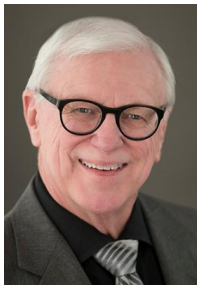
December 2025
Transcript – Coag Conversation

Alternate Warfarin Monitoring When the Prothrombin Time is Unreliable

Conversation # 3 Alternative Means for Monitoring DOACs and Warfarin

Featuring:



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Transcript of Conversation 3

Mr. Fritsma: Hello and welcome to Coag Conversations, an educational series sponsored by BioMedica Diagnostics of Windsor, Nova Scotia, Canada. Our topic for this three-part series is **Alternate Warfarin Monitoring When the Prothrombin Time is Unreliable.** We will focus on anticoagulation management in antiphospholipid syndrome.

I'm George Fritsma, faculty for the University of Alabama at Birmingham School of Medicine, Division of Laboratory Medicine, and proprietor of the Fritsma Factor, Your Interactive Hemostasis Resource.

We welcome Nicole Zantek, MD, PhD, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School. Dr. Zantek is a pathologist with expertise in transfusion medicine and blood banking. She is the Medical Director of the Special Coagulation Laboratory and conducts research in the areas of hemostasis, transfusion medicine, and blood utilization.

She is interested in general issues surrounding hemostasis test performance, utilization, and interpretation. In particular, she is exploring how medical circuits, such as ventricular assist devices and apheresis cell separators, influence hemostasis in adult and pediatric patients. Dr. Zantek is also interested in advancing transfusion medicine and blood utilization practices.

We begin this third conversation with a discussion entitled Alternative Means for Monitoring DOACs and Warfarin. And we'll turn this over to our speaker, Dr. Nicole Zantek. And let's start with talking a little bit about the DOACs. We covered this somewhat in conversation Number Two, but, if you don't mind, we'll start again. Is there a need to ever monitor the plasma level of the DOACs? And then is it important to monitor the plasma level of warfarin?

Dr. Zantek: Well, certainly DOACs, as I mentioned before, have times when they're worthwhile to check. And even though we don't have good therapeutic ranges established like we have for warfarin, we can judge against what has been reported as on-therapy ranges.

And so, in patients with antiphospholipid syndrome, the indication for that kind of testing is similar. So, you know, are they on a medication that interferes? Are they at extremes of weight? Have they had a thrombotic event while on it? And do you want to check to make sure that they were at a therapeutic level? And then, like before they go into an invasive procedure, to see if there's still 'drug-on-board' or if there's,, bleeding more or bleeding, then someone may want to check that.

But routinely we don't monitor DOACs. Warfarin, on the other hand, and other vitamin K antagonists, we typically do need to monitor because there's a fair bit of variation in response to the drug. And also, over time, people's response can vary due to things like dietary, vitamin K intake, medications, and other things that affect the levels. It is routine to monitor vitamin K antagonists, and it would be no different in a patient with antiphospholipid syndrome.

Mr. Fritsma: How do, when you're monitoring warfarin, can you use the PT / -INR? I know we talked about this a little bit in conversation number two, how effective is the PT / INR? And then let's look at some alternatives as well.

Dr. Zantek: In some patients, the PT / INR may be okay. And it's the prothrombin time that–contains phospholipids, so it can be affected by antiphospholipid antibodies. It's important to get a baseline. If the baseline is elevated, then probably, you know upfront that you can do that because it's already up. So, you're going to potentially underestimate the dosing that you'll need to actually be in a therapeutic zone. But it can be used at times in some patients.

If it's unreliable, like it is elevated, then you consider using alternative methods. The more common of the alternative methods is a chromogenic Factor X assay. And this is an assay that's done by diluting the patient's sample, so it's a single dilution, and then you add another snake venom, as snakes are key to understanding coag, Russell viper venom, and that activates Factor X. And so, Factor X is activated in the patient sample, and then you add a chromogenic substrate, something for that Factor X to cleave. And then it releases a colored compound when it's cleaved. And then you measure the generation of that colored compound. The more that's released, the more active the Factor X was. And so that test is relatively phospholipid independent, so antiphospholipid antibodies don't typically interfere in it.

And so, it can be something that's used. There is, though, unlike the standard INR therapeutic range of like 2.0 to 3.0, there isn't a universally accepted therapeutic range for chromogenic Factor X in that they've kind of varied somewhere in the range of 20-25 to 40-45 is what has been reported. And so, it can be used in place of warfarin monitoring.

They aren't the same. Warfarin dosing protocols aren't as widely established using chromogenic Factor X as they are for adjusting for based on the PT / INR. But sites adapt protocols to kind of match so that an INR of 2.0 to 3.0, if, for example, they would set it matches maybe approximately 20 to 40, where the INR of 2.0 equals the 40, INR of 3.0 equals the 20. And you make adjustments based on that sort of algorithm.

