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Reversal of Factor Xa Inhibitor ICH: ANNEXA-4, ANNEXA-I and Real-World Evidence

Announcer:
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Dr. Gibler:
Our next speaker, who will discuss reversal of factor Xa inhibitor intracranial hemorrhage, discussing ANNEXA-4, ANNEXA-I, and real-world evidence, Dr. David Seiffge, is well known to this audience. He is Professor of Neurology. He's a stroke neurologist with the Department of Neurology at Inselspital University Hospital in Bern, Switzerland. And he is someone that I think has enormous experience in the area of taking care of these patients, not just pre but post now DOAC universe. So please come up and let us hear about this.

Dr. Seiffge:
Thank you very much for this kind introduction. And I managed to come here. So yeah, it's a pleasure for me to be here today and actually Bern is not so far away from Munich, so it was just a short train ride. And although our hospital is called Inselspital, which mostly means hospital on an island, there is no island in Bern. So I don't I tried to find out why it's called like this. I never got it. Probably somebody can tell me one day. But today, I reassure you, there's no island in Bern.

So I'm going to start to speak about ANNEXA-4. You've heard about this study, which is - it was a single arm study actually enrolling patients with Xa inhibitor-associated major bleed, so it was not an ICH correlation, it was a major bleed population. And then these patients then received andexanet alfa, and were followed up for clinical outcomes. I would just like to highlight that there have been several publications here from within *The New England Journal* publication. But very recently, there was actually the final study report, so that's the full study report and the final study report, which actually then reported the final number of patients, this brought 479. So a very large number of patients actually in this study. So if you have read *The New England Journal* report, you should also read the *Circulation* report, because it reports new data then. Just want to highlight that these, as I told you, these major bleeds were in the vast majority, CNS bleeds, so 70% of these patients actually bled in the brain. So they've had some GI bleed. There were other bleeds. But we're quite fortunate to see that there is a large number of central nervous system bleeds, traumatic, but also non-traumatic bleeds. So I think, something we have to have in mind when you're talking about this data, that is a single arm, so there was no control group. And actually, the main reports were about a mixed population, including intracranial hemorrhage, but also other types of hemorrhage.

These are the main results. You have probably seen them. So this is from *The New England Journal* publication. And the main outcome or the main endpoint was actually anti-Xa activity. And so you see, always the baseline values over here, and over here for rivaroxaban, for apixaban, and there was also done a study where they enrolled a bit more of edoxaban patients because at the beginning there were not many edoxaban patients in the study. And you see that these patients tend to be on good anticoagulation. So some levels between 150, around this, and then you see the end of bolus result, and it drops down immediately, it intensively gone to 0, more or less. And this is quite consistent for apixaban, for rivaroxaban, but also for edoxaban. And then it stays until the end of perfusion and goes up slightly after a few hours. But this is something we have seen in the publications.

So this was the main result. There have been publications about a subgroup of those patients that we are interested in today. Patients with intracerebral hemorrhage. And this, as you can see up to this time point, it was not the defined full population and the efficacy population where you had some spontaneous bleeding, so nontraumatic leading but also traumatic bleeding. And these are the main results on the right you see over here, I think that's the most striking finding. You see the baseline volume, you'll see the blood volume on follow-up. So baseline volume was 9.5 mL, follow-up is 9.5. So that's just 0.1 mL of difference and this is what you see as the absolute change and change from baseline. And so this was quite a stable hematoma population after treatment.

How do these data for ICH patients compare to real-world evidence? You've also seen this study, already Natalie mentioned it briefly. This is a matched cohort because you know in ANNEXA, there was no controlled group but we have obviously real-world cohort and RETRACE-II, or the large German-based cohort study with patients with anticoagulation bleeds. And they also had a few patients on DOAC, but the majority was VKA bleed but also some DOAC bleeds. And they did good work to actually harmonize these populations to match them, actually to the match ANNEXA-4 patients and RETRACE patients, and then to compare outcomes in these patients. And the main finding is the raw number of hematoma expansion patients, there is the definition of, with ANNEXA-4, which is a change of more than 35% on the hematoma volume between baseline and follow-up. I think it's important to have that in mind because sometimes, these hematoma extension definitions slightly differ a bit between different studies. But you see, the result is 14% versus 36%, which is obviously statistically significant.

And then there is some other data out there for acute treatment. Those who attended ESOC last year and Lyrer, had probably seen the TICH-NOAC result, which was a study that we conducted in Switzerland, an academic study where we actually enrolled patients with DOAC bleeds, and we randomized them to receive tranexamic acid as add-on therapy or placebo, add on to normal standard care of treatment at that time point. This was in an area – it was conducted during a period where andexanet alfa was not available in Switzerland, so patients received PCC. So it somehow represents a standard of care population at that time point. And there was no effect of tranexamic acid on non-hematoma expansion.

But if we take this data, just the aggregate data from TICH-NOAC, and compared with the aggregate data on ICH patient that we know from ANNEXA-4, we see that these populations are quite comparable. So median age is quite comparable. NIHSS baseline is quite comparable at time from onset and in last intake seems to be quite comparable off the baseline volume, somewhere between 11 and 30 mL. So this is the normal median hematoma volume that we see in these type of bleeds. And then if we just compare the outcomes, again, just aggregate outcomes, so it's not individual patient data analysis, it's something like this. And this is what has been presented at ESOC. You see that hematoma expansion in ANNEXA with 14% and TICH-NOAC in a real-world cohort treated as we do it at nowadays in Switzerland, 44% seems to be a huge difference. But of course, this is a matched cohort. One thing that we also collected in TICH-NOAC, because it was a prospective study, of course, we also collected thromboembolic events, because we're interested in whether patients have thrombotic events. And we also observed rate of 10% of thrombotic events within the first 90 days, as you have seen also in ANNEXA 10%. So there seems to be - it doesn't seem to be very surprising to me, to be honest, because it is a high-risk population. We see patients which are about 80 years old, they all have a-fib. They all have anticoagulation. So it's – for some reason, they take these anticoagulation, and if you take away the anticoagulation, then these patients tend to have thromboembolic events. And this is what we see in all these kinds of studies.

Luckily, we don't need to rely only on matched cohort studies. But there is a randomized controlled trial ongoing, which is called the ANNEXA-I. And probably some of you are participating in this trial and randomizing patients with acute ICH on Xa inhibitors. And these patients then are randomized to receive andexanet alfa or standard of care. And it's enrolling at the moment. So I think when this trial is going to be completed, we will have a randomized controlled evidence for the treatment, which is very good to know because I think for - as you have seen for other situations, we don't have this evidence and we still treat patients so it's very, very exciting.

Announcer:
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