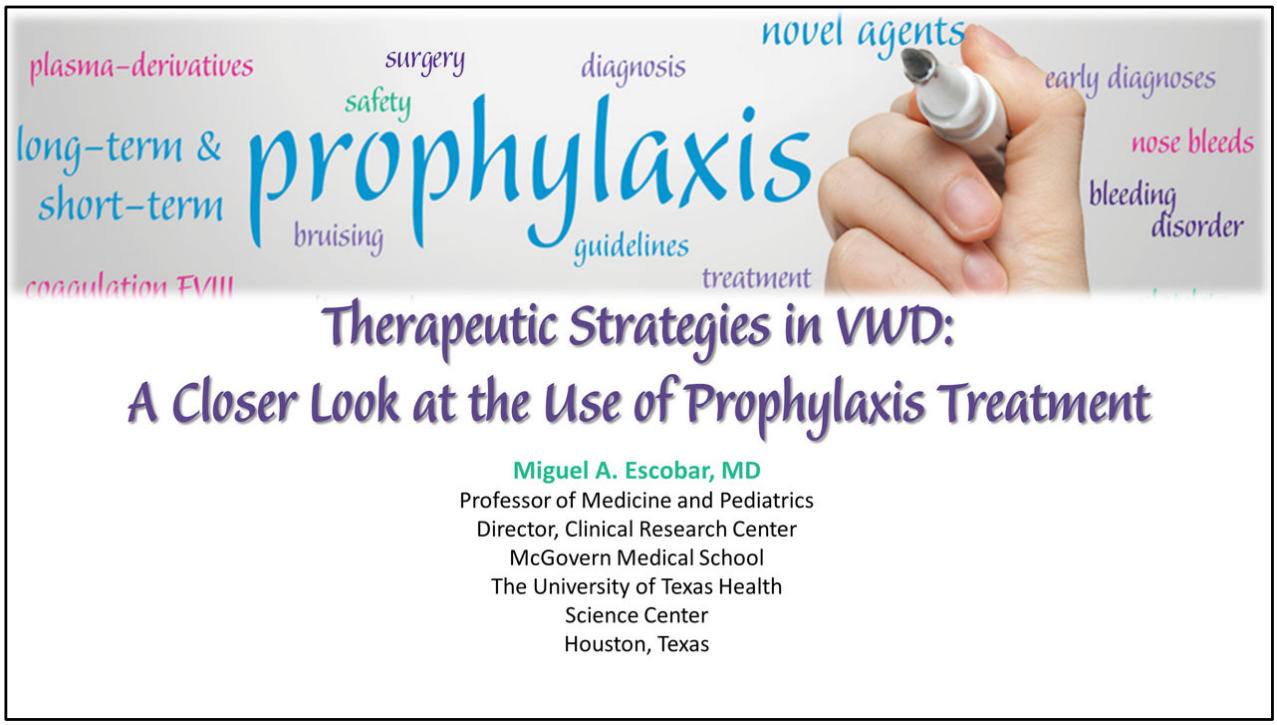
This basically just looked at the doses that patients were on. Roughly, patients were typically on two infusions per week and had a pretty low ABR of 0.5. They also did compare patients who had previously been on another prophylaxis treatment, and their ABRs did improve when they switched to Voncento (human coagulation factor VIII / human von Willebrand factor). There were, I think, four patients that previously had not been on prophylaxis, so they weren't included in that analysis.

The Rationale for Long-Term Prophylaxis in Clinical Practice

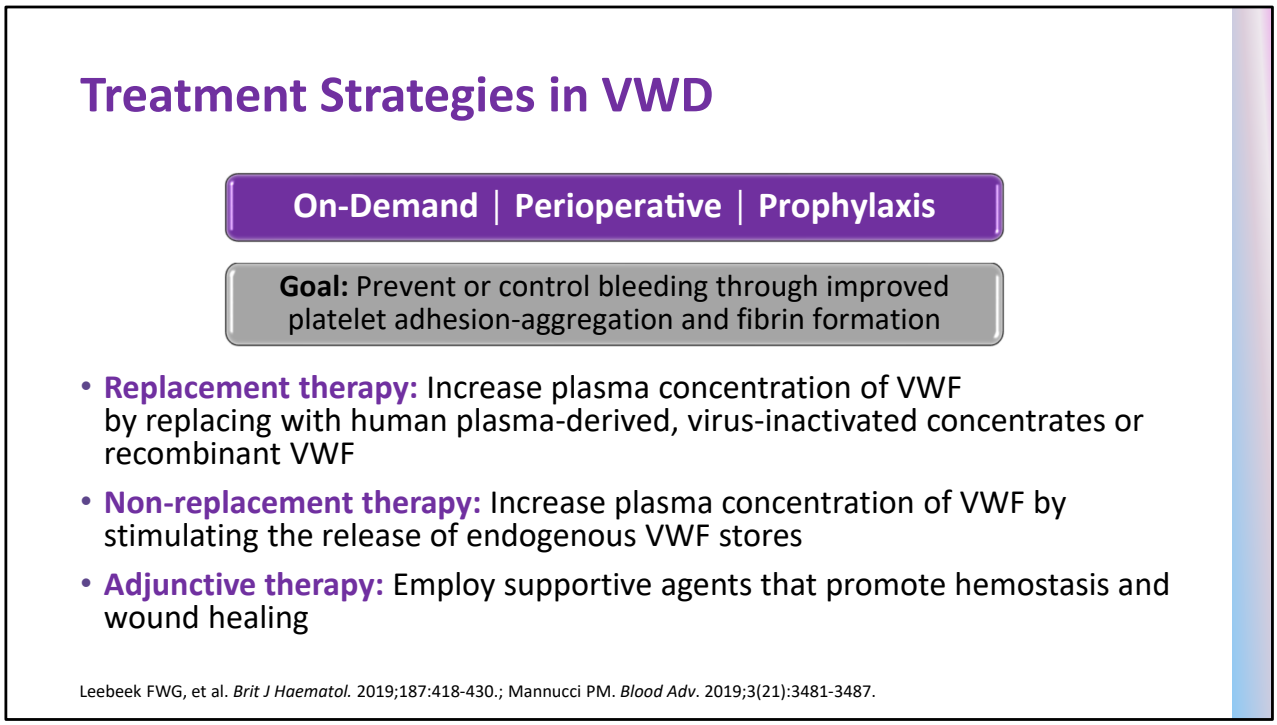
- Type 3 adult VWD patients
- Joint bleeding
- Gastrointestinal bleeding/angiodysplasia
- Severe, recurrent bleeding
- Heavy menstrual bleeding

I think there is a rationale for long-term prophylaxis in a number of our von Willebrands patients. I think Type 3 patients, especially Type 3 patients that are having severe and recurrent bleeding, patients with joint bleeding, I think there's definitely more reason to start them, and I think gastrointestinal bleeding is just so difficult to manage. We know with angiodysplasia that occurs, really a pretty long course of prophylaxis is needed to help heal all of that up.

I think heavy menstrual bleeding too. I see a lot of patients with heavy menstrual bleeding, and I think a lot of us like knee-jerk response is hormones or antifibrinolytics, but I think that a lot of these patients would clearly benefit from factor products. I think it does just become that hurdle of getting people comfortable with IV administration and having them accept that, but I think at least with heavy menstrual bleeding, it isn't a super frequent infusion. With that, I will hand it over to Dr. Escobar.



Dr. Miguel Escobar: All right. Thank you. These next 15 or so minutes, what I'd like to do is talk about some of the therapeutic strategies in von Willebrand disease and also touch on the use of the therapeutic strategies in surgery as well.



When we treat patients with von Willebrand, we're going to either treat them on demand for the acute bleeds, we're going to treat them when they go to surgery to prevent the bleeding, or we can certainly do prophylaxis that has been already mentioned. The goal is going to be the same, right?

What we're going to try here is to prevent or control the bleeding, improving the platelet adhesion aggregation, and at the end, forming a stable clot or a fiber clot, and we can do it in different ways.

We can use replacement therapy, and the goal here is to increase the plasma concentration of what is missing the, von Willebrand, using either plasma, the right product, or now using a recombinant von Willebrand factor.

We can use non-replacement therapy, and it has the same goal, which is increase the plasma concentration of von Willebrand by stimulating the release of endogenous stores of von Willebrand. An example is Desmopressin, and we can use adjunctive therapy as well. This just uses certain agents, anti-fibrinolytics to promote hemostasis and also help with the wound healing. Now, when we treat patients, we can do a combination of these depending on the type of bleed, depending on the age, and certainly, some patients are

going to surgery. We can also definitely have a combination of different products.

Treatment Strategies in VWD

- Replacement therapy products
  - Are not all the same
  - Have different ratios of FVIII to VWF (Pd concentrates)
  - Should not be considered interchangeable
- All patients receiving replacement therapy should be monitored to:
  - Maintain hemostatic levels of VWF:RCo and FVIII
  - Avoid exceeding maximum recommended levels of VWF:RCo and FVIII
  - Assess thrombotic risk
  - Institute appropriate preventive strategies

National Heart, Lung and Blood Institute. *The Diagnosis, Evaluation, and Management of von Willebrand Disease*. National Institutes of Health; 2007

Mannucci PM. *Blood Adv.* 2019;21:3481-3487.

Now, the important thing, and I think Robert already alluded about this is that not all the replacement products are the same. They have different ratios, as you already have seen in terms of Factor VIII to ristocetin or von Willebrand. They should not be really considered interchangeable.

Now, it's important to be able to monitor these patients. If you're going to do a single treatment, it's probably not necessary, but in patients that are going to be, let's say, in prophylaxis, like similar to do with hemophilia, or definitely patients that are undergoing major surgeries, it would be probably important to be able to maintain certain levels and be able to check those levels. We just don't want make sure we don't have excess amount of von Willebrand or Factor VIII. We need to definitely assess the thrombotic risk, and if necessary, we need to do some preventive strategies for these patients.

