**CMEO Podcast Transcript**

Robert Sidonio:

Hello. Good evening. On behalf of CME Outfitters, I'd like to welcome you today to today's educational activity titled, “Diagnosis and Individualized Management of von Willebrand Disease: Expert Perspectives on Synthesizing and Contextualizing the Evidence.”

Robert Sidonio:

Today's program is supported by an educational grant from Takeda Pharmaceuticals. And it's also brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide.

Robert Sidonio:

So let's get started. And I want to start it by introducing myself. My name is Dr. Robert Sidonio, Jr. I'm a pediatric hematologist. I work as an Associate Professor at Children's Healthcare of Atlanta and at Emory University. I'll be the moderator of the program. And I'm joined by my two colleagues who will introduce themselves. Let's start with Dr. Escobar.

Miguel Escobar:

Yeah. Good evening. Thank you, Robert. My name is Miguel Escobar. I'm an adult hematologist and Professor of Medicine and Pediatrics at the University of Texas in Houston. I'm the Director of the Hemophilia and Thrombophilia Center as well.

Robert Sidonio:

Thanks, Miguel. Now, Dr. Roberts.

Jonathan Roberts:

Yes. Hi. Good evening. I'm Jonathan Roberts. I’m the Associate Medical Director at the Bleeding & Clotting Disorders Institute, and also an Assistant Professor of Pediatrics at the University of Illinois College of Medicine in Peoria. And our clinic is also a lifespan clinic. So we take care of pediatric and adult patients.

Robert Sidonio:

That's great. So we have two great speakers joining me tonight. Let's go ahead and get started and dive in with our first learning objective: accurately diagnosing von Willebrand’s based on clinical assessments and laboratories, specific laboratory assays.

Robert Sidonio:

So we know that von Willebrand’s is the most common bleeding disorder in humans. It was discovered in the early 1900s by Erik von Willebrand. And most notable, the index case was a little girl named Hjørdis, who presented with bleeding symptoms that were more typically seen in males with hemophilia. Ultimately, she passed away after her fourth period.

Robert Sidonio:

We know that the characteristic bleeding signs and symptoms are typically associated with mucocutaneous bleeding, but also associated with things like musculoskeletal bleeding, joint bleeding, but a lot of easy bruising, frequent nose bleeds, heavy menstrual bleeding in women, and a lot of oral bleeding. We know that it's equal amongst both genders and ethnic groups, typically as seen a little bit more commonly in Caucasian populations as this origin of disorder is in Northern Europe.

Robert Sidonio:

And, oftentimes, it is not diagnosed unless there is a hemostatic challenge, unless there is a family history noted. And, of course, the severity goes from severe to mild, with the majority of the patients being in the mild range. So I'll go ahead and get it started here. Dr. Escobar, you see the slide here. Do your patients typically present in your clinic? You said you're an adult provider. They typically present with these symptoms?

Miguel Escobar:

Yeah. I mean, as you already alluded, the presentation could be quite variable. But in our adult population, we have patients that come in just with simple, easy bruising. The women certainly, it's going to be quite common, the menorrhagias, I think. But many of them have had it for years and they have not been addressed correctly.

Miguel Escobar:

Many of our patients actually also come for surgeries with a history of von Willebrand sometime in their life or a family history. So the surgeons might get a little bit uncomfortable. And they'll send it to us to do a workup, or sometimes actually we're seeing a lot from the OB/GYN service. They're pregnant, and they have this history of von Willebrand and they get sent to our clinics for an evaluation, kind of planning for that delivery.

Robert Sidonio:

So, Jonathan, do you get the same history where maybe somebody has a remote history or they're about to have a procedure and they may have remembered 10 years ago that they were diagnosed with von Willebrand maybe as a child?

Jonathan Roberts:

Sure. Yeah. For adults that present to us, we definitely have encountered that where they may have remembered something about von Willebrand disease. And then, the next time, they come to see us, is after they're, they've had some major bleeding complication in surgery, or the surgeon calls because there's an inpatient that's having uncontrolled bleeding, and they're unable to get it to stop.

Jonathan Roberts:

So yes, we do have those similar type of presentations. I would say also in pediatric patients, very commonly, we'll get referrals for easy bruising, girls attaining menarche. And then, also patients that may be bleeding postoperatively after a tonsillectomy, adenoidectomy, or maybe even dental work having multiple dental extractions or wisdom tooth extractions.

Jonathan Roberts:

These can be ways that patients will present, in a perfect world if we've done our job right, and there's a family history, and the patients are educated about von Willebrand disease, we also will get siblings or family members that we can then diagnose them preoperatively and put a management strategy in place for mitigating any bleeding risk they may have.

Robert Sidonio:

Yeah. We'll talk a little bit more about the team together. That's key to trying to make a diagnosis, not urgently at the time of surgery. So moving forward, as everyone knows, von Willebrand's factor plays two critical roles. First of all, it's a multimeric protein. And it's consisted of dimers, we call building blocks. And it forms something called multimers. They're stored at endothelial cells and megakaryocytes.

Robert Sidonio:

And then, they're secreted into plasma where they play a critical role in primary hemostasis. As you can see here, one of the roles is tethering the platelet to the exposed or damaged collagen. In the other critical role, it serves as a carrier protein for Factor VIII, preventing premature degradation.

Robert Sidonio:

So Jonathan, why don't you walk through the different types? We just talked about the pathophysiology. And there are multiple types and multiple subtypes as you listed here. Why don't you take us through this, and tell us a little bit about some of these?

Jonathan Roberts:

Sure. So from a big picture standpoint, there's three main types of von Willebrand disease. And you can see there's subtypes listed there at the bottom of the slide. By far, the most common, around 80% of the time, is type 1 von Willebrand disease, where it's simply a partial quantitative deficiency. So not having quite enough von Willebrand factor present to stick platelets to the site of injury, to bind collagen, to chaperone Factor VIII to the bleeding site. So that's by far what you'll encounter in patients in your practice that have von Willebrand disease.

Jonathan Roberts:

Next would be type 2, which is somewhere around 20 or so percent of patients. And this is a qualitative defect. So there's a functional deficiency in von Willebrand factor. So sometimes, level's reduced. Sometimes, it's normal. But as you can see, there's different subtypes there where there could be abnormal binding to platelets, either a lack of platelet binding, such as 2A or 2M, or an enhanced gain of function binding that can also lead to thrombocytopenia in type 2B as well as deficient Factor VIII binding in 2N that sometimes can be mistaken for mild hemophilia.

Jonathan Roberts:

Those type 2 variants will require more sophisticated laboratory testing, really to hash out what the specific qualitative defect is in the von Willebrand factor molecule. And then, type 3 is essentially complete deficiency of von Willebrand factor. And these patients present often like a severe hemophilia, because as Robert mentioned, von Willebrand factor's critical for chaperoning Factor VIII in circulation. And so, if you don't have Factor VIII or von Willebrand factor in circulation, you also don't have Factor VIII unless the VWF is replaced. So that's kind of a big picture view of the diagnostic classification. And we'll talk a little further in the coming slides.

Robert Sidonio:

And, sure, of course, we don't expect primary care providers to help discern the different types. That's our job. We just want you to make sure you get them to us to make sure that we can help make that appropriate diagnosis. So critical to this is, just recently multiple organizations, ASH, ISTH, NHF, and WFH, decided that they wanted to get back together and have a unified set of guidelines.

Robert Sidonio:

And the last set of guidelines had been decades before, it was a pretty large effort, took multiple years to put together, required a lot of coordination, a lot of meetings. And they ended up with two sets of groups. They set priority questions, so we couldn't address everything that we would like to address. But we decided to prioritize some question is to address that we felt were pertinent.

Robert Sidonio:

And two documents came out of this. One was focused on the diagnosis. That's listed there first authored by Paula James. And then, there was a second one was authored by Nathan Connell. And that focused on the management of von Willebrand’s. And it starts with that patient suspected of von Willebrand’s.

Robert Sidonio:

And then, from that, then decisions are made. And then, it branches out into what happens. And one of the first things that you should do, and I think anything in medicine starts out, getting a good history. From there, the decision on additional testing and how much testing goes on depends on that bleeding history. And we'll talk a little bit about the limitations of that in certain populations.

