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Transcript – Coag Conversation

100 Years of Von Willebrand Disease…and Upcoming Advances

Conversation # 1 History and Clinical Descriptions of von Willebrand Disease

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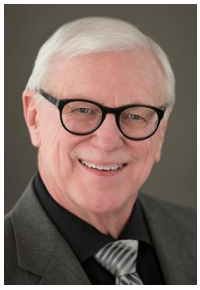

Moderator
Mr. George Fritsma, MS MLS
Laboratory Scientist

Guest
Robert F. Sidonio, Jr., MD, MSc
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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.

Our first conversation will focus on the history and the clinical descriptions for von Willebrand disease. Dr. Sidonio, 2026 marks the 100th anniversary of the first description of von Willebrand disease. Could you give us an overview of how von Willebrand disease got its start, and what are some major events in characterizing von Willebrand factor?

Dr. Sidonio: Yes, so happy to be here. So yes, so it's the 100th year anniversary. And Dr. Erik Adolf von Willebrand was a hematologist, and he described a family on the Åland Islands in the Baltic Sea. And what he noted was there was a family, and they were cousins, identified as cousins, that had significant bleeding symptoms, mostly mucocutaneous bleeding. But despite that, they had a normal platelet count. And the index case was a five-year-old girl named Hjördis. And he actually described her in 1924, but it didn't get published until 1926. So that's why we're doing the 100 years in 2026.

But I had the chance to visit this location. It's very difficult to get to even nowadays. But, she had a number of bleeding symptoms. She had some joint bleeds. And unfortunately, by age 14, she died after her 4th

[menstrual] period. And she had a number of siblings that had died of significant GI bleeding. And he studied all 66 family members at that time. And originally described it because everything was sort of through the lens of hemophilia as pseudohemophilia. [It] also had a couple other names, constitutional thrombopathy, vascular hemophilia. And so he described this and a number of other great scientists over the years like Inga Nilsson [Inga-Marie Nilsson, PhD] and Margareta Blombäck,[MD, PhD, Karolinska Institute] over the next few decades helped characterize the disease.

You know, there were therapeutic advancements for this, even though they had trouble identifying exactly what the problem was, they knew that cryoprecipitate was able to treat or at least mitigate some of the symptoms. But, it really wasn't until 1971 before there was a full differentiation between hemophilia A and von Willebrand disease. And the original name was called factor-related antigen, as you know. And this was done by the famous Zimmerman group. And then, you know, subsequently in the 1970s, there was a description of an antibiotic called ristocetin. And at that time they learned that ristocetin, this antibiotic, caused platelet agglutination in PRP of individuals without disease, but not in those with disease. And so this was one of the first ways to actually diagnose it, the functional activity.

And then fast forward through the 1970s, the great Pier Mannucci [MD] came up with a way to help stimulate the release from the endothelial cells using high-dose desmopressin or DDAVP. And if you look back at the old papers, it was really interesting. They would describe how it was much better than epinephrine. Can you imagine giving epinephrine to patients to improve VWF?

And then in the 1980s and 1985, there were actually four different groups, it's hard to believe, four different groups cloned and characterized the gene. And that's when really our understanding came. And then over the next few decades, different assays were developed that were ristocetin-based and non-ristocetin-based. And then they looked at other functions like collagen binding.

They were able to identify the binding of VWF to factor VIII, which helped identify one of the subtypes. And so, you know, when you take a look back just at that short history, there's a lot that was done, but really it was in the 1970s and 1980s where a lot of the work was done and really understanding the disease that we know today.

Mr. Fritsma: Thank you. So, when did they name the von Willebrand factor and when did we find out that it was stored and secreted from the Weibel-Palade bodies (WPBs) in the endothelium?

Dr. Sidonio: Yes, that wasn't really figured out until the 1970s when they figured out where the storage was – is it in the endothelial cells and the Weibel-Palade bodies. And it's really interesting, when we talk about therapies and gene therapy, being in that environment allows, is the perfect place for the multimerization and which makes it very difficult because there's a lot of assembly that has to be done for gene therapy.