Desmopressin (DDAVP) for VWD

- **Mechanism of action:** triggers release of VWF + factor VIII from endothelial storage sites
  - Safety point: must monitor electrolyte and fluid balance
- **DDAVP trial in Type 1 VWD**
  - "Low VWF" 30-50 IU/dL: adults presumed to be responsive; children need trial
  - VWF <30 IU/dL (possible Type 1C): panel suggests performing a desmopressin trial and treating based on results

VWD	Type 1	Type 2		Type 3
Subtype	Omit Type 1C/non-responders	**2A, 2M, 2N**	**2B**	N/A
Use of DDAVP	**First line** on-demand and perioperative therapy if no contraindication	May have partial or shorter-lived response May be helpful for **minor bleeding**	**Contraindicated** May worsen low platelets	**Do not use** No response

IU/dL=International units per liter; MOA=mechanism of action
Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.; American Society of Hematology (ASH). *2012 Clinical practice guideline on the evaluation and management of von Willebrand disease (VWD).* ASH Website. 2012. Watermark-Von-Willebrand-Disease-Pocket-Guide-1.pdf. Accessed January 20, 2022.; Leebeek FWG, et al. *Brit J Haematol.* 2019;187:418-430.

Now, specifically about Desmopressin (DDAVP), you're already familiar with the mechanism of action. Now, in terms of the recommendations for each use is mostly for Type 1 von Willebrand, in those patients that have what we call low von Willebrand levels, let's say, between 30 and 50. We assume that adults are probably going to be responsive to this strategy, but recommendation is in children, if needed, then you could do a trial of DDAVP.

Now, for those individuals that have von Willebrand levels below 30, the panel suggests performing a Desmopressin trial and treating based on those results. Some of the patients are not going to have probably an increase compared to other individuals. For those Type 1, the Type 1Cs most likely are not going to be responders, but it could be used at the first line for those patients that have Type 1, they're on demand, or if it's a minor surgery, certainly something like Desmopressin could be used.

For the 2As, 2M and 2Ns, it could have a partial response on this individual or a short-lived response. Again, it could be useful sometimes for minor bleeding or minor procedures. For the 2Bs, we usually do not use it. It could worsen if patients already have thrombocytopenia, and definitely, the Type 3s, they're not going to respond.

Available VWF Concentrates

Product Name	Ratio of VWF:RCo to FVIII:C	Half-life (h)	Regulatory Approval
Alphanate (antihemophilic factor/VWF complex [human])	1.3:1	VWF:RCo 7.67 ± 3.32 FVIII:C 17.9 ± 9.6	Yes: surgery and/or invasive procedures; except Type 3 (not indicated for severe type 3 undergoing major surgery) No: prophylaxis
Humate-P (antihemophilic factor/VWF complex [human])	1.8-2.4:1	VWF:RCo 10.5 (2.8-33.6) FVIII:C 12.2 (8.4-17.4)	Yes: bleeding and surgery prophylaxis No: prophylaxis
Wilate (VWF/coagulation factor VIII complex [human])	1:1	VWF:RCo 15.8 ± 11 FVIII:C 19.6 ± 6.9	Yes: bleeding and surgery prophylaxis No: prophylaxis
Vonvendi [VWF (recombinant)]	N/A	VWF:RCo 19.1 ± 5 (No FVIII content)	Yes: on-demand bleeding, perioperative management of bleeding Yes: prophylaxis for severe Type 3 VWD receiving on-demand therapy

ALPHANATE® (antihemophilic factor/VSF complex [human]). Los Angeles, CA: Grifols Biologicals LLC. Revised June 2018. Alphanate Prescribing Information Patient.pdf. Accessed August 8, 2022, 2022.; HUMATE-P® (antihemophilic factor/von Willebrand factor complex [human]). Marburg, Germany: CSL Behring GmbH. Revised June 2020. Package-Insert---Humate-P-1.pdf. Accessed August 8, 2022.; WILATE® (von Willebrand factor/coagulation factor VIII complex [human]). Vienna, Austria: Octapharma Pharmazeutika Produktionsges.m.b.H. Revised March 2020. Package Insert - Wilate.pdf. Accessed August 8, 2022.; VONVENDI® (von Willebrand factor [recombinant]). Lexington, MA: Baxalta US Inc. Revised 1/2022. Package-Insert---VONVENDI.pdf. Accessed August 8, 2022.

Rob already showed this slide. Again, it's to emphasize one thing, they have different ratios between Factor VIII and von Willebrand. Again, they should not be interchangeable. They have different half-lives. It can go anywhere from 7.5 hours all the way to 19 hours. As you can see here, they have different indications. They might not make a difference for you in the clinic, but maybe for the payers, it might make a difference in regards to if it gets approved or not. Most of these products are approved for treatment on-demand and surgery, and as already mentioned, we have one product of recombinant von Willebrand that recently was approved for the use of prophylaxis in severe von Willebrand disease.

Factor Concentrate Target Levels

Indication*	Dose †(IU/kg)	Target Levels‡	Duration (days)
Bleeding (on-demand)			
• Mild to moderate	20-40	Peak >50-80 on day 1; trough >30 after day 1	1-3
• Severe	50	Peak >100 on day 1; trough >50 after day 1	7-10
Intervention (perioperative)			
• Uncomplicated procedure	25	Peak >50 on day 1	1
• Minor surgery	30-60	Peak >50-80 on day 1; trough >30 after day 1	1-5
• Major surgery	50-60	Peak >100 on day 1; trough >50 after day 1	7-10
Safety parameters 1) Do not exceed VWF:RCo 200 IU/dL or FVIII 250-300 IU/dL, 2) Maintain hemostatic levels of VWF:RCo and FVIII, 3) Assess thrombotic risk, 4) Institute appropriate preventive strategies			

Leebeek FW, et al. *N Engl J Med*. 2016;375:2067-2080.; Leebeek FWG, et al. *Brit J Haemat*. 2019;187:418-430.

Now, in terms of the factor concentrate and target labels, I think this has always been an issue of discussion. I think it's also very different from hemophilia. The recommendation is somebody that has a bleeding episode, if you're going to treat on-demand, let's say, a mild to moderate bleed, recommendations, you have peak levels maybe above 50% or so on day one, and then maybe having trough levels around 30 or so after day one. The length of treatment is going to depend again on the type of bleed. It can be anywhere from one to three days if it's something minor.

Now, for those patients that have a severe bleed, the recommendation is to have a peak above 100, at least on day one, and then having trough levels above 50 after day one or so. Again, the length of treatment is going to depend on the type of bleeding. Patients that undergo surgical procedures for uncomplicated procedures, let's say a minor surgery, you can have a single dose, have a peak greater than 50 for one day, and that's usually enough.

Now, for something that is probably a little more than a simple procedure, peaks of probably about 50 to 80 on day one, and then trough levels about 30 for the next day or two, length of treatment, again, anywhere between one to five days. For the major surgeries, the recommendation is to have a peak above 100 on day one, and then having trough levels above 50 after day one. Again, treatment of length, it's going to depend on the type of surgery.

Now, it's important to be able to monitor this patient, especially the patients that are undergoing major surgeries are going to be treated for many days. Ideal is not to exceed von Willebrand levels above 200 or Factor VIII levels probably about 250 to 300 for prolonged periods of time. That's why

it's important they're monitoring these patients, then we need to assess the thrombotic risk, and if necessary, then we need to take preventive strategies for these individuals.

Phase 3 Study Comparing Secondary PRO vs ODT with VWF/FVIII Concentrates in Severe Inherited VWD

12-month, international, multicenter, randomized, open-label, parallel-group study (EudraCT 2006-001383-23)

Objective: Evaluate if prophylaxis with a VWF/FVIII concentrate was effective in preventing spontaneous bleedings in patients with severe VWD unresponsive to DDAVP when compared with ODT.

Number and incidence rate of bleeding episodes during the study according to treatment groups:

Type of bleeding episode	On-demand (N = 9)		Prophylaxis (N = 10)	
	N	*Rate*	*N*	*Rate*
Any type	172	1.41	32	0.34
Mucosal bleeding	164	1.34	17	0.18
Epistaxis	52	0.42	15	0.16
Other bleedings	112	0.92	2	0.02
Joint and muscle bleeding	7	0.05	2	0.02
Hemarthrosis	3	0.02	1	0.01
Muscle hematoma	4	0.03	1	0.01
Gastrointestinal hemorrhage	1	0.01	13	0.14

Safety: No clinical AEs attributed to study medication
PRO=long-term prophylaxis; ODT=on-demand treatment
Peyvandi F, et al. *Blood Transfus*. 2019;17(5):391-398.

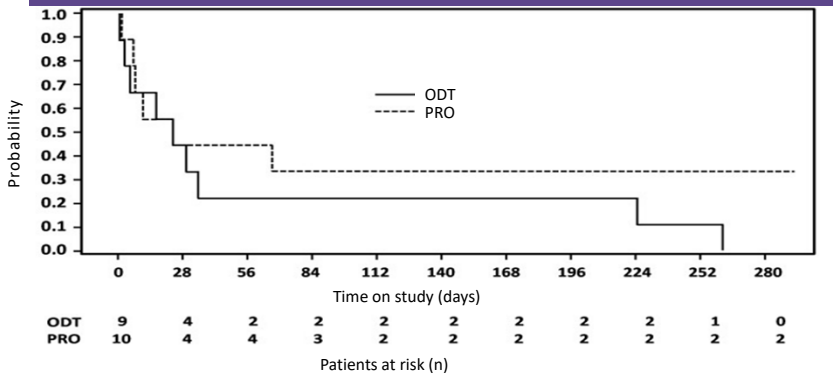
Some of the studies I already mentioned, Angela mentioned the study that was done by Ruggeri. This is another study that came from the Europeans. This was a phase three study that compares secondary prophylaxis to on-demand. This was a randomized open-label study, but they looked at individuals to see if they can prevent spontaneous bleeding in patients that had severe von Willebrand, but there were unresponsive to DDAVP when they compared to the on-demand group, and we see that the majority of those individuals, as expected, had mostly mucocutaneous type bleeding. You had the two groups, the on-demand and the prophylaxis.