Robert Sidonio:

Certainly, a two-year-old may have a very limited bleeding history compared to a 70-year-old. But we'll talk a little bit about the role of bleeding assessment tools. So, this is where you come in, Jonathan. This is an area where you've obviously done a lot of research. I think it's really critical, the utilization of all these tools that have been put into practice. So can you tell us a little bit about how you use them in tool, in your practice, and where they may be most appropriate?

Jonathan Roberts:

Sure. Thank you for that. So leading assessment tools have developed over the years. And I think you can see at the bottom of the slide, there's been many iterations, moving now to the ISTH-BAT and the Self-BAT. So bleeding assessment tools are very critical, especially in the primary care scenario for knowing which of your patients actually has clinically significant bleeding that would warrant a further evaluation for a bleeding disorder, including von Willebrand disease.

Jonathan Roberts:

So looking at the probability of VWD, really, the guideline panel recommended that for a patient that's seen in the primary care setting, that the panel recommends using a validated bleeding assessment tool as initial screening test to determine who may need further testing. And this recommendation is the strongest for adult women who have been evaluated quite a bit by the bleeding assessment tool.

Jonathan Roberts:

There's been a lot of study looking at bleeding symptoms in women in particular. And I would say that in a big picture, these bleeding assessment tools ask different domains, such as easy bruising, what menstrual periods are like, dental bleeding, bleeding with surgery, things of that nature. And basically, a patient's given a score. And if the score reaches a certain threshold, then patients are warranted to have a further bleeding evaluation.

Jonathan Roberts:

Now, depending on where you practice, you could start the evaluation before a referral to coagulation hematology specialist, or just getting a patient in the door to see us. And we can take the evaluation from there. I think where the ASH guidelines are actually recommending against doing BATs routinely, is once a patient's come to see a hematologist or if there's a family member affected by a first-degree relative with von Willebrand disease, then, really, there's not utility of doing these questionnaires.

Jonathan Roberts:

And that really it's more the coagulation hematologist expertise in what laboratory evaluation to do moving forward. And you can see there are different blood tests that are used to screen for von Willebrand disease. We measure the antigen, or the amount of protein, some measure of the platelet dependent-binding activity, and also Factor VIII. And those are kind of the bare minimum tests that we typically use to screen for von Willebrand disease.

Jonathan Roberts:

And sometimes, when there's maybe some nuances in the bleeding of your individual patient, they may not have severe von Willebrand disease. They may have what we call low VWF or mild type-1 von Willebrand disease, where their levels may be in the 30 to 50% range. And this nice study by our colleagues in Ireland, Dr. Lavin and her colleagues, looked at bleeding in low von Willebrand factor, and actually showed very nicely that the bleeding was actually related to having von Willebrand disease and not due to having some other concomitant hemostatic abnormality.

Jonathan Roberts:

So really even patients that maybe per the old criteria, before the updated 2021 guidelines, may not have met a strict criteria for von Willebrand disease but had low VWF. Now, if patients have low VWF and significant bleeding symptoms, we are categorizing them as having truly type-1 von Willebrand disease. And I think you can see here in the slide a variety of bleeding that we've already mentioned, dental, heavy menstrual bleeding, and moving into more minor bleeding, easy bruising, et cetera, are a lot of what our patients come to see us for in clinic. So it's really just kind of highlights from a primary care standpoint, where you can begin in your evaluation for a patient having a bleeding disorder like von Willebrand disease.

Robert Sidonio:

So that's great. So perfect timing to move to our case study. Let's get the audience involved in this case study. So this is patient's name is Darrell. And he's a nine-year-old male with a personal history of bleeding. You can see they're listed below. He had nose bleeds requiring cautery. He had some easy bruising, no really early life bleeding. He didn't have any prolonged skin bleeding. And of course he's nine. Like most nine-year-olds have never had a surgery.

Robert Sidonio:

He did have some oozing with dental extractions that required some good old fashioned tea bags and some repacking. And there's no family history of bleeding disorders. And he presents to his primary care physician. So remember, the setting is primary care. And so, as primary care physician, how should Darrell's PCP evaluate his bleeding? You should use a bleeding assessment tool.

Robert Sidonio:

And as Jonathan just elaborated in the guidelines, the pretest probability is quite low when you see a patient in a primary care setting. And so, you should use the bleeding assessment tool to decide whether further bleeding is needed. If he is already referred to Jonathan or myself or Miguel, then you can use the bleeding assessment tool, certainly a good way to get bleeding symptoms. But at that point, the evaluation should just be done. And certainly, if he had a sibling, it's about a 50/50 chance. And so a bleeding tool shouldn't be used to determine whether further workup is necessary. So I don't know if you have any comments, Miguel, on this.

Miguel Escobar:

Yeah. I mean, I think it's very important to be able to have access to these tools. And I can tell you, even when patients come already referred to us, I get a BAT score in everybody as a baseline and have it in our history because I think there's a lot of variability among sometimes when they get older. It might change their BAT scores depending on the treatment. So I always get a baseline at least to be able to go back always and see how that patient presented.

Robert Sidonio:

Sure. Jonathan, you guys, have you incorporated the BAT? I know there's the Self-BAT. Obviously, it can be completed by yourself or it can be administered.

Jonathan Roberts:

Yeah. I mean, we have done the BAT. It's mostly, to be honest, done in the context of studies because we've been looking to see, as you alluded to, what's the appropriate context in which to use a bleeding assessment tool. So we have a majority of our patients do have a BAT. There are some that do not. And really, I think, as of right now, the most important venue in which to use it is for primary care. Certainly, it is a helpful thing to do. Certainly, it can help us as hematologists as Miguel mentioned. But looking at the data, that's the strongest recommendation, certainly.

Miguel Escobar:

But, Robert, one thing that I think is important is using this score is they get used to asking the right questions when they look at the complete BAT, I think it's very important. So, they get used what really to ask because sometimes, that's what happens. They miss certain things.

Jonathan Roberts:

[crosstalk] Absolutely

Robert Sidonio:

[crosstalk] Sure. This is something that it can be trained. If you're administering it, you're a nurse, you're a nurse practitioner, PA, anybody on your team could be using this. And depending on your setup at your clinic, I think you should sort of adapt how you need to, so.

Jonathan Roberts:

Yeah. And I would echo Miguel's point that especially when training new staff or residents or medical students... helping them a BAT, showing them a BAT, how it's administered is a very comprehensive way to get them to think about bleeding symptoms that maybe they don't always think about.

Robert Sidonio:

Certainly. Yeah, because we always may forget one of those bleeding symptoms. And it helps us, GI bleeding for children, I sometimes will forget. So all right. Let's move it along here. So, we talked a little bit about when to test. And the guidelines really get into the actual meat of it, of the actual testing. And you can see here, they discuss the different types of testing as Jonathan mentioned. If the Factor VIII level is lower than the VWF antigen, you should consider evaluating for type 2N von Willebrand.

Robert Sidonio:

And then, there's a number of platelet-dependent VWF activity assays. And from that point, you can see there's a branch point where we focus on what those levels are. When you see VWF levels, that's referring to the antigen and also one of the functional assays, either typically the ristocetin cofactor assay or the newer GP1bM assay. And we'll talk a little bit about that as well.

Robert Sidonio:

And it's really important to continue to evaluate bleeding symptoms because this guideline only evaluates for von Willebrand. And certainly, there are people with platelet disorders that you may need to consider. So moving forward here, Jonathan, why don't you go ahead and tell us a little bit about these available screening labs that are listed on this slide?

Jonathan Roberts:

Sure, absolutely. The ones highlighted there in blue are by far the most commonly done in the U.S. So as I had mentioned, the von Willebrand factor antigen is simply a measure of the VWF protein level in plasma. So it screens for quantitative deficiency like I mentioned. It's reduced in type 1 and 3. It also is commonly reduced in type 2, but not always. And really just measures the amount of protein. How much protein is actually there? But not the function of how the protein itself works.

Jonathan Roberts:

So you look at the next level of testing, the ristocetin cofactor activity. So this really measures the ability of von Willebrand factor to bind to platelet GP1bA. And it can screen for some of the variants. Also, it's another reflection of the activity and will also be low in type 1 and 3 von Willebrand disease. But the ristocetin cofactor, without going into too much detail, is a test that has quite a degree of variability, not just within an individual's own lab, but also between laboratories across treatment centers as well.