Mr. Fritsma: Is that the chromogenic Factor X ? It's interesting. I know that that was developed and reported on back around 2008, 2009 and actually was being used in your facility. Is that a lab developed test or is it available commercially? And how often are you using that?

Dr. Zantek: It is commercially available and I would say we run several. We have several patients throughout our system that are being followed by chromogenic FX. Many of them have antiphospholipid syndrome.

Sometimes patients otherwise have reasons that the INR is thought to be unreliable. Common scenario being that we see from inpatients in the hospital are patients on direct thrombin inhibitors that are transitioning to a vitamin K antagonist. We'll see testing in that scenario as well. So, it's not all patients with antiphospholipid syndrome; some of the patients are being followed that way.

Mr. Fritsma: Does the chromogenic FX… I know that the studies I've seen, that they do have correlations like you've described that compare it to the INR. How is it at this, at detecting an overdose of warfarin? In other words, what does it have a good lower limit of detection?

Dr. Zantek: I think if you think of sort of like thresholds, so to know if someone's like in a therapeutic range, it's pretty good. If you use that 45%, saying if you're below that, you're probably in a therapeutic range and has, you know, pretty good to say that your INR is probably above 2.0. In the same patient that you're using it for, because it's unreliable, they're more likely to have an INR that's even higher.

So, in patients, if you are at an INR or a chromogenic FX of 20%, for example, you'll see patients with antiphospholipid syndrome, more of them will have super therapeutic INRs than patients that are being used for a different reason if you just were using it correlating testing like for a study. More of them will be in the 2.0 to 3.0 zone than out of the 2.0 to 3.0 zone. But as you get lower and lower in Factor X level, then it gets to be less and less reliable, just like INRs.

Dr. Zantek: The higher and higher you go, the difference between an 8 and a 10 is small differences in factor levels. So you get to, it gets to be issues there. And there's some, you know, the various forms of Factor X start to play a little bit more when you're down at that really low levels in terms of determining it. But the closer you are to that 2.0 to 3.0, but it's not perfect. And from our own data, you take a whole bunch of samples and you run them both. It's not a perfect correlation. It's a little bit of scatter. And that's been seen in on all the studies that I've seen. There's a bit of scatter in there.

Mr. Fritsma: It's usually chromogenic testing in general has better precision than clot-based testing. And it's a question as to the correlation and how sensitive and specific it is. Are you seeing pretty good precision if you're running repeat assays of chromogenic FX?

Dr. Zantek: I think if you just put it on analyzer and do intra-run and inter-run, it's, you know, it's pretty good. And patients still have some, individual patients still have some fluctuations, between like we get a sample now and they come back in three weeks, we get our sample. We'll see some variation just because of the variation. It's not, there are things though that will affect the, you know, that has pretty good reproducibility. I mean, on the same sample running it over and over again, you'll see that as well with the PT / INR. But it's sort of like, what's going to make this test be less accurate than the INR?

Sometimes it's other things. Interference from specimen color issues affect the reliability of this test. Is there hemolysis? Is there icterus? Is there lipemia? Because it's, it's a chromogenic test, they'll start throwing off the results. So those are scenarios where, we get a specimen, then I don't, that's not a comfortable result. Those will, if they have a lot of hemolysis, for example, we'll cancel it because it's going to affect this measurement.

Also, in patients where it's not like antiphospholipid syndrome, where we're trying to just get around that antiphospholipid syndrome. Patients with liver disease sometimes have unreliable INR. Here it's also a little bit tricky to figure out where's the right spot to be because they have a bigger picture that's involving, you know, the coagulation factors in the INR and how they correlate. And then if you're trying to transition somehow to a direct oral anticoagulant to and from warfarin, this test will be interfered with that. We've seen our interference with that when they've gotten testing. But on the upside, it's not interfered with direct thrombin inhibitors. It gives us an opportunity to separate those out.

Mr. Fritsma: That's interesting. Would you say that we could replace the PT / INR with the chromogenic FX altogether?

Dr. Zantek: No, I don't think we could. I mean, I don't think there's enough known to make it widespread. I think we don't, first of all, we don't have a therapeutic advantage that's clearly well uniformly accepted and established. And I think there's patients, hemolysis, icterus, lipemia, that kind of stuff.

