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Specific Reversal Therapy for Factor Xa and Factor IIa Inhibitor-Associated ICH Life-Threatening Bleeding

Announcer:
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Dr. Gibler:
So we have a panel discussion here for Dr. Seiffge and the rest of the panel. Are there any questions? After that, by the way, there are some seats up here, if you would like. Yes, please.

Male #1:
Yes. Good afternoon. I'm David from Berlin. I have a quick question regarding plasma analysis of andexanet alfa, it's quantified measurements to use or that PoC rapid test, which is more reliable? Actually, whether the rapid test either from urine from plasma is reliable?

Dr. Seiffge:
So I think I can answer this question for you. So I think there are different ways you can measure DOAC., I think, what is - if you have a point of care machine, in your department to measure the INR, you can actually use it also to get at least any idea about the anti-coagulation status, because the INR on this machine also, but it depends a bit on the agent or if you apixaban or rivaroxaban, or whatever. So you have to go a bit into the literature because this is not straightforward. The central lab results for activity that can be automated, so they can be run quick in the hospital. I know a number of hospitals where they are available as an hour, hospital within 30 minutes to 1 hour. There are urine sticks, which are available, they adjust, but they don't give you an exact value, they just have a cutoff. So they tell you whether the patient has below or beyond - beneath a threshold, so you don't get exact levels with it. And I personally also think that getting urine in a patient with acute ICH is sometimes a bit complicated, because usually they can't give you a urine, so you have to give a basic catheter, which actually prolongs the time. And I think specifically, if you have the availability of measurements, then you should do this, at least to have an idea where you are. But if it takes too long to get the results, you should probably not wait for the results. Because then as for any patient, patient history is very important, so you have to get the information. When was the patient taking last time the drug? And then you can get actually a decent idea where on the plasma curve, they are on the pharmacokinetic curve they are, to decide whether you should treat them or not. Because if you wait too long, then you lose the effect of being quick and effective. That's my point.

Dr. Gibler:
They talk about that at – actually, do you want to talk about that at UC? Because I think traditionally we're talking about a 24-hour turnaround on at anti-factor Xa levels. I mean, it may be quicker than that. So it's interesting that there may be some evolution there. But to your point, David, it ends up being if it's time constraint disease, which almost any disease that matters, the quicker you treat it, the better the patient does.

Natalie, what are your thoughts about that? Is that – have you, you know - is that something that you see used either there or in other centers?

Dr. Kreitzer:
We do have anti-factor Xa testing. It does take some time to come back now where we are, so we don't currently wait on that lab to come back to decide whether to provide reversal or not. It is based more on the history, which can be challenging; these are patients who generally cannot tell you when they last took their medication and if they're compliant with it. But if family is there, you know, they're coming from a nursing facility or something where you have good evidence to suggest that they are compliant with their medication, then those would be patients that we would empirically provide reversal for without a lab test, with the thought that, as David mentioned, you know, not wanting to take up a lot of extra time. Typically, hematoma expansion happens within those first few hours if it is going to occur. So doing it early is going to be likely more effective.

Dr. Gibler:
Did you have a follow-up question?

Male #1:
No.

Dr. Gibler:
Okay. Good.

Dr. Kreitzer:
He's got a question.

Dr. Gibler:
Yes, please.

Male #2:
So just a question with regards to the thromboembolic complications. Is there a feeling or an understanding on the severity and outcomes following those complications just to balance it with the, obviously, the hematoma expansion side of things?

Dr. Kreitzer:
In the ANNEXA-4 study, they did report that overall finding, I believe it was 10% of thromboembolic complications, those were adjudicated by a separate panel. And so it could encompass anything; it could be DVT, PE, stroke, ventricular tachycardia, almost anything can be adjudicated. Is that the one thing that did seem to reduce that number down to, I believe it was about 3 to 4%, was providing some type of DVT prophylaxis within that first 30 days. And then the patients who were able to be restarted on their oral anticoagulant, had zero thromboembolic complications within that 30-day period. That being said, with the caveat that, as you might imagine, those patients who are able to safely be restarted on oral anticoagulation are probably going to be a very different type of patient than a lot of the ICH types of patients were speaking about. So.