Jonathan Roberts:

And otherwise, there's other variants, such as the D1472H polymorphism, that can affect the level, make the ristocetin cofactor level low with actually not affecting the patient's own von Willebrand factor functioning. So meaning causing a falsely low level where it could erroneously diagnose someone with von Willebrand disease potentially.

Jonathan Roberts:

So an improvement to the ristocetin cofactor assay is one that does not use ristocetin, called the GP1bM, which is a mutated glycoprotein 1B that will measure the platelet-binding activity of von Willebrand factor in the absence of ristocetin. This is widely used across Europe and also in Canada. There's limited availability in the U.S., which hopefully will be changing in the very near future, because if you're looking at the direct measure of von Willebrand factor platelet-binding activity, to look at its activity overall, it's better to have the GP1bM than the ristocetin. So hopefully, in the next few years, that will change.

Jonathan Roberts:

Factor VIII binding is also important to look at its chaperone capabilities of von Willebrand factor to chaperone Factor VIII in circulation. It can be low in type 2N and type 3 as well. And then, we also look at the ratio between VWF activity to antigen. And this will be off, because you think if it's a qualitative defect, typically, your activity will be less than your antigen. And this can screen for some of your type 2 variants.

Jonathan Roberts:

So in looking then, and certainly others can go to the guidelines to look at the kind of diagnostic algorithm in more detail, but there are a stepwise approach, if you do have a reduced ratio in considering type 2 von Willebrand disease, do other tests like von Willebrand collagen-binding, looking at multimer analysis, looking at patient's response to DDAVP, which we'll talk about further in this presentation and can further refine the diagnosis of von Willebrand disease.

Jonathan Roberts:

So really, this is a slide that's pretty comprehensive in the different type of confirmatory tests. Just in brief, I'll mention other things like I mentioned, collagen binding, von Willebrand factor collagen binding. There are specific defects of just a collagen-binding defect with other laboratory tests being normal that sometimes can be clinically relevant.

Jonathan Roberts:

Looking at von Willebrand factor multimers, so that's looking at how von Willebrand factor forms that long ladder. I always talk to my students and residents about von Willebrand factor being like Velcro®. So if your piece of Velcro® is not long enough, you can have abnormalities and have von Willebrand binds.

Jonathan Roberts:

The platelet-binding activity, which can screen for an enhanced binding, which would be suggestive of type 2 von Willebrand disease, as well as the ristocetin- induced platelet aggregation, which is another way to get at the platelet binding of von Willebrand factor in looking for a variant. And then looking for Factor VIII von Willebrand factor binding to look and see if there's type 2N von Willebrand disease.

Jonathan Roberts:

This is important to do, especially in someone who may have mild hemophilia or type 2N. This can hash out. If their Factor VIII binding is low, then it's a type 2N von Willebrand disease rather than mild hemophilia. Propeptide is another means to look at increased clearance, which is type 1C von Willebrand disease. And then, finally gene sequencing, which has limited diagnostic utility. But it can be very important, especially if you have a variant von Willebrand factor, because there are more than 1700 different sequence variations catalog to-date.

Jonathan Roberts:

And so, this is really reserved for more unique situations that an expert coagulation hematologist should be looking at. In regards to the propeptide though, I think Robert, there was a recommendation from ASH guidelines not to do that routinely in clinical practice, correct?

Robert Sidonio:

Yeah. And I think we talk a little bit about that a little later, but this ratio is a nice, easy way of doing this. This testing is typically required to send a specialized labs and we'll talk a little bit about the role of DDAVP challenges, which may be a little easier for most people to utilize and actually will give you clinically appropriate information.

Jonathan Roberts:

Sure. So in moving forward, this is just to highlight some research that's been done in the area. So I did develop an all-encompassing multiplex activity assay, really to look at all of those different tests that I mentioned on the previous slide, to look at variants and discriminate their variant in a one-stage assay. So this is just a highlight.

Jonathan Roberts:

In our particular study, we looked at a cohort of patients who had von Willebrand disease, either variant or non-variant. And this assay overall, just kind of cutting to the chase at the bottom of the slide, over 88% accuracy in correctly assigning the variant of von Willebrand disease phenotype. So this is just a highlight that, in the future, there may be a little bit more refinement in the diagnosis of von Willebrand disease and certainly myself and our colleagues across the world are endeavoring to try to simplify, making a complex diagnostic process for a very common bleeding disorder more refined.

Robert Sidonio:

Certainly. So, more to come in the future on that. So, all right. So let's move on. Thank you very much for the insight on that first learning objective. Let's move on to our second learning objective, which focuses on the individualization or individualizing the management of von Willebrand disease. All right. So Miguel, we know you've treated a number of patients in your career. Why don't you walk us through sort of the basic ways that we control or prevent bleeding in patients with von Willebrand’s?

Miguel Escobar:

Yeah. As you previously mentioned, knowing the pathophysiology of von Willebrand disease, so we need to look at what is our goal with the treatment? And our goal is really to improve platelet adhesion and aggregation, to get to fibril formation and maintain a stable clot.

Miguel Escobar:

So there are pretty much two ways that we can do this in patients with von Willebrand. And one of them is, by stimulating the release of endogenous von Willebrand stores. This is when we use, for example, desmopressin, or the other way is by increasing the plasma concentration of von Willebrand, either utilizing human plasma-derived virus inactivated concentrate or using a recombinant von Willebrand concentrate.

Miguel Escobar:

I mean, certainly we do have adjunctive therapy, different agents that we use to promote hemostasis, like antifibrinolytics. And we can also use other strategies to be able to increase our levels like, for example, in the females hormones, come to use estrogens that could also be quite helpful.

Miguel Escobar:

So we will be treating pretty much three different scenarios. One is an on-demand treatment, meaning treat when the patient has a bleed. The other one will be to utilize our treatment scenarios or our treatment regimens when the patient is going to go for surgery. So to prevent, let's say, excessive bleeding in those individuals. Well now, more recently, we've actually been using prophylaxis in patients with von Willebrand very similar to what we've been doing for many years for patients with hemophilia.

Miguel Escobar:

So here in this table, we have at least an example of the different treatment options. As already previously mentioned, you got those patients with low von Willebrand, not necessarily being diagnosed with type 1, but definitely have low von Willebrand and have symptoms.

Miguel Escobar:

So we can easily use desmopressin in those individuals. It can be used IV. It can be used intranasal, although it's been somewhat difficult to find now lately. And you see the different dosing that it can use. Subcutaneously, I guess it could be used. I don't have a lot of experience with the subq desmopressin.

Miguel Escobar:

Now for the type-1 patients, for the majority of them, you can also use the desmopressin, if you're going to treat maybe some minor bleeds. I mean, we do have type 1s that have very level levels. In my practice, I usually go straight to replacement products. And now, for the type 2s, most of the time, we use von Willebrand concentrates, either the plasma-derived or the recombinant product. But you could possibly use desmopressin for those type 2A and definitely for the type 3s, desmopressin most likely is not going to work. So definitely, the use of the von Willebrand plasma-derived or the von Willebrand concentrate.

Miguel Escobar:

Now, to the right, we have the antifibrinolytic therapy. As an example, we have here have tranexamic acid. It could be used three, four times a day. It could be used IV. It could be used by mouth. But we also have aminocaproic acid as well that could be used quite similar. So it is not unusual to have a dual kind of treatment. For example, a patient that undergoes wisdom teeth extraction, not uncommon that they get either desmopressin with tranexamic acid or aminocaproic acid, or depending on their phenotype, they can get a concentrate in addition to an antifibrinolytic as well.

Miguel Escobar:

Now, in regards to the desmopressin for von Willebrand, remember, desmopressin, the mechanism of action is just triggers the release of von Willebrand, and Factor VIII from the endothelium storage sites. Just remember that desmopressin could sometimes produce some symptoms to patients in terms of adverse events. You have to monitor sometimes their electrolyte, especially sodium, make sure because they can get hyponatremic, especially if they're drinking a lot of free water, or if they're using it quite frequent.

Miguel Escobar:

We usually, at least in our practice, we recommend using it maximum three times, probably over 72 hours or every other day. Sometimes, they can use it, especially with the females that are in their periods. We usually recommend doing a trial of desmopressin because not all the patients respond adequately. Those individuals that have levels between 30 and 50, what we call the low levels of von Willebrand, we assume they're all respond. But I usually gotten into the habit of doing a trial on everybody.