Phase 3 Study Comparing Secondary PRO vs ODT with VWF/FVIII Concentrates in Severe Inherited VWD

12-month, international, multicenter, randomized, open-label, parallel-group study (EudraCT 2006-001383-23)

Conclusion: The prophylactic use of VWF/FVIII concentrates appeared to be associated with a lower risk and frequency of bleeding episodes in severe VWD patients unresponsive to DDAVP, although more data are needed for GI bleeding.

Probability of remaining free of a first spontaneous bleeding episode during the study:



Peyvandi F, et al. *Blood Transfus*. 2019;17(5):391-398.

What they found in this study is that the prophylactic use of this specific product appeared to be associated with a lower risk and frequency of bleeding episodes in patients with severe von Willebrand that were unresponsive to DDAVP.

Now, they mentioned here that there was probably not a lot of data on GI bleeding, and I think this is a circumstance which is quite unique for certain patients with von Willebrand. It's possible though that we might need clinical trials just for patients that have GI bleeding, especially the Type 3s, those individuals really have a very unique type of GI bleeding that we don't even see those in patients with hemophilia. Those could be quite complex individuals to manage.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

Summary of Reports on the Use of Long-term Prophylaxis in VWD

Author, year, study design	Product	# of prophylaxis/ overall pop.	Duration of f/u, mo	VWD Type 1/Type 2A-2B-2M/Type 3	Primary bleeding Indication *N* (%)	Dose FVIII:C or VWF:Rco (IU/kg) Median (range)	Frequency *N* time/week	ABR Median (range)	Outcome Excellent/ Good (%)
Dunkley, 2010 Prospective	Biostate®	4/23	12 (6–12)	5/2–6-1/6[d]	NA	23.4 (14–29.1)	NA	1 (1–17)	100
Castaman, 2013 Prospective	Haemate® P	31/121	24	9/1–5-0/16	GI = 34[b] Joint = 41[b] HMB = 17	20	2–3	3 (1–11)	92.9
Abshire, 2015 Prospective	Haemate® Alphanate® Fandhi®	11	NA	0/6–0-0/5	GI = 3 (27) Joint = 2 (18) Epistaxis = 6 (54)	50	1, 2,3	4 (0–27.7)	n/a
Holm, 2015 Retrospective and Prospective	Haemate® Alphanate® Fandhi®	95–10/105	60	13/25–9-3/54[a]	GI (23.2) Joint (23) Epistaxis (32.7) HBM (4.1)	38–73[c]		3.8 (0.2–16.8) 6.0 (3–6-7.1) 0.8 (0–3.2) 0 (0–0.4)	Significant reduction of joint bleed, epistaxis, GI
Goudemand, 2020 Prospective	Wilfactin®	32/155	36	1/13/18	GI (40.6) Joint (43.8)[d] Others (15)	45.2 (22–55) 42.2 (26–76) 46.6 (27–53)		1.1 (0–11) 0.8 (0–5.4) 1.0	n/a
Lissitchkov,2021 Prospective	Voncento®	10/19	41	1/2/7	NA	42.8 (28.5–85.8)	1 (90%)	4.37 (0–25.9)	97.9
Sholzberg, 2021 Prospective	Wilate®	91/25	24	3/5–1–0-1/14	NA	55.4 (8.3–1441.4)	1 to (85%)	1.9 (0–27.0)	99
Berntorp, 2005 Retrospective	Humate-P® Haemate®P	35	12	1/2–4-0/28	GI = 3 (8) Joint = 13 (37) ENT = 16 (45.7) HMB =3 (8)	24 (12–50)	1 to 3	Joint =0.3 ENT = 0.4	n/a
Federici, 2010 Retrospective	Alphanate® Fandhi®	15/120	60	7/3–2-0/3	GI = 9 (61) Joint = 2 (13) CNS = 2 (13)	42 (17–74)	1 to 2	NA	87%
Halimey, 2011 Retrospective	Humate® P Wilate®	32	12	4/15/13	Joint GI Relevant anemia	40 (20–47)	2 to 4		Significant reduced BS
Howman, 2011 Retrospective	Biostate®	2/43	60	0/0/2	Joint Epistaxis	NA	NA		n/a
Abshire, 2013 Retrospective	Haemate® P Alphanate® Fandhi®	59	12	5/10–8-2–/34	GI = 13 (23.6) Joint = 12 (21.8) Epistaxis = 13 (23.6) HMB = 4 (7.3) Combined = 5 (9.1)	60 (47–60) 40 (30–50) 48 (40–60) 39 (38–40) 42 (33–49)	1.5 to 3	6 (3–6) 1.3 (0.3–3.2) 6 (2.9–12) 4 (1–9) 6 (1.2–12)	n/a
Miesbach, 2015 Retrospective	Haemate® P	3		0/1–0-0/2	GI = 3 (100)	50 to 74 18 to 20	2, 2 to 6		100
Leebeek, 2022 Prospective	Vonicog Alfa	23	12	3/1-1/18	17 oral/other mucosa 3 menorrhagia 1 other location 1 hemarthrosis 3 unknown	50±10 IU/kg prior on-demand group. 1-3 x week max 80 IU/kg Switch group based on prior prophylaxis dose	1-3	0.56 (0.15-2.05) prior on demand 0.28 (0.02-3.85) switch group	n/a

Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.

Now, this is a very busy slide, but I just want to you to concentrate on the right-hand side. Here you can see the outcome of the studies that have been reported doing prophylaxis in von Willebrand disease, and you see that exactly quite effective. Do we really need more studies to show that prophylaxis is effective in certain patients with von Willebrand? Probably not from a clinician perspective, maybe in the pediatric group, we might need some of those studies, or maybe more for the regulatory agencies, most likely we're going to need studies so they can approve certain products. I think it shows very well, although the data might not be as robust as Robert mentioned in hemophilia, but I think there's enough evidence that definitely these patients benefit from the use of prophylaxis.

Phase 3 Trial Results: Prophylaxis with Recombinant VWF (Vonicog Alfa) in Patients with Severe VWD

12-month, prospective, open-label, single-arm, non-randomized, multicenter phase 3 study (NCT02973087; EudraCT 2016-001478-14)

Objective: To investigate efficacy and safety of rVWF prophylaxis in adults with severe VWD, including on-study vs. historical sABR and sABR intra-patient comparison.

Primary efficacy analysis: comparison of on-study sABR through month 12 vs historical sABR

Time period Statistic	Prior OD arm (n = 13)	Switch arm (n = 10)
Historical		
Number of treated spontaneous BEs	201	50
sABR (95% CI)	6.54 (2.52, 17.00)	0.51 (0.04, 6.31)
On-study (while receiving prophylactic rVWF)		
Number of treated spontaneous BEs	9	18
sABR (95% CI)	0.56 (0.15, 2.05)	0.28 (0.02, 3.85)
Comparison (on-study vs. historical sABR)		
sABR on-study:historical ratio (95% CI)	0.09 (0.02, 0.35)	0.55 (0.09, 3.52)
sABR percentage change from historical	91.5% reduction	45.0% reduction

Conclusion: rVWF prophylaxis can effectively reduce sABR in patients previously treated OD with VWF products and maintains at least the same level of hemostatic control in patients who switch from prophylaxis with pdVWF to rVWF, with a favorable safety profile.

Secondary efficacy analysis: sABR intra-patient comparison:

	n/N	95% CI	
sABR* reduction success (prior on-demand group)			
All VWD types	2/13	64.0-99.8	92%
VWD Type 3	9/10	55.5-99.7	90%
sABR preservation success (prior prophylaxis [switch] group)			
All VWD types	9/10	55.5-99.7	90%
VWD Type 3	7/8	47.3-99.7	88%

Safety: 1 AE (moderate headache) possibly related to study medication; no serious AEs; no inhibitors developed

ABR=annualized bleeding rates

Leebeek F, et al. *Blood.* 2022;140(2):89-98.

Now, going back to the study that Angela mentioned, the phase three trial using prophylaxis with a recombinant von Willebrand factor, Vonicog alfa in patients with severe disease. This study, again, investigated the efficacy and the safety of prophylaxis in adults. What they did was they looked at a historical, and then they put those patients on prophylaxis. They had two arms, the prior on-demand and the patients that were already on prophylaxis with a plasma, the right product, and then got switched then to the recombinant.

We see here that in terms of the spontaneous ABR, there was a decrease from 6.54 down to 0.56, meaning a 91% reduction, which is expected in somebody coming from on-demand treatment.