But, when it came to the name, I mean, it actually had other people's names on it. I went back and looked at this. There was a German scientist named Rudolf Jürgens, and for a while it was called von Willebrand Jürgens thrombopathy. I don't know why his name got removed. These kind of things are sort of lost in history. But even though he didn't understand this, it wasn't until after the 1970s and 80s when we understood that this was a distinct entity in which they decided to name it after the person that discovered and described the first patient, which was von Willebrand.

And so we have, there's actually a meeting every year where we get to meet the family and honor that family. He brings some things from the first discovery, some of his clothing and describes some of those interactions. The grandchildren of Erik von Willebrand.

Mr. Fritsma: Oh, that's very interesting. And then along came the description of ADAMTS13. And when did that get started and what's the importance of ADAMTS13?

Dr. Sidonio: Yes, so, you know, that's, like I mentioned, you know, we were able to understand the description. But it really wasn't until the 1990s when the discovery of that VWF cleaving protease, ADAMTS13, was made. And as you know, this is a critical enzyme in which it helps process the von Willebrand factor multimers. A lot of people don't realize that these multimers are highly prothrombotic.

If you have a disease that's separate from this, acquired TTP, in which you have a deficiency, either related to an immune defect or lack of production, it has some devastating effects with lots of microthrombi throughout the body. So this enzyme is really important for processing and cleaving the VWF multimers. And that discovery was made in the 1990s. And it wasn't really until that was understood and we understood the multimer assembly in which we could actually have the first classification system. And that wasn't actually until the mid-1990s from the great Dr. [Evan] Sadler, MD, PhD.

Mr. Fritsma: It's very interesting in the involvement with the TTP. We had an interview with Dr. Long Zheng from Kansas a while back talking about the ADAMTS13 and the involvement of von Willebrand factor in various problems other than simply von Willebrand disease. Yes, let's talk about the von Willebrand factor gene and what is its inheritance pattern. I know there are different subgroups. Are they all from the same gene?

Dr. Sidonio: Yes, so when you talk about strictly von Willebrand disease, you know, like I mentioned, it was cloned and characterized in the mid-1980s. It's on the short arm of chromosome 12, and it's important to know that there's also a pseudogene which can make genetic testing a little bit difficult. But when you talk about the inheritance patterns, the most common type is Type 1 von Willebrand disease.

And largely that's a quantitative deficiency. So, what makes it really difficult in comparison to hemophilia is you can have a very modest reduction and you have something called low VWF or mild von Willebrand disease. And your levels may only be 30 to 50% with normal being around 50%. And patients can have variable bleeding, usually not life-threatening bleeding, but they can certainly have bleeding events.

And if there's surgeries or procedures or trauma, they can turn into life-threatening bleeding. But then you can have deficiencies all the way down to 5% to 10%. And this category of severe von Willebrand, which we haven't really fully characterized. And so this type is autosomal dominant and this one is very clear, and this is in contrast to X-linked inheritance of hemophilia.

And if you look at the subtypes of Type 2, these also are predominantly autosomal dominant disorders as well. But what's really interesting is that we describe these disorders and the various genetic defects that happen within certain exons. But we also forget that you can have more than one genetic defect, which totally blows up the whole system and makes it difficult to categorize. And we're learning this as we do more genetic testing.

It's very common to find somebody with Type 1 slash Type 2N or Type 1 slash Type 2A. And so they have their sort of own character, you know, their own category. And then the most severe type, which is usually less than 1%, so about 70% are Type 1, maybe 25 to 28% are Type 2, depending on what you read.

And then the last category is probably 1 or 2% of the total von Willebrand diagnosis is the most severe type. It's the absence of VWF. If you run this on a gel, you don't even see any multimers. You have to make sure you actually have the correct sample in there. And these patients have almost unmeasurable VWF.