Miguel Escobar:

Now, in those individuals that have levels below 30, the true type 1s, I usually recommend doing trials in those individuals as well. And I'm sure you guys do something similar in your centers. Now, for those individuals that have the type 2s, they might not have a great response. And we definitely don't use it in the type 2Bs, mostly the type 2As. The response might be partial or much shorter response. So maybe for something very minor. But in my practice, I go straight usually to factor replacement. I usually don't like to waste time, and in definitely in the type 3s, I go straight to the factor replacement.

Robert Sidonio:

Yeah. That sounds great. So Jonathan, do you have insights? Obviously, we don't typically use it in type 2B. And there's no reason to use it in type 3. Do you typically undergo trials? I think a lot of us have done this. Until recently, the guidelines say you don't absolutely have to do it from 30 to 50. I think it's sort of been a habit for most of us to consider a trial.

Jonathan Roberts:

Yeah. I mean, I think, as you mentioned, the literature does suggest that, especially in mild type 1s or low VWF, it may not necessarily be required. However, I still have myself, probably just because the volume of patients that I treat, but I have some patients even with low VWF that do not respond well to desmopressin.

Jonathan Roberts:

The other caveats think about, as Miguel mentioned, the hyponatremia, certainly in the very young, my practice has been under two years of age, especially when very young children have the increased total body water and more difficult to limit fluids, we tend to not use it as often. We would go straight to concentrate as well.

Jonathan Roberts:

And also on the flip side, I also think about patients that may have cardiac risk factors. I personally get a little bit squeamish if I have a patient who's around 60 years of age, hypertension, maybe other cardiac risk factors.

Jonathan Roberts:

And so in that regard, I'll also go straight to concentrate. But certainly, I think that a DDAVP trial is an important thing to do. I, like Miguel, would likely not use it in variant von Willebrand disease. I think I may have used it in a few 2Ms where it's been efficacious in conjunction usually with, let's say, they have their wisdom teeth out. They may get some concentrate before a procedure. And then, they do intranasal DDAVP at home, post-op day one or something like that, along with antifibrinolytics.

Jonathan Roberts:

So it does offer that benefit of home therapy, especially in patients that aren't used to intravenous administration of concentrate or that may live a little bit farther away from the treatment center so they can't come and get infusions as readily.

Robert Sidonio:

Yeah. That sounds great. So in certain situations, obviously, like we just discussed, replacement therapy is the only option, or it could be a combination with desmopressin. Miguel, can you take us through this? And we had to list brand names here, obviously, because it's important for people understand the differences in half-life regulatory approval and, of course, the ratios.

Miguel Escobar:

Correct. Here in this table, we just have an example of some of the products that have been approved for use of in patients with von Willebrand disease. And as Robert was saying, you can say we got two categories. We got the plasma-derived that are virally inactivated, the first three products.

Miguel Escobar:

And then, we have a recombinant von Willebrand product that most recently got approved. And in those products that are plasma-derived, we see that they have both von Willebrand brand and they have Factor VIII. So they're going to have different ratios. And they're not the same. So you have to kind of get an idea what you're going to be using and what you want to use it for. But you see the ratios vary from some of them going from one to one and some of them going to even greater than two to one.

Miguel Escobar:

So you have to be aware that there are differences among these products. Now the half-life, again, is going to be somewhat variable. For example, of the half-level von Willebrand is going to be anywhere from eight hours to maybe about 15 hours, depending on the product. And the half level Factor VIII is going to be anywhere from 12 to probably 18 or 19 hours as well, which is here seen in the middle column.

Miguel Escobar:

Now, if you look at the last column on the right, the regulatory approval, you see that none of them have been approved for prophylaxis. It is something that more recently, I think, we're starting to do in our practice. But the majority of them are... been approved for surgery and certainly for on-demand for these products?

Miguel Escobar:

Now, in terms of what is the dosing, what target levels do you want to do, I mean, this is something that is going to be quite variable. And I think we learn by experience. Certainly, there are a lot of guidelines and ways maybe to do this. But I think in general, if we have a patient, let's say, if you want to treat him on-demand, meaning you're going to treat him when he has a bleed, if he's a mild-to-moderate bleed, if you're using a von Willebrand concentrate, you can give a dose anywhere from 20 to 40 units per kilo. What are the target levels you want to stay? Maybe a peak about 50, somewhere between 50 and 80 in the first day. And then, your trough level can be greater than 30 after day one.

Miguel Escobar:

If it's a mild-to-moderate bleed, most likely, you're going to treat that patient for one or two, maximum three days. Now, if it's a severe bleed, we definitely let to go with a higher dose, somewhere close to the 50 unit per kilo. When I have that big peak and for that initial bleed, probably it's going to be greater than a hundred, at least in the first day. And then, you can keep troughs around 50 or a little higher after day one.

Miguel Escobar:

And the treatment is going to vary depending on the severity of the bleed, anywhere from seven to 10 days, depending on what it is. Now, if you're going to take a patient for surgery, if it's a very uncomplicated procedure, maybe a single dose of 25 unit per kilo might be enough. you'll get a nice peak over 50. And you're done with that patient.

Miguel Escobar:

Now, if this a minor surgery, usually 30 to 60 unit per kilo, keeping peaks of maybe a little bit over 50 to 80 on day one, and then troughs of about 30. And again, the number of days is going to depend on the treatment. And if it's a major surgery, let's say, you're going to undergo a knee replacement or a big abdominal surgery or something like that, then, we go with a higher dose, 50 to 60 unit per kilo, having a high peak of a greater than a hundred on day one, and having those troughs at least about 50 for... I usually do at least for a couple of days. And the treatment again is going to depend on the type of surgery that individual undergoes.

Robert Sidonio:

So this is a great point. When we are taking care of patients, and certainly at our center when we're getting ready for a procedure, there are a lot of other health care members, members of our team that are involved in this coordinating it. And so I know our nursing and nurse practitioners and PAs often are really critical in making sure everything is done correctly. Everybody is emailed and plans are in place in the chart. Is that similar situation, Jonathan? Can you talk a little bit about the other members that I may have left out as well that help to make sure the coordination in- and outpatient?

Jonathan Roberts:

Yeah. It's absolutely critical. And I think that's an important reason to have a multidisciplinary care team at the treatment centers. So yes, our nurses are in close coordination with the pre-op and post-op nurses, with the surgical teams. We draft treatment letters with recommendations for, if it's inpatient management or also out for outpatient management. And we also, if a patient's going to be inpatient, we will follow levels of von Willebrand factor levels in the hospital setting.

Jonathan Roberts:

Usually, we tend to monitor von Willebrand factor and Factor VIII levels just depending on a surgery, for example, like say a woman with more severe von Willebrand disease that's going to deliver a baby. We would make sure that we had had a third trimester laboratory studies completed to see what arises and then coordinate with the OB team for appropriate treatment.

Jonathan Roberts:

And then, following those postpartum levels as they drop off and treat with antifibrinolytic at the same time. So it's definitely a lot of moving parts and I think making sure that our colleagues outside of hematology, whether it be ENT, OB/GYN, general surgery, dentists, et cetera, that they're aware of our treatment plans and that they're comfortable and keeping close communication with our team so that we can ensure the patient doesn't have any unexpected bleeding complications.

Robert Sidonio:

Let's talk about surgery now with tranexamic acid, also commonly known as Lysteda in the oral preparation. So we talked about minor procedures. And the guidelines really weighed in on this. And so they suggest, so not a strong one, that increasing the levels to greater than 50 with desmopressin or factor concentrates with the addition of tranexamic acid. So this makes sense, this is pretty much what most of us have thought about. And Dr. Escobar just mentioned about doing the desmopressin with factor concentrate.

Robert Sidonio:

Where it gets a little bit difficult and little bit different than some people's practices is they suggest using tranexamic acid alone over increasing levels greater than 50 for certain situations. So minor mucosal procedures. So maybe minor dental work, maybe not wisdom teeth extraction, but maybe a one cavity, mild bleeding phenotype patient, or in somebody that has levels greater than 30. So those in the 30 to 50% range, you could consider giving tranexamic acid alone for these minor procedures.

