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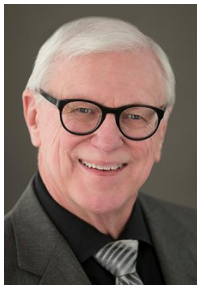
**Transcript – Coag Conversation**

# 100 Years of Von Willebrand Disease…and Upcoming Advances

## Conversation # 2 Von Willebrand Disease Subgroups and Laboratory Testing for Diagnosis

**Featuring:**



**Moderator**
**Mr. George Fritsma, MS MLS**
**Laboratory Scientist**

**Guest**
**Robert F. Sidonio, Jr., MD, MSc**
**Medical Director, Clinical Research Office, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Professor of Pediatrics, Emory University School of Medicine**

**Mr. Fritsma:** Hello, I'm George Fritsma, proprietor of the Fritsma Factor, Your Interactive Hemostasis Resource, introducing our presentation, 100 Years of Von Willebrand Disease.

We welcome Dr. Robert Sidonio, pediatric hematologist and oncologist. Dr. Sidonio is the Medical Director of the Clinical Research Office at the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta and is a Professor of Pediatrics at Emory University School of Medicine. Dr. Sidonio graduated from the medical school of the University of Alabama at Birmingham, completed his pediatric residency at the University of Louisville and his clinical and research fellowship at the University of Pittsburgh. Dr. Sidonio's clinical interests are in the management of pediatric hemophilia patients with inhibitors, women and girls with bleeding disorders and in patients with von Willebrand disease.
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This is our Conversation # 2. And in this conversation, we will be talking about the von Willebrand disease subgroups and the labs [laboratory testing for diagnosis]. Just to begin with Dr. Sidonio, how does von Willebrand factor stop bleeding?

**Dr. Sidonio:** Yes, it's a great question. So there's a couple of ways that it does this. And so it's really important for platelet adhesion. So, when there's damage to the endothelium, this is where VWF is really critical. You have platelets that are recruited and it's important for that platelet adhesion. And secondarily, it also protects factor VIII from degradation.

When they came up with new products for hemophilia, they tried to decouple it from VWF, and we always worried that it was going to interfere with hemostasis when it comes to VWF delivering it to the site. But it doesn't seem to matter as much. And I know we'll talk a little bit about the role of factor VIII in von Willebrand disease as well. But those are the two main functions It also provides some collagen binding as well when it comes to hemostasis.

So, usually when I describe it to my patients, we always talk about, when you're building a house, you can have all the components there, the bricks there, the basement. But, if you don't have a really good mortar, all it's going to take is a little bit like an earthquake or really stiff breeze, and it's just going to knock the whole thing over. And so you need that base to form because coagulation occurs on top of the platelet surface, as you know, in the phospholipid bilayer.

And if you don't have that platelet adhesion, you don't have that strong bond, that clot is going to be a weak clot or it's going to fall off or become shed off prematurely.

**Mr. Fritsma:** Is that true both in arteries, veins, and in capillaries?

**Dr. Sidonio:** Yes, it's the same in there. And the reason it's difficult for us to measure is that you have to measure VWF. We don't have really good ways of measuring it under high flow situations. And so we know that it's important in that situation as well.

You know, people look at, it's interesting when you look at other groups of physicians that order VWF. They care about it as a marker in cardiovascular disease. Our rheumatology colleagues use it as an inflammatory marker. So when they do a workup, for example, for lupus or any autoimmune disorder, they're actually sending VWF. We've actually gotten patients diagnosed because they sent a VWF level on somebody with dermatomyositis who may or not have had bleeding symptoms.

So, we've actually picked up patients that way as well. So, it does have some other roles with regards to inflammation, probably some other non-hemostatic roles that we're not aware of. It seems to be important that some of the knockout mice when it comes to infection and things like that. And so there probably are other roles. There are probably more minor roles, but certainly platelet adhesion is probably the most important.

**Mr. Fritsma:** Well, let's look at one of the main issues with the diagnosis of von Willebrand disease, and that is how do we… First of all, what are the types, subtypes, and variants of von Willebrand disease? And then we'll go into how we determine which is which.