The other reason is that it's more inconvenient if you're just going to be routinely followed by INR. A lot of times you can do, you know, patient self-testing with a home monitor or you can go in to a clinic and just have a finger stick and do it on a point-of-care device where this is a venous draw and, you know, only some labs in an area will run it. So many times it has to be sent in. Then it has that extra step and a delay between the testing and the response and management of the patient's warfarin. I don't know that it would replace it. I think even though it's more precise, it has its own issues. One of the scenarios, too, where we see issues correlating with INR is when someone starts and stops. When you first start on warfarin, the INR is really driven by FVII and it's half-life.

And FX takes a little bit to catch up because it has a longer half-life. When you're kind of stable, then it kind of works well. They're much better. But the same if you stop warfarin, the FVII will, you know, has a shorter half-life, so it'll correct. The INR will correct, but the FX will kind of lag behind. So, we see some issues with how things look and kind of when you're moving, I would say, on warfarin anticoagulation. And that can be a tricky time to use the test sometimes.

Mr. Fritsma: Thank you. That was sort of a loaded question, of course, you know, I challenged you with that. But, it does seem as though the chromogenic FX has a lot going for it. But I do understand that all of the chromogenics do have the problem that if it's a highly colored specimen, that that can affect the results.

Is there any other assay that you've considered than the PT / INR in following warfarin therapy? For example, I know thrombin times have been modified to follow the vitamin K antagonist. You mentioned Factor VII levels. Would Factor VII assay be more sensitive to the changes since Factor VII is, you know, a low concentration factor. Have you tried anything like that, thrombin time or Factor VII?

Dr. Zantek: We haven't. The thrombin time, that I wouldn't. It must be a modification because generally the thrombin time itself is normal in an individual on therapeutic warfarin. So, it might be a modification of that. I'm not sure of that one. Just like FX, chromogenic FX, you could measure other factors. So, you know, the other vitamin K, FII, FVII, FIX, FX. FX is used in part because there's a nice chromogenic assay. But also, FII and FX are the key sort of to really control thrombin generation.

There's been some data that suggests that FVII and FIX, I mean, they're important obviously, but they're not as vital to really getting thrombin generation under control, which is what you need to prevent the thrombus. The other assay that some labs have used has been FII testing, then to test for that other major component. Yes. The FII testing is often still done with the classic one-stage method. You know, you dilute the patient sample, and you mix it with FII deficient plasma.

That assay again doesn't have a standardized therapeutic range. But hopefully, the dilution helps you get around some of the effects of the antiphospholipid antibodies. But it's problematic if the patient actually had the type of lupus anticoagulants, so the hypoprothrombinemia, so that they get associated with low Factor II, then that assay doesn't work. I think that using a Factor II assay, is still possible, but I think that labs have moved away from it because it has more potential for interference. And I just think the targeted range has even been less well established. So, I think it's [possible], although there's less guidance on how to use it.

But, it's certainly, you know, something. And then there are other modifications of the Prothrombin time and I haven't seen any of these used in the in the US. But, like where they the fixed PT where they make it more focused on the FII and FX activity by absorbing plasma and then adding it to your sample.

But you know, there are other strategies being looked at and I certainly think we can improve upon your big old generic PT / INR to sort of narrow it in to hardening the real effects of the vitamin K antagonists and getting away from things in interference. So, I think there's still opportunity to make new tests and to improve upon the tests we have.

Mr. Fritsma: Well, this has been really interesting. I was really surprised to learn that there are several facilities that do use the chromogenic FX~~a~~ successfully just in the conditions that you've described.

And I've also, there was a time, probably around 2014 or 2015, when I thought, and maybe everybody thought, well, warfarin has seen its last days. We aren't going to have to bother monitoring warfarin anymore. So why bother with the PT / INR or the chromogenic Factor X? Truth is, I believe we've got almost as much warfarin therapy going on now as we did even before the DOACs came along, or at least there's still quite a bit. Is that what you're seeing also?

Dr. Zantek: I think definitely we're seeing new people. You know, general indication used for anticoagulation that many of those new starting anticoagulation are being put on the direct oral anticoagulants. And then the antiphospholipid group, you have that, are they triple positive and things like that to make that some decision.

I think if you're stable on vitamin K antagonists, it's a relatively cheap drug and there's so much history with it and we have readily available reversal agents and people know how to use it and respond to it. I think at least I don't see it disappearing. It's going to persistently have a role in that anticoagulation realm. We'll fine tune it. This patient might be better to this one or that one, but I think it's not going away.

Mr. Fritsma: Very good. This has certainly been a good series and a great opportunity to look at not only lupus anticoagulant and antiphospholipid antibody testing, but also to look at some of the pitfalls and some of the challenges in managing that testing and in managing the therapy as well. Thank you so much, Dr. Zantek, for sharing your expertise with us.

And thanks to everybody for listening to Conversations 1, 2, and 3 on this subject.

And watch here for more conversations in the future.

Thank you and goodbye.

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

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