Robert Sidonio:

And certainly for those that are higher risk for thrombosis, avoiding those prolonged exposures, as mentioned before, in which the Factor VIII levels may be in excess of 150 for more than a few days. In these situations, you may want to reduce the extended use of tranexamic acid. So really trying to dial in the dosing where it's just high enough but not too high.

Robert Sidonio:

So one great thing about the guidelines is they really honed in on specific patient populations and scenarios, so heavy menstrual bleeding, pregnancy and aging. And, really, this has been very helpful because these are common scenarios. These are things I'm sure everybody that's listening has encountered. And we did try to address many of those. So let's take each one of those.

Robert Sidonio:

So first, heavy menstrual bleeding. Well, we decided we wanted to really define it in a way to make it straightforward and there's a definitions paper that accompanies these guidelines. And so, it's very simply menorrhagia or heavy menstrual bleeding: bleeding that lasts at least eight days, consistently soaking one or more pads or tampons every two hours on multiple days, requiring the use of more than one item, so a pad and a tampon at one time. Changing it if you have to get up in the middle of the night to change it, passing large clots or clots the size of a grape, and then having a score, if you see there listed, it's a semi-quantitative assessment bleeding assessment score of greater than 100.

Robert Sidonio:

And we put a link on here with a reference to a website that was involved in this one. And so, I'll pause here briefly just to see, we talked about it before, but at least half of my patients and probably my trainees feel like it's probably 75% of my patients. Heavy menstrual bleeding is extremely common. And it's a very common scenario in which we diagnose a patient. I'm assuming the same scenario with you, Miguel.

Miguel Escobar:

Yeah, absolutely. I think this is one of the most common certainly consults that we see, mostly in the outpatient, coming from primaries, coming from internists, coming from OBs. So definitely, I think is important. And it's something that sometimes we just don't feel comfortable talking about, asking our females, "How are your periods? How heavy they are?" You got to go into the details because most of them will tell you it's normal. But they don't know what really normal is because their mom was the same way or their sister is the same. They think it's normal and they're bleeding excessively. So I think this is very important.

Robert Sidonio:

Yeah. And Jonathan, I'm assuming you have trained your trainees to make sure you get that question, not just, are their periods heavy or not, because you may get a short answer.

Jonathan Roberts:

Yes. Absolutely. I mean, as is outlined here on the slide, we ask essentially all these questions and as yours and Miguel's experiences as well. I mean, this is profoundly common consult that, I mean multiple patients every week.

Jonathan Roberts:

The other thing I would say is even sometimes I'll be referred patients for iron deficiency. And then, turns out, no one's taken a good history. And then, I'll diagnose them with von Willebrand disease

Robert Sidonio:

[crosstalk] Exactly.

Jonathan Roberts:

And treat their iron deficiency. So it's another thing that should really go hand in hand for us taking care of women with excessive heavy menstrual bleeding, is to look for that iron deficiency because it's undertreated. And it causes symptoms. It causes morbidity, fatigue, and difficulty with school performance, et cetera. And it's really easy to treat. And oral and IV preparations are great. And so, I would say that's probably the largest impact I see. But it is very common in practice, especially among women who have von Willebrand disease.

Robert Sidonio:

Yes, definitely. So good advice. So let's move on, and see what the guidelines had to say about heavy menstrual bleeding and von Willebrand’s. Well, the panel suggests that either using a hormonal therapy, so that could be an IUD or combined oral contraceptive or potentially a progestin only, or tranexamic acid. And this is over desmopressin to treat women with von Willebrand in heavy periods.

Robert Sidonio:

And this is specifically in the population that is not interested in having children. So these are all your teenage patients or women that have no desire or do not wish to conceive at this time. So obviously, starting them on birth control pills would prevent pregnancy in most situations. And so, it makes sense. And so, it's really important that we consider hormonal therapies in this population. It may not work for everybody. But at least consider it or Lysteda or tranexamic acid.

Robert Sidonio:

And the panel suggests using tranexamic acid over desmopressin to treat those that wish to conceive. So, obviously, not using some hormonal method if they want to conceive. And it's really important to understand that prophylaxis could be used as well, case to case basis, certainly is a second-line therapy, or if patients aren't able to tolerate, or it's contraindicated to give hormonal therapy.

Robert Sidonio:

All right. So let's get onto the second case study now that we've discussed heavy menstrual bleeding here. So this is Shayna. She's a 25-year-old. And she is planning to conceive. She's been followed at your center since age 10 for heavy periods. And in that setting, a diagnosis of type 1 was made. She has heavy periods with flooding. They last more than seven days. Some easy bruising. And then, maybe a little bit of bleeding after her tonsillectomy, so pretty classic case. You can see her labs there. They're in the 30 to 50 range, mostly in the 40s. And certainly her PBAC score is elevated.

Robert Sidonio:

All right. So let's talk about the treatment of choice for managing her heavy periods. So that makes sense. So hormonal therapies wouldn't be an option. Certainly, tranexamic acid is the correct option ‘cause this was not going to have an effect on fertility in any way.

Robert Sidonio:

And generally, desmopressin we’ll talk about isn't recommended as the first line, certainly could be an option in some patients. So let's talk about those special populations. We talk about heavy menstrual bleeding. Now, let's talk about pregnancy and delivery. And this was addressed. There's very limited data. But what from they had, they are able to make reasonable suggestions here.

Robert Sidonio:

And so, during childbirth, women should have their levels of at least 50 immediately prior to delivery. And it's really important to understand that majority of women with mild type 1 will have levels over 50. And these levels should be maintained for three to seven days. Certainly, there are types, like type 2B, where it make it worse. Platelet count may delay.

Robert Sidonio:

And it's a really important to really surveil for delay post-tonsil … postpartum hemorrhage, sorry. These kind of things could interfere with breastfeeding, certainly cause significant anemia, exacerbate issues following delivery. And for women who are having neuraxial anesthesia, so epidurals during labor, they suggest targeting a level of 50 to 150, and then overusing a very high target level. So there doesn't seem to be any data. And certainly, if you're concerned or targeting closer to a hundred is totally reasonable. And it should be kept at least for six to 12 hours after it's removed.

Robert Sidonio:

And then to prevent postpartum hemorrhage, the panel suggests the use of TA over not using it at all in women with type 1 or low VWF. These are really good options to prevent postpartum hemorrhage. It's been extensively studied. And so, this is where there is pretty significant amount of data. And just very briefly, are these strategies that you typically are utilizing in your patients, it sounds mostly they're referring to milder patients, of course. We'll start with you, Miguel.

Miguel Escobar:

Yeah. This is pretty much what we do in our practice. Definitely, it is quite common. This lady is going into delivery. And you have to be prepared because many of them might be ready to... They are going to go vaginal, something happens, and they need to switch to a C-section.

Miguel Escobar:

So you need to make sure that you know what are your different plans in this scenario. But yeah, for example, for epidurals, my goal is usually above 80 or so to keep it. If it's not, I usually do not recommend doing epidurals. So it is not easy with the severe or some of the type 2s or very low type 1s. And we use actually a lot of tranexamic for our deliveries as well and factor replacement if needed.

Robert Sidonio:

Sure. Jonathan, briefly, are you using the same strategies generally for this?

Jonathan Roberts:

Yeah. We're using the same strategies. I think, like Miguel, I tend to target closer to a hundred. That's just my clinical practice.

Robert Sidonio:

Totally reasonable.

Jonathan Roberts:

Yeah. But think TXA using tranexamic postpartum is important. We usually use it for two weeks postpartum, which actually even outside of von Willebrand disease, there was a recent study in The New England Journal that showed that was beneficial for preventing postpartum bleeding in women.

Jonathan Roberts:

So we use that. And then, also I would just say another caveat is that delayed bleeding is, as levels reach back to baseline towards day seven postpartum, even if your patient doesn't have bleeding initially in the first day or two, still be mindful of monitoring their lochia and making sure that you're treating excessive bleeding as it develops.

Robert Sidonio:

All right. Great. So last slide, before we finish up this objective, so the other population was aging, probably the most controversial part here. And there may be some questions associated with this. The question like what we have with young children, can you age out of asthma? And we've wondered, can you age out of von Willebrand’s?