**Dr. Sidonio:** Yes. So, right now, and there are always evolving different other subtypes, and we have discussions about these all the time. But right now, there are six main types:

So, there's Type 1, von Willebrand disease, where it's typically a quantitative deficiency. There's one subgroup Type, I guess, so you could say that there's seven types called platelets, Vicenza Type or platelet Type 1C von Willebrand disease.

And so, in von Willebrand Type 1C, there's an accelerated clearance of VWF. And so it looks like there's a deficiency, but it's not because it's not being produced, it's being sort of cleared prematurely.

And then there's other subtypes. So, there's Type 3. It's also a quantitative deficiency. But there's absolutely no VWF produced. And so that's where you have absolutely no VWF activity, antigen, or factor VIII. Since it is, as mentioned before, it protects factor VIII from premature degradation.

Because there's no VWF, the half-life of factor VIII goes down to only a few hours compared to 8 to 14 hours or so when there is VWF. Then there's multiple different subtypes.

There's a Type 2A in which there's a defect, and all of these Type 2s have a significantly lower function activity compared to antigen, so it's more of a qualitative defect. There's a loss of the high molecular weight and intermediate weight multimers in addition to the diagnostic labs.

Type 2B is von Willebrand is an interesting one because there's also loss of high molecular weight multimers. But many patients often present either with normal, low normal, or thrombocytopenia, and it can masquerade as ITP if you're not careful. And there's some specialized testing that can help diagnose that.

And then Type 2M von Willebrand has normal multimer distribution. but has a qualitative defect in which the functional assay is lower than the antigen.

And then the other type that's really interesting is Type 2N with the N standing for Normandy. It's a really interesting defect. And so the problem is not in the typical VWF, but it's in the function, it's in the factor VIII binding. And so this is the only type in which the factor VIII level is typically lower than the VWF level.

And so you can guess that many patients are incorrectly diagnosed with mild hemophilia versus Type 2N von Willebrand disease.

And there was, CDC had done a study years ago where they were doing genetic testing and they figured out that some of these mild hemophiliacs were actually Type 2N von Willebrand patients. And so, you need two different genetic variants to have a defect.

The most common is Type 1/Type 2N, and so that one's difficult to diagnose. You need genetic testing because it's not going to fit perfectly in the textbook description. But the Type 2N/Type 2N. And sometimes we actually pick up these Type 2N carriers. They might have a borderline low factor VIII and everything else is normal. The only real way of diagnosing them is genetic testing.

**Mr. Fritsma:** Now, differentiating among the various types and subtypes, What's the first thing you do if you're just suspecting von Willebrand disease? What's the first test that you do and what's the methodology for that?

**Dr. Sidonio**: Yes, so I mean the first set of labs when you see a patient with bleeding symptoms, even take a step back, is you're obviously going to get a CBC and then you're going to do some of the common coagulation studies, so PT, aPTT, fibrinogen, and then thrombin time. And in most of the cases, those are all normal, right? Except for the Type 2B von Willebrand, you might have a low platelet count.

And then if you have a really low factor VIII level, depending on your labs, you know, that varies a lot. If your factor VIII is above 40%, you're probably going to have a normal PTT and you always will have a normal thrombin time and PT. And so we always do that first.

And then our first tier labs, which are similar to what other, I think, centers do, is we've created a profile at our center. And so I think everybody always gets the VWF antigen. And that's typically an immunologic assay. It's a pretty reliable assay. It's one of those assays where I feel like just about anybody, any lab could do this assay. And typically it's measured through a spectrophotometer and with the latex beads and anti-VWF antibodies. So that one's usually pretty straightforward.

You have to measure the factor VIII. That can either be one stage or chromogenic, just depending. It's normal in most of the patients with von Willebrand, but they will be low in some Type 2, and then certainly in Type 3, and then the rare Type I that are really severe as well.

And then you need a functional assay, and that's where it gets a little bit complicated. And so in the guidelines, we recommended moving away from the ristocetin-based cofactor assay, so the ristocetin cofactor assay. And that's mainly because the coefficient of variation is so wide on that assay. And so, for example, I can send it and get a lab value of 40, and then I can send it again and get 55, and that's actually acceptable, right? And also, a lot of the assays are sort of homegrown in each lab.