Many, like the labs that are not sophisticated can't even measure it. They just say less than 10 or less than 15. And so this is the complete absence of VWF. And obviously these patients have significant bleeding.

This is the autosomal recessive disorder. It can be either homozygous mutation or it could be a compound heterozygous. And as in the case of the first, the index case, that was a genetic defect, both of the cousins had the same defect, and so they had a homozygous mutation or deficiency.

And so these are less common, certainly, we do find these patients. And it's interesting when you talk about the term carriers, it doesn't really apply so much in here, because most of the time, if you have a child with Type 3 von Willebrand, both parents could have Type 1 genetic variants create a child with Type 3 von Willebrand disease.

Thankfully, it's the most rare, but I know we're going to talk a little bit about there are a lot of good therapies to help treat this, you know, in comparison to, you know, back in 1926.

Mr. Fritsma: There's really great complexity here with the genetics, and we'll get into that a little bit more, I think, in our third discussion. However, If we could, let's just go on to how do the symptoms appear? And do you have any difficulty with assessing the bleeding in patients?

Dr. Sidonio: Yes, so the thing like, in all medicine, is the easiest, cheapest thing to do is getting a good bleeding history, right? I mean, that's like the easiest thing to do is, and I do this every time I do a consult. I go see a family, a child has been bleeding. Surgeon doesn't know why. And then all I do is ask the family about their bleeding. [Has] Anybody been diagnosed with a bleeding disorder?

And oftentimes it's sometimes it's as simple as that. So, just really getting bleeding symptoms. And so this is largely a mucocutaneous bleeding disorder. It's not all of the bleeding symptoms, but the majority, if you look at clinical trials, if you look at large cohort studies, most of the bleeding symptoms are nosebleeds, oral bleeding. For women, they have reproductive tract bleeding, so that can be either heavy menstrual bleeding or postpartum hemorrhage, perimenopausal bleeding.

And so when I see a patient, that's mostly what I see. It's either a teenage girl with heavy menstrual bleeding, a young child with recurrent nosebleeds and oral bleeding. And then they can have surgical bleeding as well, or procedural bleeding, because oftentimes the symptoms may go unrecognized on previous family members. And so it's really just getting that bleeding history. And probably the best way to do it is to use a sort of a systematic approach.

They have these bleeding inventories called bleeding assessment tools. They're all widely available online. ISTH has a bleeding assessment tool. There's one for children, one for adults. There's a cutoff for each one. That's probably the best way to start with that is documenting the bleeding symptoms.

So, it not only documents bleeding symptoms, but how many have occurred and then what intervention was needed. So, if you were a teenage girl with heavy periods that had to get put on birth control but then got admitted to the hospital and then got a blood transfusion, you get a higher score, the more interventions that are needed. So, It helps sort of organize the thoughts of all our trainees when we see these patients.

Mr. Fritsma: I've seen articles talking about the bleeding assessment tools, and one thing that seems consistent is that they work better on women than men. Is that true?

Dr. Sidonio: Yes, I think what probably the reason for that is so in children, it's difficult. So, you can imagine if you are an affected family member and you have a three-year-old in front of me, they haven't lived long enough and they haven't had enough hemostatic challenges. And so the threshold is much lower for bleeding for them. And so it's sort of the score has a high negative predictive value. We just don't want to miss any patients. So we're going to test a lot of patients, but we're not going to miss too many of them, right?

And as they get older, so women just have so much more interaction with the medical system. Once you turn 11, 12, 13, you're having a period almost every month. And so your body is really getting challenged to see, can it stop bleeding? And so, as women get older, they often have those more interactions and more challenges to the body.

And obviously, as you get older, you have more surgical challenges that could help us figure out whether there is any bleeding. But it's always difficult because you could have gotten lucky with one surgery and doesn't mean that you're not going to have it. And so, have any issues with the second one.