Robert Sidonio:

And certainly, there are patients that have low VWF that the levels become normal prior to me transitioning them to the adult clinic. And so, we did talk about this. The panel suggested reconsidering the diagnosis, as opposed to just removing it. So really assessing their bleeding risk. Certainly, patients with levels that have normalized, they have little-to-no bleeding. It's reasonable to do a course in which patients may have procedures or are managed without anything. And then, you may tell the patient to return if they have more bleeding symptoms, and certainly retain those the bleeding symptoms don't seem to get better.

Robert Sidonio:

And on the flip side, we talk about managing those as you get older. Just because you have von Willebrand doesn't mean you can't have cardiovascular disease. And they commented on this as well. Those with von Willebrand and CVD, who require treatment with antiplatelet or anticoagulation therapy, the panel does suggest giving that needed antiplatelet or anticoagulant therapy over not doing anything, and assuming their von Willebrand’s will protect them. Obviously, reassessing multiple times, and then really being very careful about desmopressin. This is a population, as Jonathan mentioned, where you don't want to increase the risk of thrombosis.

Robert Sidonio:

So let's move on to our third object, probably one of the more interesting things. And we'll talk about long-term prophylaxis. And it's really important that this is off label. But there's some merging evidence. And I think it's reasonable to talk about what we're doing in clinical practice. So we're going to talk about evaluating the evidence for long-term prophylaxis in patients with von Willebrand’s.

Robert Sidonio:

And so, I think this is where we're all going to talk a little bit. I'll make a few comments. And certainly, I'll let you guys jump in. But you can see here, we always are balancing the benefits versus the barriers. Certainly in von Willebrand’s, as you can see here on the timeline, there have been significant innovations in hemophilia. And particularly in the last 15 years, there's just been explosion of new therapies.

Robert Sidonio:

And there has been a recombinant VWF concentrate recently. And so, there hasn't been as much innovation. Certainly, it may be because a lot of patients are not on prophylaxis. And a lot of patients may not have good venous access. They may not have the skills to do prophylaxis. And they may not see that there's a benefit. So I'll let you start out, Miguel. This is something we're always talking about. And it's certainly evolved over, I'm sure, your career as well.

Miguel Escobar:

Yeah, I think, as you said, we can probably learn a lot from hemophilia. In hemophilia, we've been doing prophylaxis, I don't know, for many decades now. And certainly, we know it works. So I think in von Willebrand, we've been, like you said, quite maybe slow to take off and be aggressive in their management because, I can tell you, I have women which they get, we can call, prophylaxis just during their periods and they do great. They're really happy now knowing that their bleeds can be controlled.

Miguel Escobar:

Sometimes, they don't respond to the hormone, to the antifibrinolytics. And just by giving prophylaxis three days of their period, it's a huge difference. And I think once you start, prophylaxis certainly comes all the different barriers of a, I guess, you can put it as a chronic treatment that we can see here on the table.

Robert Sidonio:

It's not for every about it. Yeah.

Miguel Escobar:

But I think you have to take every patient individually and make an assessment and see what their goals are, and then go from there and offer the different treatment regimens that we have available, which one of them is prophylaxis.

Robert Sidonio:

Sure. Jonathan, do want to add anything about prophylaxis? Obviously, this is an emerging topic.

Jonathan Roberts:

Sure. Yeah. I think a lot of it too in von Willebrand disease is the patient culture because for many decades now in hemophilia, that's been the culture, that prophylaxis is the standard of care. And I think that there's a couple things in von Willebrand disease. There's not as many patients or I should say there's more patients that are not diagnosed. And so, they may come to us later in life.

Jonathan Roberts:

So doing something like intravenous access can be a bit of a personal barrier in wanting to do something like prophylaxis. But I think also it's probably the clinicians that just haven't brought it to the forefront, like some of our European colleagues that I think have been a much more adoptive of von Willebrand prophylaxis than we have here in the U.S. So I think it's something that I have, in the recent years, like maybe the last five years, brought up earlier with my patients, letting them know that there is something we can do besides just tranexamic acid or just the DDAVP at home that may not be as efficacious.

Jonathan Roberts:

And like Miguel said, I also have patients that, for their periods, they come in. I've had some that are having a particularly difficult time with epistaxis that we do prophylaxis. And then, certainly, some of my more severe von Willebrand disease patients with gastrointestinal bleeding, joint bleeding, like in hemophilia. And those patients have been on prophylaxis for many years. So I think it's something that we need to raise awareness from a clinician standpoint as well, and then help to shape that patient culture to know that, hey, this is something that is available and can be beneficial in helping you live a life with reduced bleeding.

Robert Sidonio:

Certainly. So to that end, the guidelines did, the panel decided to weigh in on prophylaxis. And it seems like a fairly benign statement: “In patients with VWD with a history of severe and frequent bleeds, the panel suggests using long-term prophylaxis over not doing prophylaxis, and then periodically assessing bleeding symptoms.”

Robert Sidonio:

But that statement was actually pretty good. If you look at their original guidelines, they don't even talk about the role of long-term prophylaxis, when they use the term prophylaxis to typically referring to treatment before a bleed. I think it's really important to point out what's not in the statement. So, you don't see subtypes listed here. So, is it just for severe type 1 and type 3?

Robert Sidonio:

It really focuses on the bleeding symptoms and the recurrence of them in an effort to improve quality of life. And so, to that end, Jonathan alluded to this, we do need to do more studies in this. There's been a longstanding history. Hemophilia has done great studies over the years, as Miguel alluded to. So we're going to talk about two recent phase three clinical trials that give us some data on long-term prophylaxis. And, Miguel, why don't you start us off with the first one that focused on recombinant VWF?

Miguel Escobar:

This is a phase three, prospective, open-label, non-randomized, but is a multi-centered study, looking at prophylaxis where a specific product was a recombinant von Willebrand factor that was used in patients with severe von Willebrand disease. And they have very strict criteria.

Miguel Escobar:

And the objective of this study was to look at efficacy and safety of this product using prophylaxis in adults again. And you can see here to the left, we got, they were able to get historical information from those individuals. There were a group that were on-demand and then a group that was on prophylaxis with a plasma-derived product, a switch, we'd called a switch-arm group. You have here total of 23 patients.

Miguel Escobar:

Now if we look to the left, the time period, you see those historical numbers of spontaneous bleeding events, it's either quite high. And the prior on-demand 200 and the switch arm 50. Now, when we looked at on-study while receiving prophylaxis with the recombinant von Willebrand, we see the number treated spontaneous bleeding events and the on-demand was nine, and the switch arm was 18.

Miguel Escobar:

Now, overall, if we look at the comparison, on-study versus historical, what is that percentage of change? We see that in the prior on-demand. There was a 91.5 reduction in bleeds. And in the switch arm, there's a 45% reduction.

Miguel Escobar:

Now, with secondary efficacy analysis, they looked at the spontaneous ABR intrapatient comparison. We can see here on the right, the two graphs, the spontaneous ABR reduction success for all types of von Willebrand, the on-demand group was 92%. On the type 3s, it's 90%. And then, for the ABRs, continuous ABR, and the prior prophylaxis was for all types, 90% and for the type 3, 88%.

Miguel Escobar:

So as conclusions from this study, you can see that recombinant von Willebrand prophylaxis was quite effective in reducing spontaneous ABR in patients that were previously treated on-demand. And they were on plasma-derived von Willebrand that got switched to a recombinant product.

Miguel Escobar:

Now, in regards to the individuals that were on the prophylaxis previously, they were able to maintain the same level of hemostasis control in those individuals when they compare them to the ones that switch. But definitely, there was a huge difference from the on-demand group.

Robert Sidonio:

So, yeah. So great. So it showed that it was efficacious that there were no serious adverse events and no inhibitors [crosstalk].

Miguel Escobar:

Right. No, there were no serious adverse events. No thrombosis. No antibodies that we're always concerned about.

Robert Sidonio:

Yeah. So great. So not large numbers. But these studies are very difficult to conduct for sure. So the next trial was done in Europe. And I'll let Jonathan walk us through this poster.

Jonathan Roberts:

Sure. So this is phase three study looking at secondary long-term prophylaxis versus on-demand treatment, this time using plasma-derived VWF Factor VIII concentrate in severe von Willebrand disease. And really, their objective was to evaluate if prophylaxis with concentrate was effective in preventing spontaneous bleeding in patients with severe VWD that was unresponsive to DDAVP when compared to on-demand.

