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ESO Guidelines for the Management of ICH in the Anticoagulated Patient

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Steiner:
It's exciting times to do guidelines, particularly in a time when there are five randomized control trials that have been published within the last 4.5 days – weeks, sorry, and one still coming up tomorrow. And so we decided we will not present final guidelines at ESOC today. But we certainly had some information before the trials were published, not for all the trials, but for some. Unfortunately, not for the ANNEXA-A trial which was published today. But I'll give you an overview of what you can expect.

We have six areas, the third area of the guideline is dealing with hemostatic therapies. And it is divided into two pieces, in spontaneous and into anticoagulated-associated ICH. And this is what we are talking about today. And this is divided in three – in four sections. I'm talking about section 1, 2, and 4. We have heard from Natalie about the INCH trial, when we did the literature search, the inclusion criteria were we go for randomized controlled trials first, and if there are no randomized controlled trials, then we go for meta-analyses or observational studies, if these - when these – or if these observational studies fulfill certain criteria.

And there are actually two trials that show up. The one trial is the INCH trial that dealt only with intracranial hemorrhages or intracerebral hemorrhages. And another trial was the trial from 1999 where they looked at major bleedings. So I'm referring to the INCH trial. The INCH trial compared PCCs, 4-factor PCCs, by the way, with plus vitamin K, with fresh frozen plasma. For reasons that you have heard from Natalie, this was a clinically important question. And primary endpoint was the speed of normalization of the INR and, to make the story short, the trial was obviously significant. You can reach a normalization of the INR within 2 minutes when you apply PCCs. That had an impact, though this was not the primary endpoint, on survival, as you can see that here.

And this is the slide I wanted to show to you. This is two studies on serious adverse events. And you see that this serious adverse events is on the side of prothrombin complex, which is not the case when we talk about thromboembolic events, which definitely occur more in the PCC group. But the difficulty with analyzing thromboembolic events is, number one, that it is counting up to 90 days. And the other thing is that in the INCH trial, there was a rescue therapy for those who had not a normalization of the INR within 3 hours, and they all got PCCs, all in the FFP groups. Many of those that then get PCCs, and so there is a mixture and makes it difficult to talk about thromboembolic events.

So this is, in short, the evidence for that area, leading us to andexanet alfa, published today, a comparison of andexanet alfa and usual care. Primary endpoint was this combination of hematoma expansion, an NIH increase of greater than or equal than 7, and no rescue therapy. And this is the analysis of the group when the trial was stopped, and you see there is a difference in increase of 13.4%. So there's no doubt there is an effect of andexanet alfa on hematoma expansion.

We see this also. There is also the effect on the factor Xa activity, which is significantly lower in the andexanet alfa group. So there is a

hemostatic effect also on the coagulation.

And then we heard about the appearance of thromboembolic events, particularly in stroke. So that means, for us, when we are coming up with a recommendation, we have to weigh the risk and benefits. David has already pointed out his analysis where they weight the effect on outcome of the hemostatic efficacy and the effect of thromboembolic events on outcome. And we will take this certainly into consideration.

This leads me to the final drug, which is idarucizumab. Idarucizumab was not tested in a randomized, controlled fashion, but in a prospective case series. Idarucizumab was given to patients who came in with a bleeding, either because the physician thought the bleeding needs to be stopped or there is need for an emergency procedure. Two times 2.5 grams were applied. And the primary endpoint was the occurring clotting time and the diluted thrombin time.

And here is a subanalysis of those patients who had an intracranial hemorrhage, 118 patients. And what you can see is actually the same effect as you can see it in the full group, and that is that you have a normalization, in this case, of the dabigatran concentration, or lowering of the dabigatran concentration within minutes. And it doesn't matter whether you look at subarachnoid, subdural, or intraparenchymal hemorrhage. And because there's nothing, and we wanted to get an idea of what does that mean, there is - the only thing you can do is you can look at more – difference in mortality. And the mortality in the dabigatran trial, when there was no idarucizumab, was much higher in those patients who had a bleeding than compared to those times when there was idarucizumab.

Dr. Gibler:
Thorsten, this is open for discussion. I had – I wanted to ask a question, and this is at a bleary-eyed moment at 3:00 in the morning, when I was reading ANNEXa-I, but it appears that there were more patients with atrial fibrillation in the andexanet alfa group compared to the usual care group. And I was wondering if that could be a reflection of why there was more thromboembolic events and stroke in that. I just, I don't know if it was 90 versus 84%. And I don't know if that's - I just, when I had two experts here, I wanted to ask you all.

Dr. Seiffge:
Can I answer on this question? I can't give you the answer on this question, but I can highlight you that there will be an analysis presented later today by Mike Sharma, I think in the afternoon session about the predictors of thrombotic events in the ANNEXa-I trial and the ANNEXA-4 population. So I think if you are asking the question, you probably can go there and see whether it has been analyzed or not, and whether it is associated or not, so go there.

Dr. Gibler:
Okay. Is that your answer too, Thorsten?

Dr. Steiner:
Yeah, that would be my answer too.

The other thing, there are a couple of things that you should pay attention to. For example, when you look at the time until treatment, which is actually longer than you would expect it, this has nothing to do with the trial. I mean, the trial is a trial. You have to go through the randomization process and so forth. But knowing that we are dealing with a disease, intracranial hemorrhages - intracranial hemorrhage where it is even more true to be as fast as you can, it would be interesting to see what would have happened if we have the routine times applied to this trial.

Dr. Gibler:
Interesting. Interesting. Adrian, what are your thoughts?

Dr. Parry-Jones:
Well, I was – just following on from that, I was – because in the UK, we don't have andexanet available yet, but we may in the future. But whether anyone on the panel who's had experience of using both PCC and andexanet alfa see any differences between andexanet alfa and PCC in terms of the efficiency of the process of reversal. Because if I think about PCC at our center, we've rectified this, but it used to be kept in the blood bank. So you used to have to go up a couple of flights of stairs, fill some forms in, get it, go back downstairs. So, you know, the storage of the drug may be different, and the process of drawing it up and administering it may be different. I don't know whether you've any thoughts on whether andexanet alfa might be quicker for some of those reasons.

Dr. Kreitzer:
Yeah, what's interesting in the ANNEXa-I trial, the time to administration was the same for both groups, kind of reflecting that point that it wasn't different. So I think for us, you know, our experience, it does take some time to reconstitute, and our pharmacists do that. If it's during the daytime and there's more of them, it's faster. And then at nighttime, it's a bit slower.

Dr. Seiffge:

We keep prothrombin complex concentrate, but also idarucizumab and andexanet alfa, all three in a fridge in the emergency department, so they are all available at the same spot. To be honest, the first time we used it, I was the first user in our hospital, we had to find it at that time, so it took a bit longer that day. But then now we know that it's in the same fridge and it's easy to grab, actually. And it's prepared by the emergency department nurses in our case. So actually, the time to mix it up is virtually the same, like for PCC, probably a bit longer, but doesn't - if you have it available over there, and there's no hurdle to get it, to grab it, actually, then you can be as fast as for PCC, I think.

Dr. Steiner:
I think there are large differences in systems. We have never thought about that in Germany, that this might be a problem. Because it's like David said, it is in the emergency room. And I think that makes a big difference.

Dr. Gibler:
Thorsten, thank you very much.

Announcer:
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