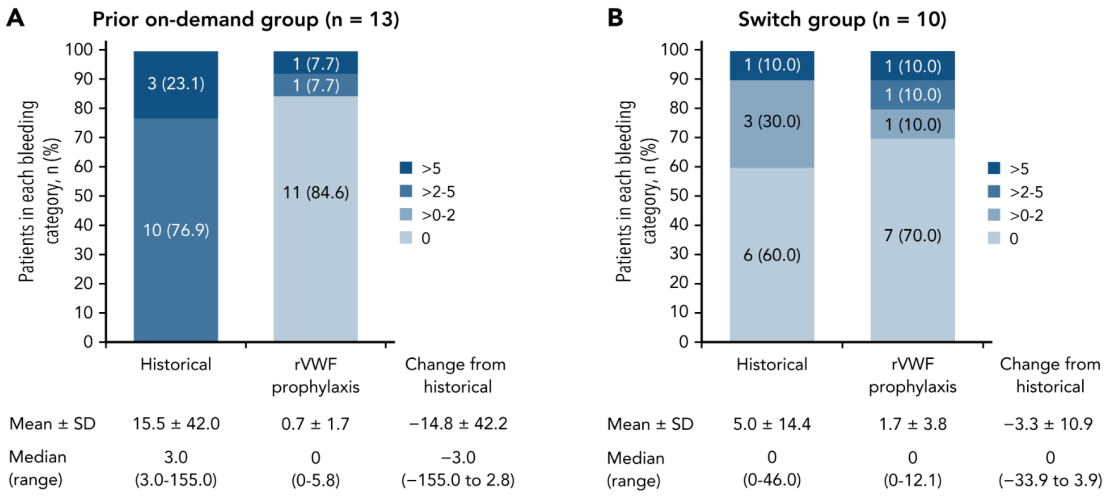
Then in the switch arm, again, with those individuals that were in prophylaxis with the plasma and got switched to the recombinant, we see there is a decrease from 0.451 to 0.28 with a 45% reduction. This was not significant, but those patients maintain their hemostasis.

Now, in terms of the secondary efficacy analysis, looking at the spontaneous ABR intra-patient comparison, and those individuals looking at reduction success, more than 25% for all types of von Willebrand, it was 92%, and for the Type 3, specifically, was 90%.

When we looked at the spontaneous ABR preservation success, meaning those patients that were prior prophylaxis and got moved to the recombinant, we see that for all types of von Willebrand, 90%, and for the Type 3s, it was 88%. Quite effective as well.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

Treated Spontaneous ABRs



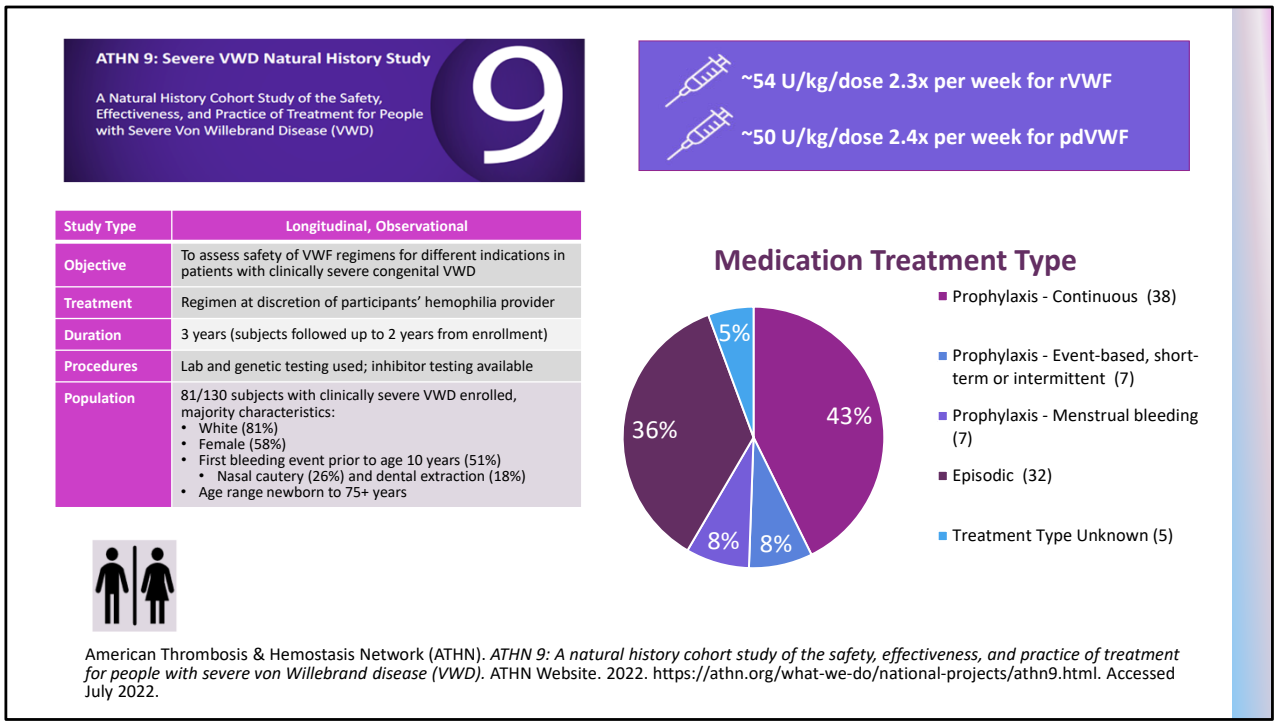
Leebeek F, et al. *Blood.* 2022;140(2):89-98.

Now, the secondary efficacy here treated spontaneous ABRs.

Now, to the left, you have the prior on-demand group. You can see that at least 77% of those individuals had between two and five bleeds. They got switched to the prophylaxis arm and you can see that 84.6% of those patients had zero bleeds during the trial.

To the right we've got the switch group, 60% of those individuals had less than two bleeds, compared to 60% and 70% had zero bleeds. Very similar in terms of the comparison between the switch group and the recombinant von Willebrand.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



American Thrombosis & Hemostasis Network (ATHN). *ATHN 9: A natural history cohort study of the safety, effectiveness, and practice of treatment for people with severe von Willebrand disease (VWD).* ATHN Website. 2022. https://athn.org/what-we-do/national-projects/athn9.html. Accessed July 2022.

Now, just to briefly mention, there's another study, the ATHN 9 study. This is looking at the natural history of severe von Willebrand disease. This is a study that is ongoing, at least I think until the beginning of the year. There are already enrolled about 81 of a total of 130 individuals. What they want to look at here is certainly seeing the safety of the treatment, how effective it is, and the different practices treating patients with von Willebrand. The doses, right now, they vary between 50 and 54 units per kilo dose, an average of about two times per week, both for the plasma and the recombinant product. You see here the treatment type, the distribution of the different treatment types.

I think it'll be an interesting study to see the results of that. If you have opportunity to enroll patients, we definitely encourage to do so.

ASH ISTH NHF WFH 2021 Guidelines

Surgery Management with Tranexamic Acid

- **For minor procedures,** the panel suggests increasing VWF activity levels to ≥50 IU/dL with **desmopressin or factor concentrate with the addition of tranexamic acid**
- The panel suggests giving **tranexamic acid alone** over increasing VWF activity levels to ≥50 IU/dL for:
  - Type 1 with baseline VWF activity levels >30 IU/dL
  - Mild bleeding phenotype
  - Minor mucosal procedures
- **For patients at higher risk of thrombosis,** avoid the combination of extended increased VWF and FVIII levels (>150 IU/dL) and extended use of tranexamic acid

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.; World Federation of Hemophilia (WFH). WFH Website. 2021. https://elearning.wfh.org/resource/ash-isth-nhf-wfh-guidelines-on-the-diagnosis-and-management-of-vwd/. Accessed January 20, 2022.

Now in terms of, again, surgery management, briefly just to talk about tranexamic acid, the recommendations from the guidelines is for minor procedures. Panels are just increasing von Willebrand activity levels greater than 50, with desmopressin or factor concentrates with the addition of tranexamic acid.

The panel also suggests giving tranexamic acid alone or increasing von Willebrand activity levels greater than 50 for the Type 1 with a baseline von Willebrand activity greater than 30 for a mild bleeding phenotype or for a minor mucosal procedure.

Now, for those patients that have a high risk of thrombosis, avoid the combination of extended, increased von Willebrand and factor VIII levels and extended use of tranexamic acid as well.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

CLINICAL GUIDELINES

blood advances

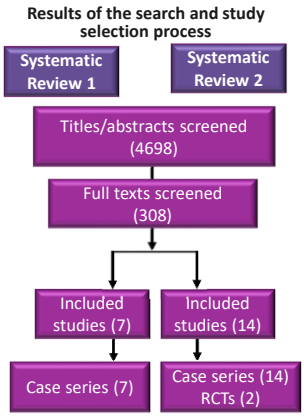
Surgical Management of Patients with VWD:

Summary of 2 Systematic Reviews of the Literature

Given the low-quality evidence for guiding management decisions, a shared-decision model leading to individualized therapy plans will be important in patients with VWD who are undergoing surgical and invasive procedures

This systematic review directly informs clinical practice guidelines for the management of VWD and includes recommendations:

1. Target both FVIII and VWF activity levels of ≥0.50 IU/mL for at least 3 days after major surgery
2. Increase VWF activity levels to ≥0.50 IU/mL with desmopressin or VWF concentrate with the addition of TXA after minor surgery or invasive procedures, and
3. To give TXA monotherapy for minor mucosal procedures in patients with Type 1 VWD and baseline VWF activity levels >0.30 IU/mL and a mild bleeding phenotype