Jonathan Roberts:

And so you can see this was also 12 month, international, multi-center, randomized, open-label trial. And you can see, again, the numbers here very small in on-demand versus prophylaxis, a majority type of bleeding, like we've been talking today, mucosal bleeding, joint and muscle bleeding, and more severe, and also some gastrointestinal bleeding.

Jonathan Roberts:

And you can see the number of incidents, the rate of bleeding episodes during the study were organized in these treatment groups. Again, it's important to note that there are no clinically significant AEs attributed to the study medication throughout this.

Jonathan Roberts:

And if you look over at the right side of the slide, you can look at the on-demand versus prophylaxis that the probability of remaining free of a first spontaneous bleeding episode was improved for those that were on prophylaxis. So really, this study's conclusion was that the prophylactic use of von Willebrand factor and Factor VIII concentrate appeared to be as associated with a lower risk and frequency of bleeding episodes in severe von Willebrand patients. And again, these were those that were unresponsive to DDAVP although more data is needed for gastrointestinal bleeding based on this study.

Jonathan Roberts:

So again, just another publication, giving us more to discuss with patients when considering prophylaxis. I mean, I think in my clinical practice, whenever I bring up studies, picture paints a thousand words. And so sometimes, reviewing some of the data we have, emerging data, for prophylaxis and in VWD can be beneficial when making the argument that it may be efficacious for the patient that's having bleeding problems in front of us.

Robert Sidonio:

Yeah. That's great. So two great trials. And let's talk about one more trial here that's ongoing. So this is the ATHN 9 study. It's being conducted by the American Thrombosis and Hemostasis Network. I'm one of the PIs. And Jonathan's also involved in the study as well as my co-PI, Angela Weyand. And this run really is it's a different type of study. It's a longitudinal observational study.

Robert Sidonio:

And really, the focus is of looking at the safety of these treatment regimens, specifically for those with what we're calling clinically severe von Willebrand. And there'll be an extra focus on prophylaxis. And you can see here there's about 80 or so patients that have been enrolled. The majority are Caucasian as expected with this disorder. And we have people as young as newborns and as old as 75-plus years of age.

Robert Sidonio:

We currently have about 28 on what we're calling continuous prophylaxis, and eight of them that are on menstrual bleeding prophylaxis as Miguel alluded to before. And you can see the dosing there for recombinant. It looks like it's about twice a week and as expected for plasma-derived, because, traditionally, the regimens have been about two to three times a week.

Robert Sidonio:

And so, since we have very little data, we're really just going on what we've seen on the clinical trials. So this study's got a few more years before it's left completed, but more studies coming soon. So don't want to minimize the role. But obviously, it's really, really important that we talk about the team approach. We've already talked about it a few times in this. It's a patient-centered approach. The patient's in the middle here. We have a number of people involved, nurses, pharmacists, gynecologists, sometimes primary care providers.

Robert Sidonio:

We have physical therapists, social workers, and of course the hematologist nurse practitioners and PA. So I know when we have our clinic in our children's hospital, it's an army of people that are taking over the clinic room. And so, I'm assuming it's the same. And I think, we certainly have figured this out in this disease state compared to others. I'm assuming it's the same for you, Miguel. I know I visited your center in the past.

Miguel Escobar:

Yeah. I mean I cannot make enough emphasis on this part because I think that you could have your hospital, the best surgeon, all the products, your laboratory. But if you don't have the right team, the possibility of that success I think is not great. And that's what is so important to be able to, these patients get seen with all the different specialties, because, I mean, we have learned from hemophilia already for years doing this. And that's the best model, I think, right now that really take us to some success.

Robert Sidonio:

And Jonathan, I know you have a similar approach and feeling about this team-based approach.

Jonathan Roberts:

Yeah. Absolutely. And I think we've even gotten to the point where we're, like you mentioned, heavy menstrual bleeding is a very large population of patients. So we have, like I know you do as well, women's focus clinics where we have women's health care providers alongside our comprehensive care team, physical therapy, pelvic floor dysfunction, many other things that are taken care of comprehensively for the patient. So yes, the thing is you need to have a great degree of preparedness in managing complications that can arise. So yes, a multidisciplinary approach is essential.

Robert Sidonio:

And that's just the coincidence that the hematologist looks like, Dr. Escobar, here. So, moving up, we're finishing this slides up. So just as a summary, you should use validated clinical assessments, laboratory tests, to accurately recognize, screen, refer, and diagnose patients with a suspected bleeding disorder. It may not always be von Willebrand’s. You should be thinking about it, of course. Optimizing patient outcomes by proactively incorporating a team-based approach, focusing on the individualized care of that patient.

Robert Sidonio:

Same thing we do with hemophilia. We should do the same for von Willebrand’s, and certainly using the guidelines. If you read the guidelines, it's very clear, this is not the standard of care. But there are strategies that you should consider to accurately identify patients are candidates for long-term prophylaxis, inpatients while trials are being currently being conducted. All right.

Robert Sidonio:

So let's take those questions. Let me just pull them up here. So the first one here, and I'll just call somebody out on here, drug shortages are frustratingly common, believe me. In the pharmacy world, how should you handle a shortage of intranasal DDAVP. Are injectables my only option? I know Miguel mentioned he isn't using a subq DDAVP. Do you want to weigh in on this one, Jonathan?

Jonathan Roberts:

Yeah, I mean, I think most of our patients, we have switched to using von Willebrand factor concentrate. I know there are some providers and patients that are very partial to DDAVP. But our strategy has really been just to switch to VWF concentrate. And certainly for times when you need precise measurement, even within the same patient, the DDAVP response can be variable. So we tend to have used concentrate. I think there through various mechanisms, the intranasal DDAVP is becoming available. So hopefully that will be over shortly. I know European colleagues have used subq quite a bit. It's I think, limited in practice here in the U.S.

Jonathan Roberts:

And certainly, it can be used also in an inpatient setting using like the IV form. But I don't know. In my mind, I use VWF concentrate if I'm going to give an IV medication.

Robert Sidonio:

Yeah. And certainly those are ones that it's difficult to give subq. And so, let's take some more questions here. The VWF concentrate product's different in ratio. And so which one do you prefer? As a pharmacist, I would prefer the one that has a one-to-one ratio that may limit prescribing years. We're not always the ones prescribing it. Is there a benefit or not a benefit of having the two to one? So a couple of questions there. Miguel, do you want to start us out on there? Do you have a preference, or I'll let you answer that.

Miguel Escobar:

I mean, I think there are a couple of things here. One is certainly what product is available in your institution because sometimes you don't have control of that. But if you do, I think a lot has to do with what their baseline levels are of that patient. If the von Willebrand levels are quite low, I might prefer a high ratio von Willebrand to Factor VIII.

Miguel Escobar:

I mean, having in mind also that certainly you don't want to keep the Factor VIII levels too high as well. So I guess it all depends on what that baseline level is and what you're going to use it for. If it's a one-time dose, probably I will prefer to have, if it's low von Willebrand, to have the highest amount of von Willebrand and then if you can also figure out how you're going to dose it, you're going to dose it based on the one von Willebrand level. You're going to dose it based on the Factor VIII amount. So we usually go with the lowest, whatever it is. And that's how the way we dose it.

Robert Sidonio:

Yeah. And we certainly, we lean toward using the one-to-one ratio since it's a little closer to what's normally in humans. But certainly, what's available on your Medicaid and what's available in formulary, that's what you're going to use for most situations. And I don't think you're going to be wrong by choosing one over the other. But you really need to understand that there's a difference. Jonathan, anything to add to that?

Jonathan Roberts:

Yeah. I mean, I think I'm comfortable with all of the products that are on the market for most minor bleeds. There are some nuances that I think about with repetitive dosing, like a major surgery where I don't want to drive Factor VIII levels really, really high. And then, maybe using a product where I can specifically dose von Willebrand factor and not give concomitant Factor VIII or less concomitant Factor VIII can be beneficial. But all these products are very efficacious.

Jonathan Roberts:

I mean, if you look at further, which we didn't really talk about, there is sometimes some differentiation in the multimer size of the different products in the final preparation. So I think the bottom line is whatever is efficacious in your patient. So a majority of patients will be well treated with any of these products.

Robert Sidonio:

Sure. All right, here's a great question. It says, "Hello. I appreciate knowing what testing should I do as a GYN nurse practitioner. What should prompt me to refer to hematology?" So is there a certain testing that you recommend being done, Jonathan, locally versus what should be waited for to do, or should just be a prompt referral based on bleeding history?