And so, of course, you're going to get some variation from center to center. And then on top of that, a significant number of African-American and Hispanic patients will have a polymorphism. in which it doesn't

bind ristocetin adequately. So it's a problem with the assay, not a problem with von Willebrand disease, and they'll have a falsely low ristocetin assay.

Everything else will be stone cold normal except for that one. So, mostly in the U.S., we've moved away from that, not everywhere. But most of the large centers have moved to the GP1bM activity assay and that one is a non-ristocetin-based assay, and it has this latex bead, and it has a gain-of-function mutation. And so as many of your listeners know, that you can't put VWF and you can't expect to measure it without inducing it. It just doesn't measure in static conditions.

So, that's when they discovered that ristocetin could be used. This one uses a gain-of-function mutation, so it'll bind spontaneous to it, similar to Type 2B von Willebrand disease. And so that's the typical functional assay. We also recommend sending the collagen binding assay. There are a number of patients that have just a low collagen binding.

I think we have three or four patients, that's the only assay in which is low. And if we didn't do that assay, we would have just said, you don't have von Willebrand, see you later. And so I think that's an important assay. It's also helpful because we don't always do the multimer analysis. If anybody's ever done multimer analysis, it's a pain in the 'butt'. It's very laborious. I don't think anybody enjoys doing it

And so the collagen binding, if you have a normal collagen binding, your multimer distribution is likely normal. And so we usually send that upfront. So, factor VIII, VWF functional assay, VWF antigen, collagen binding. And then we do additional testing later. We always keep a saved specimen because I don't like, children don't like to be stuck. I know it's hard to believe. So, adults probably don't like it either. And so that way I can, if I get a positive result where it's deficient, I can send some of those other assays off that have been frozen.

**Mr. Fritsma:** Okay. So the glycoprotein 1bM That's the one that does not use ristocetin, is that correct?

**Dr. Sidonio**: Yes, the GP1bM assay is ristocetin independent, which makes it desirable to make sure you're not missing those or you're correctly identifying those patients just because of all the issues. It's pretty good. I feel like we've been using it for the last few years. And you know, it's oftentimes an ELISA, just depends on where you're getting it from, but it's commercially available now.

For a while, we only could send it to Wisconsin to have it done. But right now, we can do it now on our platform and at our center, which makes it nice because they can get it back a lot faster.

**Mr. Fritsma:** And is that one FDA cleared?

**Dr. Sidonio:** I believe that is FDA cleared for this because we're using it in our assay. I think a lot of these assays got caught up with patent rights, you know, and so this caused a lot of delays in us getting any of these assays. And I know we often had to send it, which is fine to have to send off, but we have limited access to any of the other assays. There's an antibody assay, there's a GP1bR assay, which we don't have access to. Those are largely done in Europe. And so some of this is the commercial companies, some of this is the patents from the people that designed it.

And on my end, I just want those assays. I just want to get to be able to send those assays easily from our lab, which, but we can do the GP1bM assay at our center. So we're happy about that.

**Mr. Fritsma:** Yes, that's good. And they are. That's the one [GP1bR] that requires ristocetin.

**Dr. Sidonio**: It does require ristocetin. So probably not as useful in the United States with a diverse population, with the issue with the ristocetin in general. So, the guidelines want us to move past those at least to the GP1b assays. And GP1bM is probably, I wouldn't say it's the one endorsed, but I think it's probably mostly preferred in the United States.

**Mr. Fritsma:** I have to confess something to you. I did a survey last month on Fritsma Factor, something we call the, well, a monthly survey. So, I just asked, and of course, there's no sampling effort here. It's just whoever answers. I just asked, what are you doing? Are you doing ristocetin cofactor, glycoprotein 1bM, glycoprotein 1bR? And I think I put collagen binding on there too. And it was overwhelmingly, it's about 40% ristocetin co-factor. So a lot of us are still doing it.