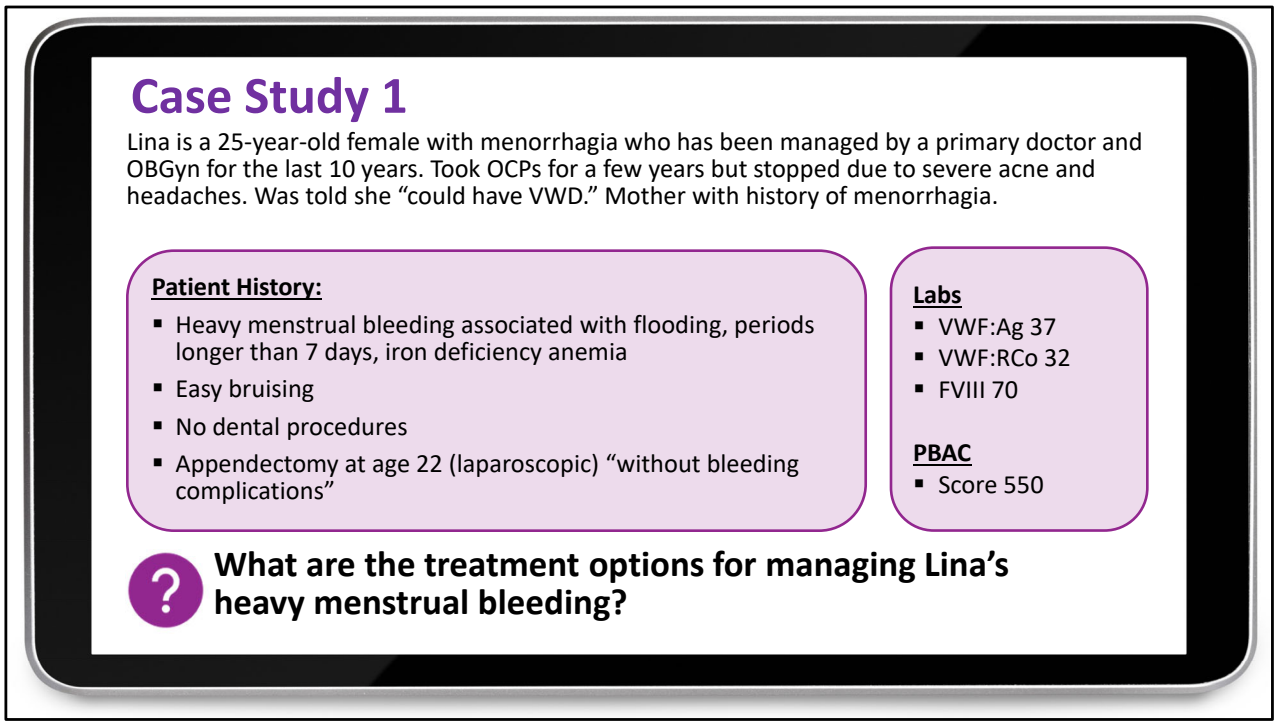
Bignardello-Petersen R, et al. *Blood Adv*. 2022;6(1):121-128.

To finalize, here again, we have less data in regards to clinical trials on patients with von Willebrand disease undergoing surgery. There's a summary of two systematic reviews in the literature. As you can see at the end, there's a lot of case series and very few randomized, really, clinical trials and surgery. Given the low-quality evidence for guiding management decisions, a shared decision model is important here. I think this is when it's very important to be able to have the comprehensive team and be able to make individualized decisions for our patients.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

With this, I think we're going to discuss a couple of cases.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



Our first case is a 25-year-old female with history of menorrhagia who has been managed by a primary doctor and an Ob/Gyn for the last 10 years. She took oral contraceptives for a few years but stopped due to severe acne and headaches. She was told she could have von Willebrand, and her mother had a history of menorrhagia as well.

Now, her personal history is of heavy menstrual bleeding associated with flooding periods longer than seven days, iron deficiency, anemia, history of easy bruising. She had no dental procedures, but she had an appendectomy at age 22 with laparoscopic and apparently there was no bleeding complications.

You can see to the right the results of her studies. She had an antigen of 37, a ristocetin of 32, and a Factor VIII of 70%. The pictorial chart was pretty high as well. I think this is something that we typically see in our clinics. The issue here becomes what is the best treatment option or treatment options to manage this young lady?

Polling Question #1

What are the treatment options for managing Lina's heavy menstrual bleeding?

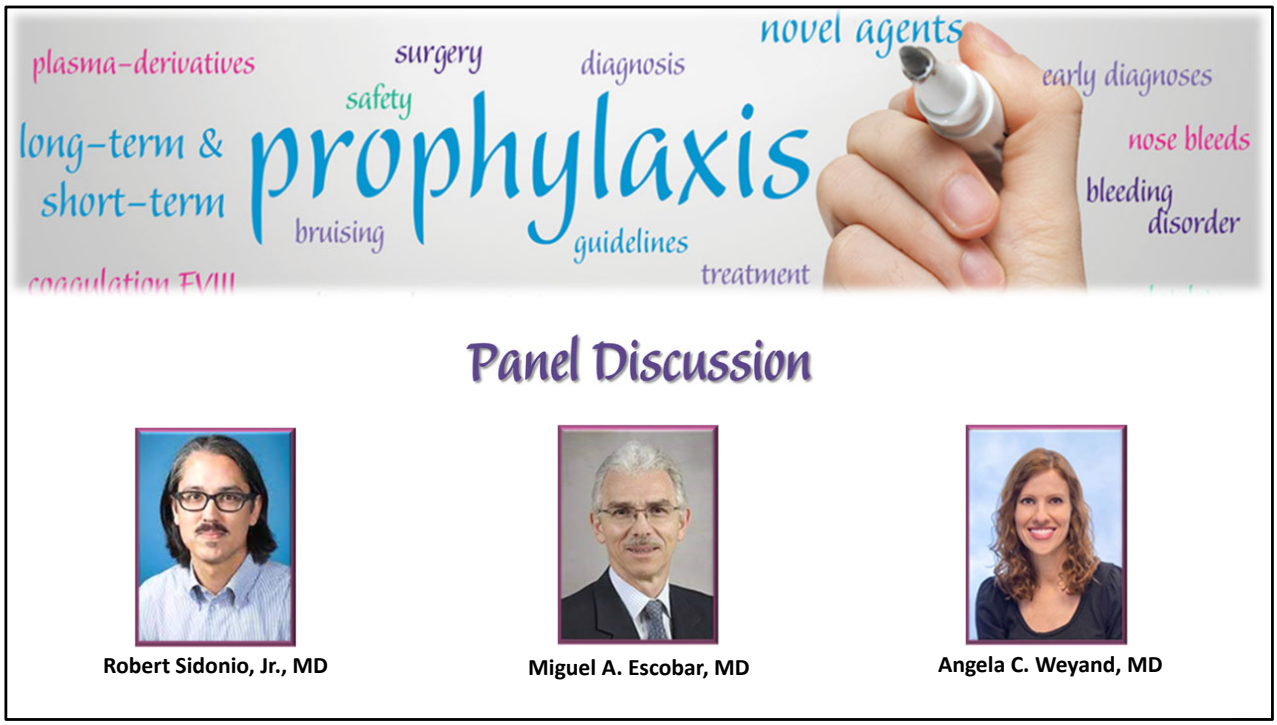
A. Intranasal DDAVP
B. Tranexamic acid
C. VWF concentrate
D. Levonorgestrel IUD
E. Combination of the above

Please respond using the question box below the video window.

What are the treatment options for the management of this young lady that has heavy menstrual bleeding?

A. Intranasal DDAVP
B. Tranexamic acid
C. VWF concentrate
D. Levonorgestrel IUD
E. Combination of the above

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



I think this is a very typical case, right, Robert or Angela, what you see in your clinics. What is your approach? Let's say you got a brand new patient coming in. Do you have maybe some sort of algorithm or some sort of approach that you undergo with somebody coming brand new to your clinic?

Dr. Robert Sidonio: Yes, I can start it out. Typically, the patients may have had a negative experience whatever product they have and it could have been just the right product in the wrong hands and not the right treatment strategy. We always say there are lots of different birth control options, controlled COCs. Just because that one didn't work or it didn't work the right way, maybe it wasn't implemented the correct way.

Certainly, you have to take in things like migraine headache, history of thrombosis, things like that as well, and then whether there's any history of-- concern for depression or anxiety when you're considering these hormonal therapies as well. We obviously have to have a discussion. This is a 22-year-old, so you don't have to bring in the parents' decisions on here, but really asking questions about are you sexually active? Typically at that age, they are.

That may help guide you down one path of products that may also control, heavy menstrual bleeding as well as offer birth control. There are patients that come in clearly that have no desire to be on any hormonal option or have had lots of different side effects from it. We talk about things like tranexamic acid or non-birth control options. We typically start with the least invasive. I know my Ob/Gyn colleagues often will offer IUDs upfront. Younger clinics, we don't do that. Of course, a

22-year-old, that's something you could offer up front as well.

Dr. Miguel Escobar: Angela, what is your perspective?

Dr. Angela Weyand: Yes, I agree with everything Robert said. I think when we were making the guideline, there was a guideline recommendation on the treatment of heavy menstrual bleeding. I think one of the big forks in the road is whether they want to conceive. Because they may be sexually active but not wanting to conceive and in that case, a hormonal therapy is not going to be appropriate for them. That is a big part of the conversation. I think a lot of it has to do with their bleeding pattern and also their own values and preferences.

With bleeding pattern, I see mostly pediatric adolescent patients. I find that if you have really prolonged bleeding, like girls that bleed for the majority of the month, tranexamic acid isn't great because it doesn't actually decrease your number of days of bleeding. It decreases the amount of flow you're having. It's still super disruptive to be bleeding for most days of the month versus having a patient who maybe bleeds for five days. It's just very heavy during that time.

Taking tranexamic acid three times a day is doable, although again, it's three times a day. Some people would prefer to have that, take three times a day, but only while I'm bleeding, versus a hormone of taking once a day or whatnot. I think in a lot of ways, we tend to think of these things as most invasive or least invasive. I think I try to flip that in my head because I think with the IUD, you can say that's invasive, but it's actually like you put it in, and then you're done. You don't have to take a pill every single day or like VWF concentrate.

You come in. Yes, you have to get an IV or you do an IV at home, but it's one or two doses and then you're done. Versus in some ways, intranasal DDAVP, which has a lot of side effects people often don't like. I think weighing all of those things together and it's not always as clear what the most invasive or the most work or the most burden of treatment is going to be.