That's always the challenge is I see a patient, they didn't bleed from their wisdom teeth extraction, but now they need a tonsillectomy. I'm not going to take that risk. Obviously, we're going to try to be conservative and treat that patient and prevent bleeding.

Mr. Fritsma: Is there any relationship with iron deficiency anemia? I'm seeing some studies that show von Willebrand people with IDA.

Dr. Sidonio: Yes, I mean, particularly in sort of the women and girls health realm, you're going to see a lot of that. I mean, most of my workups in clinic are recurrent nosebleeds. And oftentimes, if they're really bad, they're going to present with iron deficiency, right? You lose blood and you're not able to keep up. That certainly happens. And then certainly with women, average age of menarche is around 11 to 12 now. And so if, and in this country, we don't do a really good job of sexual education and anticipatory guidance with regards to periods. And so, girls often go many, many months with terrible, really heavy periods. before it alarms anybody. And then they end up in the emergency room.

We have hundreds of girls. We've done a number of studies looking at this, getting blood transfusions, getting iron infusions. I think our lowest hemoglobin we've seen was around 2.0 to 3.0 [g/dL], which just shouldn't happen in this country, I think. So oftentimes it's just a lack of recognition. And the family members also may have heavy periods and they just think this is something that's common in their family, 'Like, oh, you know, Aunt Jane had really heavy periods too, so this is just something we have in our family'. And so iron deficiency is commonly associated with this.

When we see teenage girls, we have a whole algorithm in our emergency room, in our clinic, where that's obviously addressed. And we can talk about with regards to testing, because it makes it complicated to test patients when they're anemic or they're under, they're actively bleeding. Because of the acute phase reactant, VWF, you often have to wait or retest patients when they're at a steady health state because of that issue. And so fixing the iron deficiency is important because it leads to such poor quality of life.

Mr. Fritsma: Similar problems in pregnancy, isn't that so? During pregnancy, does the von Willebrand factor level go up?

Dr. Sidonio: So, at times of stress, any endothelial stimulation, so even like, it's interesting, even heart disease, the VWF levels will go up from the stimulation. And then, stressful events, so, my nurse coming at you with a needle, you're obviously going to start thinking, getting a little stressed out, maybe bad traffic in Atlanta for an hour or two to get to my clinic, even if things like smoking a cigarette, running for 5 minutes, all those things elevate the levels in a short term and could sort of lead to a, what looks like a normal level, but maybe if you checked it again in a steady health state.

And then certainly these levels rise as you age, unless you have severe Type 3. They rise naturally with age. And so you may have had a deficiency when you were a child, but as you've aged, your levels have risen and now you don't have that deficiency. And usually bleeding symptoms get better, but it goes up during pregnancy in response to the hormonal changes. And then some of the studies done by Andy James [Andra

H James, MD] shows there's a pretty rapid drop in the next week or two. And so, they're at risk for postpartum hemorrhage in the subsequent weeks. And so they've done a number of studies looking at this pretty rapid drop in the subsequent weeks.

Mr. Fritsma: And finally, what is the, I read that if you are just basing your diagnosis on laboratory tests, you could say von Willebrand disease affects something like 1% of the population. Is that accurate?

Dr. Sidonio: Yes, so that's where, yes, that's one of those challenging things. If you just took, like, if you just went to an elementary school and you just tested everybody, about 1% would have levels less than 50%. And so there's that. Whether any of those patients are actually bleeding is another thing, right? And that's where the challenge has come into this. And so it's very difficult. Von Willebrand disease is just very interesting this way. If you look at patients that have significant bleeding and a reduction of VWF, it's probably more like one in 1000 or one in 500, somewhere in that range.

Probably the most interesting study that was done was done by the late Joan Gill, MD in Wisconsin. It was an excellent study. Dr. Veronica Flood, MD was involved in this. They took a lot of children and they were undergoing a tonsillectomy. So, as soon as they went under, they got their levels. They had no bleeding history. So, all these children had zero bleeding history and they batch tested this. So, we didn't even know what the levels were when they went for that tonsillectomy. And if you look at it, there was a significant portion of those patients that had a reduction of VWF levels that would have met the criteria of von Willebrand disease, and almost none of them bled from the tonsillectomy.