**Dr. Sidonio:** Yes, so the Wisconsin has stopped doing it as part of their clinical practice. And we had so many issues with it. So, it's a good screening one. If it's normal, it's probably normal. It's that's sort of good for that purpose. And I think a lot of the commercial labs like ARUP and LabCorp and some of the other ones, that's a, it's still commonly used. And we just always want people to make sure, because sometimes it's just labeled as activity. And so for, you know, that's fine for the general public, but for hematologists, we need to know which assay they sent.

**Mr. Fritsma:** Yes, actually, it's interesting because Dr. Emmanuel Favaloro follows the Fritsma Factor. Anything I post in the evening, it's morning where he is. And so, I get a response right away. And he, even before I totaled the results at the end of April, he wrote, well, you know, people should be doing the GP1bM. What have we been talking about here?

**Dr. Sidonio:** Yes, it's great. And he wrote that nice paper on the 100 years of Von Willebrand. So, it's like fresh on his mind where he's like, you know, this is the way. I think that we're all headed that way. It's just difficult. You know, when we talk about research, you know. I talk to my Irish colleagues, and I think about like, how do they get so much research done? Well, all the labs go to Dublin, right? Every single person in that country, the labs go to one single lab. So it's much easier to do a study that way, right?

That's certainly not the case. Even in our state, they don't go to the same place.

**Mr. Fritsma:** Yes, that's right. Let's see, there was something else. Oh, I think you had a paper using a nanobody. Very early, I know, but that looked really interesting.

**Dr. Sidonio**: Yes, and still undergoing some evaluation. So, Dr. Renhao Li is the lead scientist on this, and he was trying to come up with a way to identify von Willebrand disease, maybe in a simpler sort of ELISA format using these nanobodies. And we're still trying to figure out which candidate works better. What's interesting is that some of them work better at discriminating between yes and no, they don't have von Willebrand, and some are better on the lower end.

So I have a feeling it'll be one of these things where we can, and we still are working on publishing some of this data where we took patients that we have standard von Willebrand labs, and then we performed the nanobody testing. And so we were trying to figure out what to call it. And one of the things we didn't want to call this GP1bN, because it sounds way too close to GP1bM. You couldn't say that over the phone.

Yes, we don't want to do that. And so, yes, so he's been actively working on this. And so we should hopefully have a paper later this year on, you know, sort of validating this assay and trying to figure out how this assay could work. So yes, he's done a lot of good work in VWF.

**Mr. Fritsma:** I'm excited that you're using the collagen binding. That test has been around for years and years and not many people have adopted it. I think mostly because the, you know, the solid phase antigen was somewhat variable.

**Dr. Sidonio:** Yes, and I think the other thing is, is like which collagen are you evaluating, right? And so that's the other thing, and we don't know exactly what, you know, how useful it is. But I think it's really found its place, and the way that Wisconsin uses it in their algorithm, at Versiti™, is that if you have a normal collagen

binding, your multimer, you know, there's no reason to waste your time doing multimer analysis, it's going to be normal.

And so I think that's it's saved lab time with regards to that and only focus on those that have low collagen binding where the multimer analysis would be helpful.

**Mr. Fritsma:** I think fewer and fewer people are doing a lot of multimer work. Let's see, there's a couple of other things that popped up in my mind. For the von Willebrand Type 1C, I think there is a test for that. Are you using that?

**Dr. Sidonio:** Yes, I mean, so the one way you can do it, like the old-fashioned way, the easy way that anybody can do, right, is you test the patient, you give them DDAVP, and then you check their levels at one hour, four hours. And what you'll see is that there's a rapid rise.

And then there's a rapid drop. And so that's one way to help identify. That's the easiest way if you don't have a lot of resources. We don't have intranasal DDAVP. There's a pharmacy that does compound it, but it's not widely available in the US like it used to be when CSL and Behring produced it. But yes, you can do a propeptide.

You can measure that to see whether there's an accelerated clearance from the mature protein and see if there's a discrepancy and help identifying this. The main reason it's important is that, when you're taking someone to surgery, you need to know whether I should use von Willebrand factor concentrate. So, you'd want to use it in these patients because the DDAVP will have a very limited, it'll look great in the first hour, but then four hours later when you really need it to still be working, you don't want it to be back to baseline. And that's what can happen because you have this accelerated clearance.