Dr. Robert Sidonio: Then we have to ask additional questions about pain, other side effects and consequences of that period as well, because some of the patients feel very strongly about having a period once a month, and that's their personal belief and that's their preference. If that's something they desire, obviously, that helps guide us on the treatment. I 100% agree with the tranexamic acid. I won't use it if it's chaotic menstrual bleeding throughout the month, you can't be on TA all month long.

Dr. Miguel Escobar: Now, in this specific, would you guys offer DDAVP upfront on someone like this?

Dr. Robert Sidonio: Yes. With the limited availability of stimate right now, that's made it difficult. I found that it's very difficult because oftentimes, with periods, they're associated with headaches, water retention, so that medicine can definitely be not something that a lot of women don't desire.

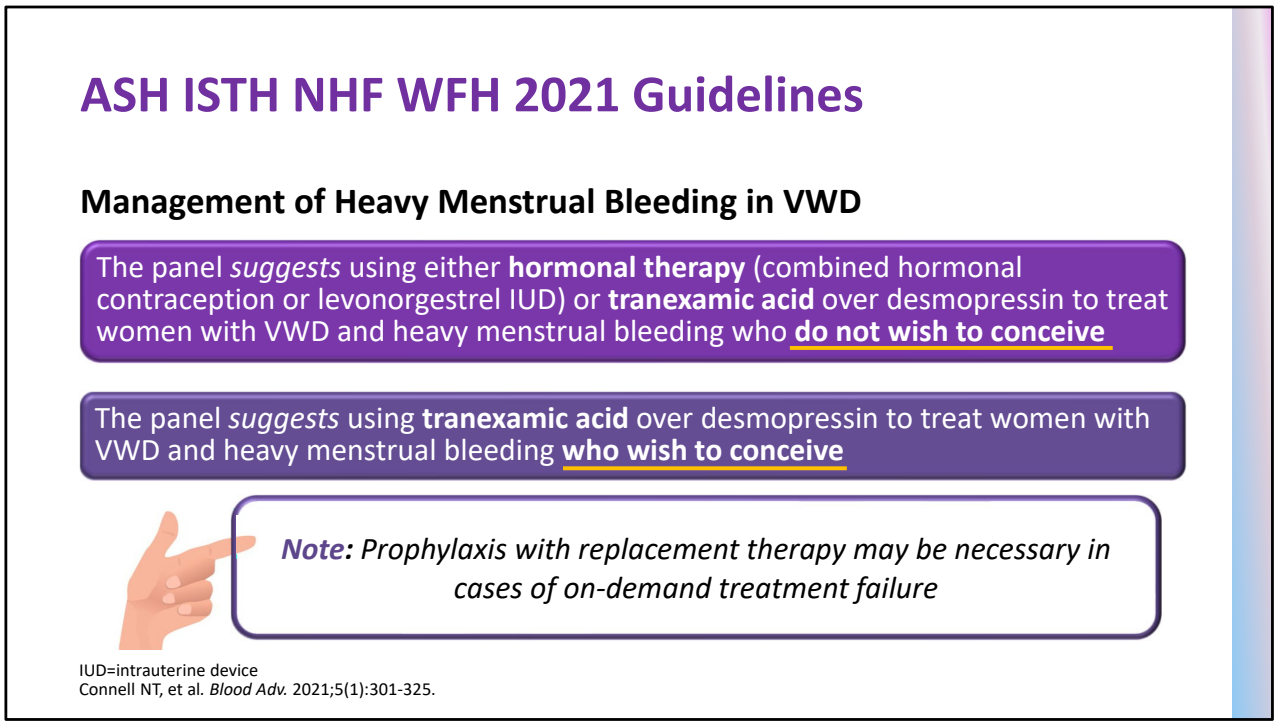
Dr. Angela Weyand: It was interesting, we talked about intranasal DDAVP for this question when we were doing the guidelines and there's not a great study that shows that one is definitively better than the other, but really, the patient representatives on the panel were very opposed to DDAVP and talked about in all the groups, everyone hates DDAVP. They've never felt so bad as when they take it. It was enlightening for me because when stimate was available, we prescribe it right a lot, and I think-- I wasn't always hearing that from patients, but definitely on the panel, it was very much like, "Even if it worked better than everything else, it's not worth it."

Dr. Miguel Escobar: My impression is that I think we're using it less and less. Not because it's not available, but even before that, I thought we were probably using it much less especially in a specific-- in these types of patients.

Dr. Robert Sidonio: I think if you do decide to use it, if there's somebody that has a good response to it, giving it at night can be helpful because then, the fluid restriction's easy, because they're sleeping. If they have a headache, hopefully, it's happening while they're asleep as well or nauseated as well. We've done that strategy. It's a tough long-term strategy to say you're going to do this for 12 months, but we have done that in some patients. Typically doing it on the first and maybe third, fourth day to avoid the tachyphylaxis that can sometimes occur with it.

Dr. Miguel Escobar: Now, do you guys usually do a trial on these ladies?

Dr. Robert Sidonio: For a response, yes. I think there's pretty good data from Michelle Lavin and the Irish group that the adult patients overwhelmingly respond, that if they have levels of 30 to 50%. It's not really clear in children whether they have that overwhelming response. I know we looked at some of this data in the Zimmerman project and it wasn't as well. The response rate was nowhere near as high, but I would advocate to do it. I think the levels were in the twenties so I think definitely would advocate for a trial.



Dr. Miguel Escobar: Thank you. As Angela discussed here, the use of the panel suggested use either hormonal therapy, or tranexamic acid over desmopressin to treat women with heavy menstrual bleeding and von Willebrand disease that do not want to conceive. The panel also suggested using tranexamic acid over desmopressin to treat women with von Willebrand and heavy menstrual bleeding who wish to conceive as well.

ASH ISTH NHF WFH 2021 Guidelines

Role of prophylaxis in VWD

In patients with VWD with a history of severe and frequent bleeds, the panel *suggests* using long-term prophylaxis rather than no prophylaxis

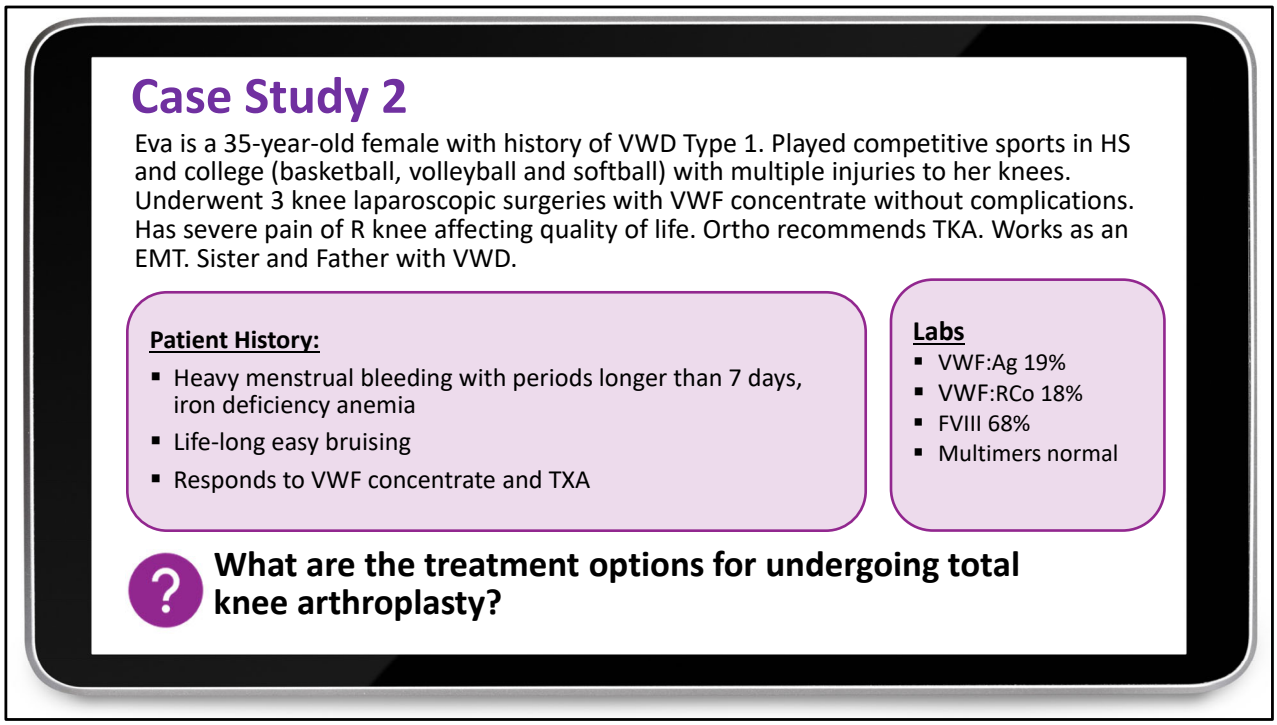
- Bleeding symptoms and the need for prophylaxis should be periodically assessed

- **Justification**
  - Although the published evidence is limited, the large costs to patients with severe and frequent bleeds were considered to be worth the net benefit of this recommendation. **Long-term prophylaxis is likely to be acceptable and feasible to implement, and this recommendation is likely to increase equity.** Thus, the desirable consequences are greater than the undesirable consequences

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.

We discussed already the issue about role of prophylaxis. I guess once-- and some of those treatments fail, as we all do in our clinic, we have many patients now that have been on prophylaxis, especially during those maybe first few days of their periods.

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences



Let's go to our second and last case. This is also a young lady, 35-year-old history of von Willebrand Type 1. She played competitive sports in high school and college basketball, volleyball, softball with multiple injuries to her knees. She underwent three knee laparoscopic surgeries covered with von Willebrand concentrate without any complications. Now she is not doing as many sports because her quality of life really have been affected now with that right knee, having a lot of pain, she has been evaluated by orthopedics and they do recommend to do a total knee replacement. The lady, even though she's so young, but she's got a lot of damage in that joint.