There were more patients that bled with normal levels, significantly more, 10 times more that bled with normal levels than did with that [low VWF]. One of the challenges of that study is that it's a static level, and everybody has a different rate of rise and sustaining of their levels. We learned this when I was doing VWF. When I was doing hemophilic carrier studies, the levels we showed that hemophilic carriers, their factor VIII levels and VWF levels are not sustained, which could explain their bleeding.

And so there's this idea of stress response protecting humans. You know, if you were like a caveman running away from a lion, your VWF levels are going to get pretty high, right? And so some people's gets higher than others, and some are sustained longer. And so that's probably where there's a little bit more nuance than just one static level of VWF.

Mr. Fritsma: Not only that, but there's also a lot of people who just say, oh yes, I bleed a lot. Then, if you test, it crosses over, doesn't it?

Dr. Sidonio: Yes**.** So, there's another entity that's sort of an emerging thing. It's probably worth a separate conversation with some of those experts, but patients that we thought had von Willebrand disease, but probably didn't. Maybe they had, there's a discrepancy in some Hispanics and African-Americans in which they have a SNP in which they don't respond to ristocetin, so they get a falsely low ristocetin cofactor assay. And this was discovered years ago in Wisconsin. And that's what sort of made us move to other assays. And so some of those patients, I would test them with a new assay, it's completely normal. But they obviously presented with bleeding symptoms.

And so we have this sort of new group. It's sort of like a placeholder. It's called bleeding disorder of unknown cause. Used to be called bleeding disorder of unknown origin. It's these patients that bleed. We don't know why they're bleeding, but we know things like anti-fibrinolytics and DDAVP help them. And so we don't get rid of them because we want, you know, maybe we'll figure out what's going on at some point.

We're sort of like in the early stages, like von Willebrand, you keep these patients, you don't know what's going on, but you're going to manage them and treat them until somebody figures it out.

Mr. Fritsma: Interesting. Is there anything you'd like to add about the history or the clinical presentation?

Dr. Sidonio: Yes, I think it's just important to understand is that we don't have a good severity system for von Willebrand disease. We have the different subtypes, Type 1, 2, and 3. Those were proposed; I guess they're now 30 years [old]. You know, I'm a child of the 90s, so it's hard to say that out loud. But 30 plus years ago, this classification system has largely remained unchanged, but we've never been able to really fully grip what's mild von Willebrand. I don't even know what's moderate von Willebrand because we don't use that term very much. And what's severe von Willebrand disease?

And so that's something I think we're still trying to figure out the classification for sure. And then obviously we're trying to help improve diagnosis outside of the upper income countries where hemophilia has been identified well, but just not very well outside of the upper income countries.

Mr. Fritsma: Well, I find it interesting. I chat with friends who are intelligent, non-medical people, and I say, well, we're going to be talking about von Willebrand disease, and nobody's ever heard of it.

Dr. Sidonio: Yes, I know. It doesn't have a very good PR person, right? So, there's not enough famous people with von Willebrand. That's why I think so.

Mr. Fritsma: I guess that's right. Yes.

Dr. Sidonio: Yes.

Mr. Fritsma: Well, this concludes our first conversation. And Dr. Sidonio, thank you for your expertise. We encourage participant questions and comments. There's a link on the BioMedica Diagnostics website for you to access the video and download a transcript of today's talk, and also to forward your questions or comments.

And please join us next month for Conversation # 2, entitled Von Willebrand Disease Subgroups and Lab Applications. Thanks to BioMedica Diagnostics for sponsoring Coag Conversations and thank you for your participation.

Questions or Comments? Please email to: Webinars@BioMedicaDiagnostics.com

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