Jonathan Roberts:

Yeah. That's a great question. I think it's going to vary depending on where you're located and what availability you have in your local lab. So if you're in a place that has to send out all von Willebrand factor studies, then, my advice would be just to refer to your center, because if you have to send out to one of the big reference labs, I mean, I think as all three of us on this presentation are aware, there’s a lot that can go wrong in the transportation of the sample. And you're going to get an invalid assay.

Jonathan Roberts:

So we're going to repeat it anyway. So I think the best thing to do is to refer to a coagulation specialist. Now, certainly, there could be things as we talked about besides von Willebrand disease that could cause bleeding too. So if you can get a quick coag profile, a CBC, check of platelet count, make sure they don't have thrombocytopenia, maybe even depending on your institution, a PFA, platelet function analysis, a really quick and dirty screen of platelet function. Those are things that you can do. But I think the most important thing is if this has reached your threshold where you have a positive bleeding assessment tool score that then you should refer to a hematologist.

Robert Sidonio:

The weather's totally cool in Houston. You never have those problems with transporting in Houston, I'm assuming. Miguel, anything to add?

Miguel Escobar:

No. Believe me. I know. I fully agree with Jonathan, especially this big commercial laboratory. There's so much variability, so definitely not. Now one of the, I think, important points here is that a lot of times we see that as a screen and they do PT/PTTs. And I don't think they're really good enough to tell you the truth for von Willebrand or not. So, don't think that because a PT/PTT is normal and the patient has bleeding symptoms, everything is normal.

Miguel Escobar:

Now, if you want to do the testing, then go ahead and do, at least, the von Willebrand basic. If not, then go ahead and refer to one of the hematology centers because PT/PTT is not sensitive enough to be able to pick up some of the von Willebrand disease.

Robert Sidonio:

Oh, certainly. And the majority will have a normal PTT. Yeah. that's a great point, Miguel. Yeah. So, all right. You'll see the next question. So this one's a tough one. At what point do you consider bleeds to be severe enough to warrant VWF prophylaxis? Is this based on clinical presentation or just labs or both? You want to start that one off, Jonathan? That's a good one.

Jonathan Roberts:

Sure. Yeah. That is the million-dollar question. I think it really depends on the patient and how much is the bleeding affecting their life, right?

Robert Sidonio:

Yeah.

Jonathan Roberts:

So if you have a patient that say, we've talked a lot about heavy menstrual bleeding, if you've tried antifibrinolytics, maybe hormone therapy with antifibrinolytics hasn't worked, or maybe there's a reason, I have some patients that just say, "I don't want hormonal therapy," or they're wanting to conceive. And so, that's not indicated. So I think if you've done, you know they're iron deficient, you've replaced it. Maybe, you've had to do it a few times. They’re refractory to kind of first-phase therapy, which I think a lot of us think are antifibrinolytics. Then, I think it's worth having that conversation of, “This is something we can do logistically for you. How would that work out?”

Jonathan Roberts:

I have some even young girls that are in their teens that are adopted intravenous administration of von Willebrand factor concentrates very readily. I think a lot of it has to do with individual patient and kind of their home support system and their personal beliefs and goals.

Jonathan Roberts:

So it’s really, it kind of gets into the art of medicine, I think. But my opinion is, if it's impacting their daily life, even if it's not every day, but certainly heavy menstrual bleeding or in the wintertime, they have really bad nose bleeds, that they're missing school and work, well then, as a physician, we have treatments to help. And that's when you should really bring up the conversation of prophylaxis. Certainly GI bleeding, joint bleeding, that's a no brainer. You're going to put those patients on prophylaxis. But some of the other more nuanced, I think, is a discussion with the patient.

Robert Sidonio:

Sure. Yeah. Recurrent joint bleeding, that makes sense. But some of them are tougher. And sometimes, patients may not accept that jump. Miguel, anything to add to that?

Miguel Escobar:

No. I mean, I think that the good thing is that we got options, right, and that those are the ones you need to put on the table. I usually tell my patients, "Try for three months and you come back and tell me if you see a difference or not." And most of the time, they'll say, "Wow, I can function now those five days over my month very well compared to what I was doing." So definitely, I think it's important.

Robert Sidonio:

All right. We have a little bit more time here. So does on-demands mean only treatment of active bleeds? What about treatment before potentially risky activities, like maybe hiking a mountain, riding, maybe mountain bike riding, things like that. What are your considerations for that? You want to start that out, Jonathan?

Jonathan Roberts:

Oh, sure. I would think of it similarly to the advice I give my patients with hemophilia or other severe bleeding disorders, especially if they've done that activity and had a bleed, then, no question. They need to do that. Are they going to go hiking in the mountains for a month and they're going to be away from any type of treatment care facility? Well at least being trained, if they have severe bleeding, being trained, how to administer an emergency dose would be pertinent in that scenario.

Jonathan Roberts:

I think it really goes to the type of bleeding that you have. So I have some patients, even we talked about levels of von Willebrand disease and variance and type 2, 3, et cetera. But there are some patients with mildly low levels that bleed a lot more than others. So it really goes to what type of bleeding would you anticipate doing that type of activity.

Jonathan Roberts:

If it's just mucosal bleeding and you've been mountain biking before, and you probably have never had bleeding, then, you probably don't necessarily need to prophylaxis before that. But it really comes down to the type of bleeding you in particular experience. And what are the other players? And how you could get emergent treatment if the need would arise?

Robert Sidonio:

So I'm going to go through a couple quick ones. And we'll just do kind of lightning round questions here. So what about pre-treatment to patients before vaccinations? We'll start with type 1 von Willebrand’s brands versus severe. Miguel. Any, anything that you recommend for vaccinations like a COVID vaccine, for example?

Miguel Escobar:

Yeah. I think that it all depends on the levels.

Robert Sidonio:

Sure.

Miguel Escobar:

Really, patients have probably levels above 10%. There's usually not an issue I'll say with vaccinations. IM vaccinations should be fine. Now, the COVID vaccine, sure, there's no contraindication for these patients. Actually, they're using a pretty small needle. So I wouldn't have any issue. Maybe that's severe von Willebrand, if we know that it has very frequent bleeds, you might consider doing maybe a low dose of concentrate before. But otherwise, I don't see an issue.

Robert Sidonio:

All right, Jonathan, let me give you a quick one here. If somebody has type 1, the parent probably does, should I start with just the antigen or should I order the whole screening lab? So what do you think?

Jonathan Roberts:

Yeah. Good question. I still would do a Factor VIII antigen in an activity. The reason being too, there can be compound heterozygote. Mom or Dad could have one defect, and the child could inherit another one from the other parent. So I would tend to still do it.

Robert Sidonio:

All right. And so, yeah. Miguel, I'm going to give you the last one. And then we're going to close it out here. We have lots of questions. Sorry, we couldn't get to all of them. So this person works in emergency room. They don't have access to full medical record. What would you recommend if having in the emergency room for traumas if you know they have von Willebrand’s but you don't know the type? If you're going to pick something to have available as sort of first-line therapy, what would you recommend? So that's a great question.

Miguel Escobar:

I mean, we've talked a lot about tranexamic acid, as being actually multiple trials and trauma and OB, so it's a drug that all the ERs have available. I wouldn't hesitate to use it in somebody that comes in with a possible history of von Willebrand actively bleeding, I don't think is going to really hurt that individual. So at least, you can get more information what type of von Willebrand, because I mean, this is a common kind of scenario.

Miguel Escobar:

A lot of patients come in, oh, there's a history of von Willebrand. And we have no idea what kind it is. Ideally would for them to come with some sort of bracelet or some ID that says what type it is. But I think tranexamic could be something that could be used very fast. And everybody has it at least to start with [crosstalk 01:23:17]

Robert Sidonio:

Sure. Big bolus dose. Yup.

Miguel Escobar:

Yup.

Robert Sidonio:

You can visit the CME Outfitters Hematology and Virtual Education hubs for additional activities as well as resources, animation, and patient education. And finally, to receive CME credit for today's program, you have to complete the post-test and evaluation. Then, you'll be able to download and print your certificate immediately upon completion. Thank you for joining us. Be safe, and take care. Thank you.