She works as an EMT. Her sister and her father have von Willebrand. Her history is of heavy menstrual bleeding with periods longer than seven days, history of iron deficiency, bruising and she does respond to the concentrate and tranexamic acid. To the right, we have her results, antigen of 19, resto of 18 and a Factor VIII of 68 with normal multimeric.

Polling Question #2

What are the treatment options for undergoing total knee arthroplasty?

A. Intranasal or IV DDAVP
B. Tranexamic acid
C. VWF concentrate
D. A and B
E. B and C

Please respond using the question box below the video window.

This again is a major surgery, what are the treatment options for this patient undergoing surgery? If you want to, reply again on the website.

A. Intranasal or IV DDAVP
B. Tranexamic acid
C. VWF concentrate
D. A and B
E. B and C

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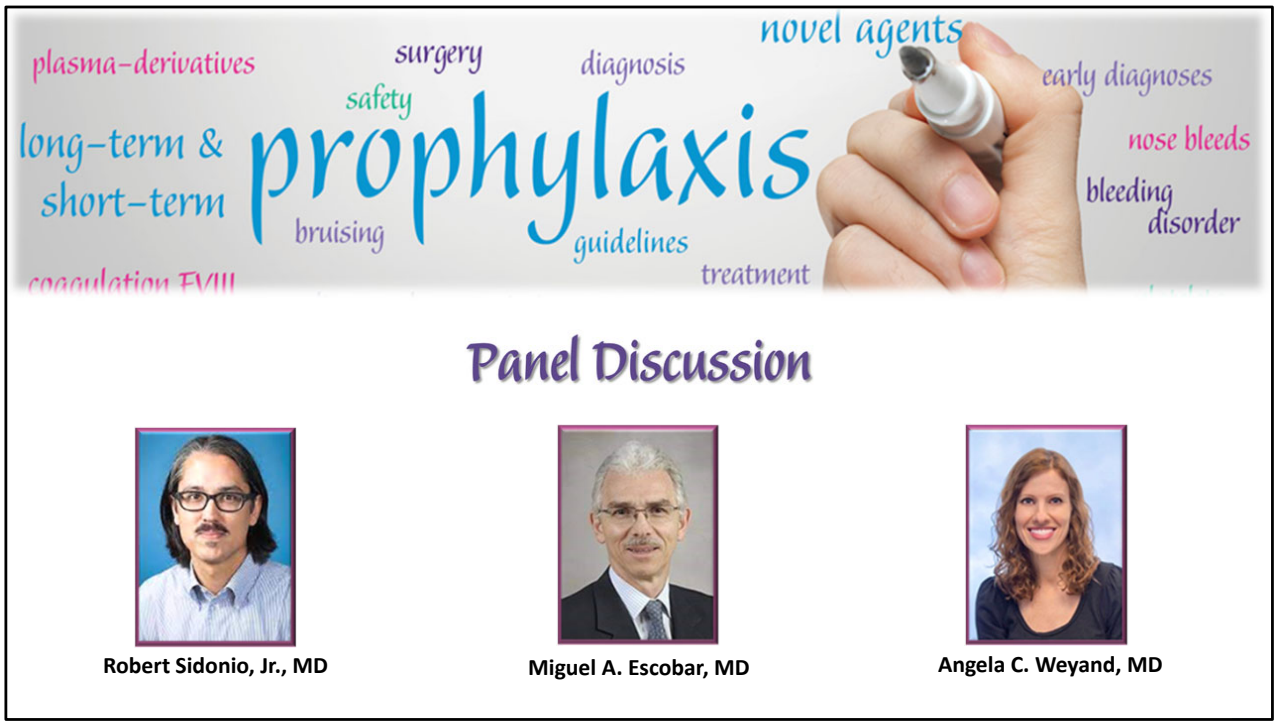
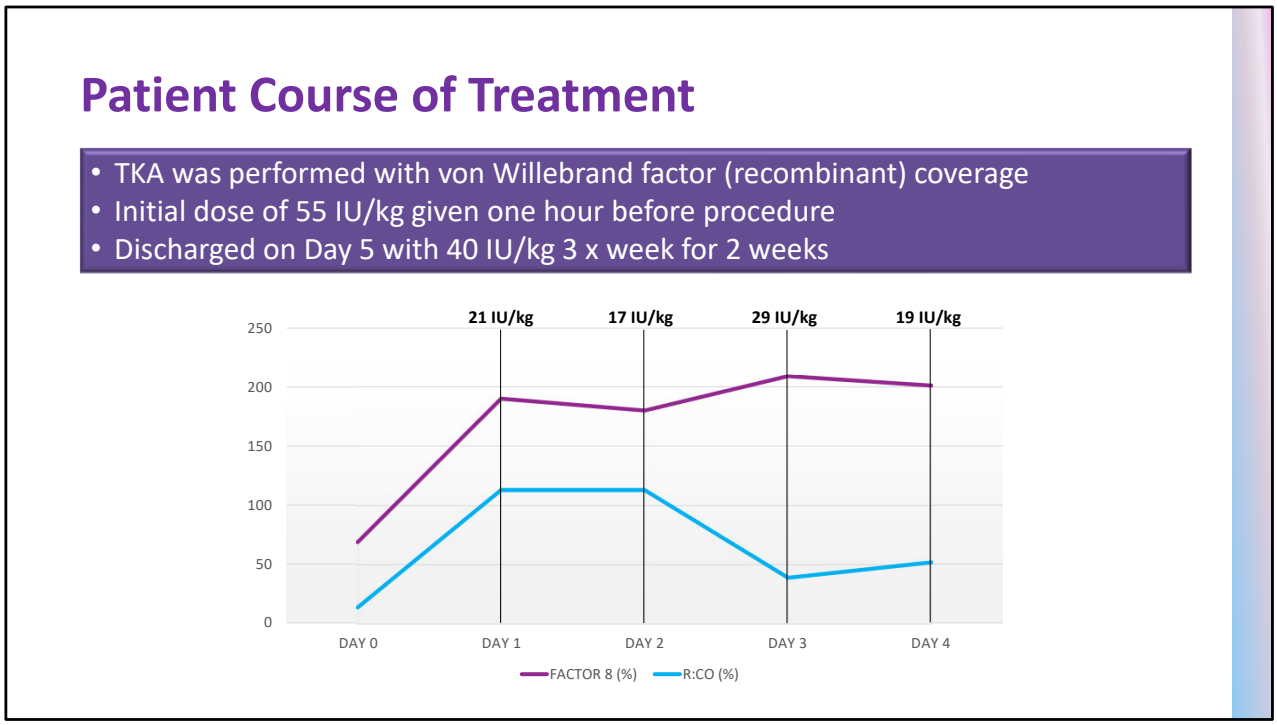


The question, what is your experience in these type of surgeries in your institutions?

Dr. Robert Sidonio: It's interesting because in the United States, that's true with the concentrated antifibrinolytic. If you did the same poll in Europe, you'd find they would mix in DDAVP. You see this pretty frequently and we all get alarmed by it like, "How can you do that?" That seems impossible. Particularly with the fluid restriction issues for some long-term surgery. I think the principles that you outlined before about giving treatment, making sure they have an adequate recovery, making sure you have the ability to check levels on a fairly frequent basis.

This isn't someone that's going to get one or two doses, they're going to get fair number of doses, so you want to ensure that you can have those troughs. One of the challenges that we have because we can't turn around our ristocetin co-factor assay very quickly, it makes it quite challenging. We can get antigens much quicker. I know this is a challenge at certain institutions that can't do this. That's regardless of their ability to do GP1bM, but I know you're going to talk about the dosing here.



I think, more and more, we definitely are doing surgery in our patients with von Willebrand, and definitely, major surgeries. This lady underwent the procedure she got on initial dose, as you can see here, 55 units per kilo of recombinant von Willebrand. You see the levels of von Willebrand Factor, ristocetin, and Factor VIII levels. Since her Factor VIII was pretty decent, that's why we made the decision that she could be treated with the recombinant von Willebrand product.

She did quite well, by day four or five, she was out of the hospital and was receiving 40 units per kilo three times a week at least for two weeks or so while she did her physical therapy and had no problems. Again, it comes to the point, how are you going to do that monitoring? I think as Robert alluded, it's very important to be able if you can have those levels because sometimes, you'll be surprised, you can get very high levels, especially when you sometimes you use a plasma-derived-- levels can get quite high and you don't want to keep those levels for too long that high.

There are some institutions where they use DVT prophylaxis for those patients, but I think that's when it is important to be able to rely on your laboratory, to be able to monitor these patients pretty closely.

Dr. Robert Sidonio: Miguel, I'm curious this patient clearly has had joint bleeds and you

could say they're maybe from traumatic bleeding events from competitive sports, but is there a discussion about whether maybe they should be on prophylaxis indefinitely to limit the long-term damage? You have one knee that's repaired. I'm sure the other one isn't perfect, and so I don't know if that discussion happens?

Approach to the Surgical Management of VWD Patients

- Characterization of VWD subtype and assessment of bleeding phenotype
- Preoperative assessments of plasma VWF levels/PK study
- Stratification of surgical risk (major and minor)
- Treatment options
  - Antifibrinolytic therapy
  - Desmopressin
  - pdVWF
  - Recombinant VWF
- Perioperative management
- Thromboprophylaxis

O'Donnell JS, et al. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):604-609.