And so that's a specialized assay. We have to send that to Wisconsin to see if the ratio is different because you want to see if is it being cleared faster than the premature from the mature protein.

**Mr. Fritsma:** And the ratio between the functional and the quantitative assay is set now at, is it 0.7?

**Dr. Sidonio:** Yes, we keep changing it, right? So yes, it used to be 0.6. There was a lot of discussion about trying to ensure we weren't missing any patients. So, we thought it'd be better to include more patients. And this is where it gets challenging too. You can do it one time and it'll be less than 0.7 and then the second time you repeat it, it's not. And so which one do you go with? And so, this is one of those logistical things.

Usually if you get one time abnormal, we would send it. And so, we usually use the cutoff of 0.7 right now for activity to antigen ratio and usually use the GP1bM. Because as you know, if you have Type 1 von Willebrand, you know, you're going to go down, you know, you have a quantitative defect, so you're functionally, you should go down pretty similar. But, usually the activity is always a little bit lower, but it shouldn't be that much lower.

**Mr. Fritsma:** Thank you. Is there anything else you'd like to add?

**Dr. Sidonio:** Yes, when it comes to the diagnosis, I think one of the major things that happened with the diagnosis, and the guidelines, is what do you do with those patients from 30 to 50%? This is a topic that comes up at every meeting for decades.

And so for initially, if you had the level of 30 to 50%, the first descriptor was called *Probable von Willebrand*, which is a terrible name. Nobody probably has something, right? It's just a terrible name. And so you can imagine it's very difficult to tell patients that they have, they probably have von Willebrand and it's really mild and don't worry about it.

And so over time we evolved it to low VWF because it was seen as more of a risk factor than an actual disease. And we know those patients, a lot of them will, they'll normalize as they get older. If I see a seven-year-old and they have a level of 45, by the time they're adults, they're certainly going to be normal. And they may not need to be seen by a hematologist, but you know, if they bleed, they certainly do.

And so they created this system where if it's 30 to 50 and you need to have some bleeding phenotype to make a diagnosis, which is helpful. It's not helpful for the kid, the two-year-old that I send labs on because their brother has it. I'm going to treat him, obviously, I'm not going to wait for him to bleed before I say, oh, yes, you have von Willebrand. If you're less than 30, it's considered von Willebrand. And if it's 30 to 50, you need some bleeding symptoms.

And there's a lot of discussion about is it a risk factor? Is this a total red herring? Are these patients actually have something else and we're just incorrectly attributing it? But it's just important to follow those patients regardless and repeat the levels at least more than one time if you can. There are some labs that do it three times before they rule somebody out.

But usually if the levels are, if the factor VIII is normal and the VWF levels are 100% or higher, there's probably no reason to repeat it. We did studies on this where we didn't see any benefit. The predictive value was pretty low. If you have a normal factor VIII and your levels are above 100, there's probably no reason to repeat.

**Mr. Fritsma:** Yes, that 30 to 50 issue. I've been around long enough to see change over and over again. It just tells you we really don't quite know.

**Dr. Sidonio:** Yes, and that's where most of the patients are. Like, the vast majority of the patients [that] I take care of live in the 30 to 50 range. And so. they're included. We want to, you know, in America, you have to have a label, an ICD-10 code. We're up to ICD-10 now. And so, you need a label or you can't get, I can't prescribe anything. because they don't have a diagnostic code. So, that's why it was important. Even though other countries are like, we don't care about diagnostic codes.

**Mr. Fritsma:** Very good. Well, thank you. This concludes our second conversation. Dr. Sidonio, thank you for your expertise.

We encourage participant questions and comments, and there's a link on the Biomedica Diagnostics website for you to download a transcript of today's talk and to access the video. And you can forward your questions and comments.

Please join us next month for Conversation #3, entitled Advanced Lab Assays and Von Willebrand Disease Management.

Thanks to Biomedica Diagnostics for sponsoring Coag Conversations, and thank you for your participation.

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