Dr. Gibler:
Great, thank you. Did you have a question?

Female #1:
Thank you, I'm Dr. DiNapoli from Florence. I'm doing a job that is different from this of all the people on the main number people present in this room, because I work in a thrombosis center. So I would like to define this this problem, the determination of DOAC concentration on the blood is technically easy. It could be done on the same coagulometer that do PT INR. So the problem is to ask a laboratory to do this. And to implement these diagnostics is easy. Turnaround time is the same when it is organized than that to have a PT INR. So I think this place where I need to say this, because it depends in, great part, by the clinician that should ask a laboratory to do it. Because the problem is some time as the laboratory said, 'nobody asked me, so I don't make the test,' and so on, now we have to enhance this opportunity to. Thank you.

Dr. Gibler:
Thank you very much. Yes?

Male #3:
Yes, congratulations for the beautiful presentation. And I want to come back to the cases you reported. These were typical cases. And you also have sometimes cases in smaller hospitals, where you don't have available the calibrated factor Xa chromogenic assays. And for these hospitals, there are other tests may be available. And one of the tests is the determination of DOACs in urine samples. And a small study from Australia just published in *Stroke*, showed that this urine test takes only 20 minutes compared to the chromogenic

substrate assay for determination of the presence or the absence of the DOAC. And for clinical decision, the negative results in patients is important for medical treatment. So this, therefore, in future might be that there are also alternative tests, specifically demonstrating that the negative results, the absence of DOACs then enable specific treatment for stroke patients or for patients with intracranial hemorrhage.

Dr. Gibler:
Thank you very much. Go ahead.

Dr. Seiffge:
I think I agree that's a very good point that when we - I just like these numbers for levels to illustrate the actual anticoagulation status of these patients, but I think we are all stroke physicians and we are trained to treat ischemic stroke as quick as possible so we have these needle times that we would like to reach as benchmarks, we'd like to go to 30 minutes total needle time for ischemic stroke. And I think what we have learned so far from ICH treatment is that we also need to be very fast, very quick and to strike quick, and then I think we should probably also have some - that's my personal opinion, but have some benchmark numbers for ICH treatment, why can't we do reversal times 30 minutes or 60 minutes. And then to have some –

Dr. Gibler:
Did Adrian ask you to say that leading into his presentation?

Dr. Seiffge:
No. But I think to add this up, we have to consider whether these kinds of tests give us really information that is it valuable to delay the treatment for 20, 30, or 40 minutes in the settings. Because an ICH, in ischemic stroke, we try to get through would have all tests before getting thrombolized. If we don't really need, and if we can skip a test, that's always a good idea to give further treatment.

Dr. Parry-Jones:
And I think if you could have a point of care test that's easy to do. And I think getting, as you've already said, getting urine is difficult, and I suppose it gives you an average reading for the time in which that urine has been accumulating in the bladder, doesn't fit as well. So but if you had a test where, you know, you could - the positive/negative was calibrated at the point where it would allow you to decide whether or not to reverse, then that would be fantastic, but I guess we're not there yet.

Male #4:
So yes, I'm Dr. Nazim from Switzerland, maybe to continue on the testing regarding the dosage of andexanet alfa, because in the ANNEXA-4 study, there were low-dose and high-dose, and maybe this is also relevant, what kind of testing you use, and what your way to choose for lower or higher dose in these patients regarding on the test you have available?

Dr. Parry-Jones:
Well, the, you know, the product label is that it you use the higher dose if you're taking a higher dose of either rivaroxaban or apixaban, and you're within 8 hours of the last dose, and also if it's unknown, I think. So that's the current product label but beyond that, it's a good point. So if you don't know, and they'll also get, it could be anything but maybe erring on the side of caution so you avoid catastrophic expansions, might be the way to go in the meantime.

Dr. Gibler:
Excellent. Thank you.

Announcer:
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