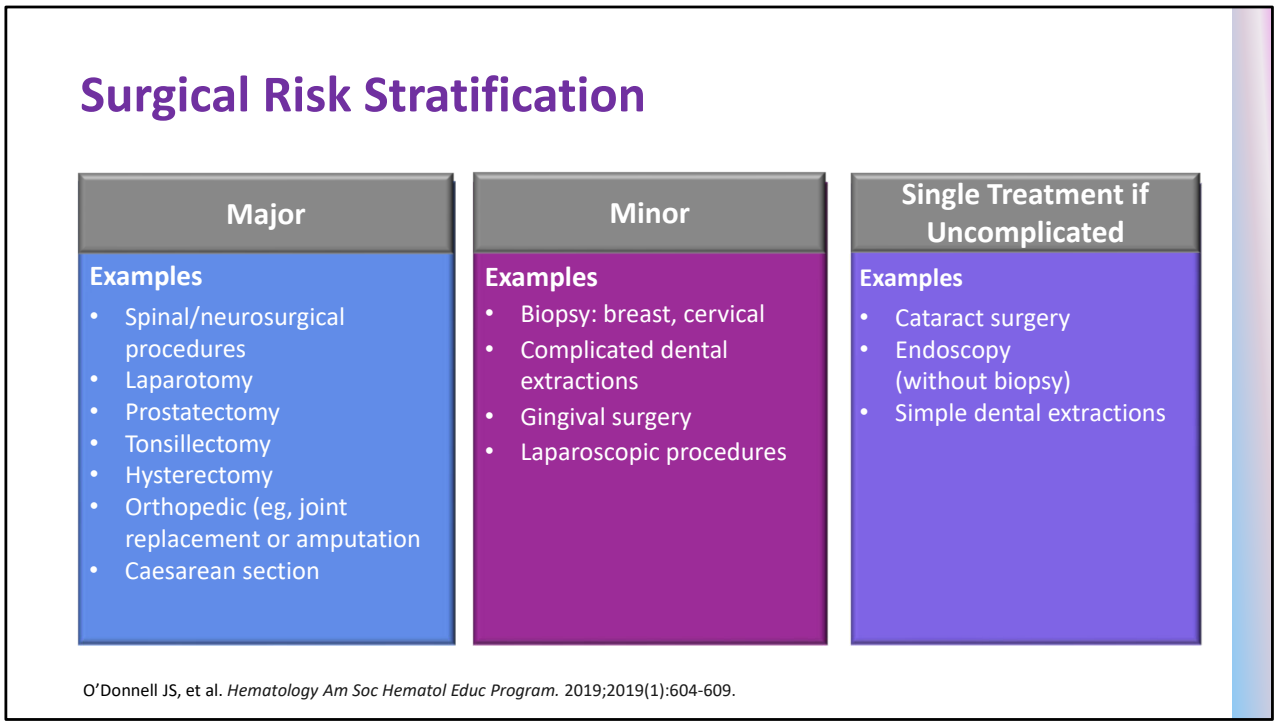
Dr. Miguel Escobar: Yes, she had a lot of traumatic injuries. This girl was very active. In addition to that, is very heavy as well, so that has been something that has been brought up for discussion, certainly the possibility of doing prophylaxis. She has been reluctant to do it. She might have done it maybe for a short period of time especially when she was doing a lot of sports, but I think it's a good point. Something that maybe down the road, she could definitely benefit if she continues to bleed.

Dr. Angela Weyand: I think having the recombinant product for these sorts of situations is really nice. Just if you have a patient who's heavy and then their Factor VIII, to begin with, is pretty good, and then they are having a big orthopedic surgery where they're going to be immobile, I feel like it's really nice to not have to worry about that Factor VIII going super high the opposite problem where they have a thrombosis.

Dr. Robert Sidonio: Absolutely. I think it's really important to look at the dosing. Oftentimes, people just read the guidelines and they suggest dosing. They don't mention anything about what your levels are. Your levels could be 30% to 50% or they could be 2%, I think oftentimes you see people giving an appropriate dose in the beginning and then giving very high dosing afterwards and then they're shocked why the Factor VIII level is 400%. I think you noticed how Miguel managed that patient and those dosing, he

personalized it and dosed it appropriately to what the levels were to hit the trough.

Dr. Miguel Escobar: I guess the privilege that we are able to get levels every day on time so that we usually will make a decision when that result comes out. That makes it probably a lot easier.



It's something that we already discussed here, but that surgical risk stratification is important, seeing what kind of procedure that patient's going to have. Is it a major, is it a minor or something that could be treated with a single dose?

It's always important to be able to plan ahead for these types of patients, make sure you got your multidisciplinary team, both as an outpatient and in your hospital, and a follow-up for these patients as well.

Recommended Dosage Regimens of Concentrates of VWF/Factor VIII or VWF Only in Patients with VWD Undergoing Surgical Prophylaxis

Indication	Dose Regimen	Target plasma VWF:RCo/ FVIII:C level*
Major surgery	40-60 IU/kg once-daily until wound healing is complete	50-100 IU/dL maintain levels for 5-10 days
Minor surgery	30-50 IU/kg once-daily (may require for only 1-3 days)	>30 IU/dL
Dental extraction or other invasive procedure	20-30 IU/kg (usually a single dose prior to procedure)	>30 IU/dL for >12 h
*These dosages are indicated for patients with VWD with reduced factor VIII activity/VWF ristocetin cofactor levels <10 IU/dL)		

Franchini M, et al. *Ther Adv Hematol*. 2021;12: 20406207211064064.

Again, this is something we already discussed, the recommended doses for surgical procedures, major and minor procedures, as well as dental extractions.

Summary Points

- In patients with VWD with a history of severe and frequent bleeds, there is expert opinion to support using VWF prophylaxis
  - This includes reproductive tract bleeding
  - Bleeding response should be evaluated, and dosing adjusted
- Heavy menstrual bleeding often requires a multimodal approach and may include the use of VWF replacement
- The diagnostic approach and clinical management to VWD is different than hemophilia
  - Clinical research investigation needs to be tailored to the unique characteristics and bleeding patterns of VWD

Hopefully, you've left here thinking that in patients and persons with von Willebrand with a history of severe and frequent bleeds, there is expert opinion, there is data, there's community support to consider prophylaxis as a regimen. Even just thinking about Miguel's patient, this person's obviously had multiple joint bleeds.

If that was a hemophilia patient, we would be saying absolutely should be on prophylaxis, but she doesn't have the support probably from her community to say, "Hey, that's a no-brainer." I think that's something we have to change. This includes reproductive tract bleeding and bleeding response should be evaluated and dosing should be adjusted. We want to make sure people are getting the appropriate dose and just like in hemophilia, we sometimes have to personalize the dosing.

Hopefully, you understand that heavy menstrual bleeding often requires a multimodal approach. Maybe include the use of VWF replacement. Typically, often, if they're failing other options or if there's a contraindication. We certainly have a number of experiences at our center of lots of Type 2A patients that respond very well to different types of products. The diagnostic approach in clinical management is different than hemophilia. Hopefully, you leave understanding that. Hopefully, have annoyed you enough for you to understand that.

Clinical research investigation really needs to be tailored to the unique characteristics and bleeding patterns of von Willebrands. It's like we talked about in the last DEI sessions, you'd like to just start over and say, "How do we do these trials? How do we get at the answer that we need to get these

products approved for prophylaxis?" We want a lot of products available for these patients not just one. I think that's really important.

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Additional Slide References, Footnotes and Abbreviations

Slide 41 - Factor Concentrate Target Levels

*VWF–factor VIII or VWF concentrate is administered in patients with Type 3 disease and in patients with Type 1 or 2 disease who do not have a response to desmopressin or in whom it is contraindicated. †Dose of factor concentrate depends on the type of concentrate used. If VWF–FVIII concentrate is used, the dose also depends on the brand of concentrate. The dose is based on an anticipated in vivo recovery (2 IU per deciliter for every unit of factor VIII activity infused per kilogram of body weight and 1.5 IU per deciliter for every unit of VWF ristocetin cofactor activity infused per kilogram) and the target levels of both VWF–ristocetin cofactor activity and factor VIII activity. If high-purity or recombinant VWF concentrate is administered, a single dose of factor VIII concentrate should also be administered in order to achieve the target level of factor VIII immediately. ‡FVIII activity, and preferably also VWF–ristocetin cofactor activity, should be monitored regularly in all patients undergoing surgical procedures and all patients with severe bleeding episodes. If measurement of VWF–ristocetin cofactor activity is not immediately available at a local laboratory, dosing should be based on factor VIII activity levels.

Slide 47 - Summary of Reports on the Use of Long-term Prophylaxis in VWD

BS=bleeding score; GI=gastrointestinal; CNS=central nervous system; ENT=ear, nose, throat; VWD=Von Willebrand disease; NA=not available.
a Type of VWD given for the overall population. b Number of bleeding events. c Means, expressed according to the frequency and type of bleeding.
d Others: included epistaxis, Heavy Menstrual Bleeding (HMB), hematoma.

Dunkley S, et al. *Haemophilia*. 2010; 16(4): 615–624.; Castaman G, et al. *Haemophilia*. 2013; 19(1): 82–88.; Abshire T, Cox-Gill J, Kempton CL, et al. *J Thromb Haemost*. 2015;13(9):1585-1589.; Goudemand J, et al. *J Thromb Haemost*. 2020;18(8):1922-1933.; Sholzberg M, et al. *TH Open*. 2021;5(3):e264-e272.; Berntorp E, et al. *Blood Coagul Fibrinolysis*. 2005; 16(Suppl 1): S23-S26.; Federici AB, et al. *Haemophilia*. 2010;16(1):101-110.; Halimeh S, et al. *Thromb Haemost*. 2011;105(4): 597-604.; Howman R, et al. *Haemophilia*. 2011;17(3): 463-469.; Abshire TC, et al. *Haemophilia*. 2013;19(1): 76-81.; Miesbach W, et al. *Thromb Res*. 2015;135(3): 479-484.