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Audience Q&A with Panel

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Dr. Gibler:
Thank you very much. And actually, doctors Kreitzer and Seiffge are going out into the audience. We've got a couple of things that we would be interested in seeing here. One, first, we want to bring it to you all, do you all have questions, including of Natalie and David, of our panelists. Are there questions that you have about the data that you saw here, or any aspect of the presentations thus far? Because we're moving into bringing the audience into it, and we actually would like to talk about a couple of cases that we really want input. Yes? Dr. Kreitzer?

Dr. Kreitzer:
We've got a question over here.

Male #1:
Hi, question to Dr. Parry-Jones. You talked about being aggressive and early in reversing in your bundle, and you've talked about anticoagulation. What are your views on treating blood pressure? How aggressively we should be doing it and what targets we should be trying to achieve, i.e., INTERACT2 talked about doing it within 1 hour, to get it below 140 which is, I think, not practical, and only 30% in INTERACT2 actually achieved that. So what should be the goals that we should be trying to achieve?

Dr. Parry-Jones:
Yeah, thank you. So from experience of scaling up our care bundle across the north of England at multiple centers, you know, I think there's several steps to the process, isn't there? There's the time it takes you to scan the patient, which applies across your whole stroke service. There's the time from the scan happening to starting your first dose of antihypertensive. And then there's subsequently the time from that first dose to hitting the target. And I think you need to look at your data and see where the delays are, because if it's time from scan to first dose, that's the easiest to fix. You know, you can - you just need to get on it quickly when you see a hemorrhage. And, you know, I think you can achieve very quick times. And I think, you know, in our – at some of our centers that have done this project, they have managed to do so.

I would also highlight the INTERACT4 trial that we just saw today. And I think that's really strong evidence that the earlier you manage blood pressure, the better these patients are going to do, and the less hematoma expansion you'll get. So I think we should, we should just use QI approaches. Think about your process in your hospital, and target the easy stuff to begin with, but keep chipping away and get that time as short as possible.

Dr. Gibler:
Thorsten, do you want to add to that?

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Dr. Steiner:
I would like to add on this. Referring to INTERACT4, because timing of the treatment has two aspects. The one aspect, can we go pathophysiologically-wise, low in a very short time? Is that good for the patient or not? And that question might have been answered, at least in parts today, by the INTERACT4. It does not, and I'm talking only about the intracranial hemorrhage patients in that trial, which was 43%, obviously it can be.

The other aspect is a practical aspect, and that is, can we do that with the tools we have? And there, it becomes tricky, because in INTERACT4, most of the patients did get your urapidil. And in Europe, most of the patients do get, please correct me if I'm wrong, urapidil in many countries. And that is a drug with a much - with a long half-life time. So for practical reasons, you always try to be - and for pathophysiologically, you try to be careful, because if you apply urapidil in a too high dose too fast, then you have an overshoot of the effect, which leads us to the discussion of stability and sustainability. So my question is, my question back is, do we use the right drug? And this is something we should follow up on.

Dr. Gibler:
Dr. Seiffge, you have a question over there, and then Dr. Kreitzer has one over here.

Male #2:
Yeah, thank you. Sorry, it's probably a bit because you're talking about treatment. My question is about diagnostics. Is about the CT, angios, MR, etc. When do you do them? Do you do 3D CTA versus 4D CTAs? Is there any particular protocol you follow? Is there any guideline you can support? Because this is we face it quite often, really, and it's very variable depending on the center.

Dr. Patel:
So there are two aspects to it. First of all, you know, in terms of immediate treatments, what's a CTA going to add? And given that, we've talked about the time-critical elements of things like anticoagulation reversal and blood pressure management when you have an intracerebral hemorrhage, then actually, I would say that those factors take precedence. In reality, if you are – and we're talking about purely intracerebral hemorrhage, we're not talking about subarachnoid hemorrhage, which is a different disease and much more easily recognizable on a scan, the second thing you're talking about then is secondary prevention, essentially stopping intracranial vascular abnormality from rebleeding. And I think you have time on that, and by time, I mean you have hours and days, rather than the immediate need for anticoagulation reversal and blood pressure management. So by all means, if it's part of your workflow, do it. But I don't think that it needs to be done straight away.

With regard to when we use a CT angiogram, we'd probably use the process set out and the DIAGRAM study in that unless it's, and I suppose simply put, unless it's an obviously deep hematoma in somebody that's got signs of high blood pressure, so cardiomegaly, ECG changes, or background history of hypertension, then we would essentially do a CT angiogram as a screening tool.

Dr. Gibler:
Dr. Chrysler?

Dr. Chrysler:
Can I ask you two questions? First, we talked about hematoma expansion, is the hematoma expansion the same pathophysiology in a primary intracerebral hemorrhage and a hemorrhage secondary to anticoagulation, because the pathophysiology of a hemorrhage intracerebral primary hypertensive is different from the pathophysiology of an anticoagulant-induced hemorrhage. So is there really a hematoma expansion in the second that is and if so, is it lesser than a primary intracerebral hemorrhage? That's question one.

The question two was, I was hearing about the presentation. We talked about STICH I and STICH II. STICH I, STICH II use predominantly deep-seated hematoma. And the results were that the medical arm, the surgical arm were equal. No, in fact, the medical arm did little better than the surgical arm. Now if the ENRICH is trying to talk about lobar hematomas, we very well know that lobar hematomas have a better surgical outcome. So whatever you achieve in surgery, as far as deep-seated basilar ganglion, hematoma is a concern.

Dr. Gibler:
Two questions there, one about the pathophysiology of the actual hemorrhage, one anticoagulated, one not anti-coagulated, spontaneous. David?

Dr. Seiffge:
I think as an answer to your first question, I would disagree with this approach. I think a brain doesn't bleed just because you're on anticoagulant. I think a brain bleeds because of vessels rupturing. So even in a patient who bleeds on anticoagulants, there's usually an underlying small vessel disease, underlying hypertensive disease, or some angiopathy, or a mixture of both. So I as far as I know,

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neither Xarelto nor apixaban makes the holes in vessels and makes them bleed. But you are right that the blood then is anticoagulated, so they're bleeding longer and they're bleeding more. That's, I think, the point. So I think the pathophysiology why the brain is bleeding, I think it's the same as, this is my personal opinion, as non-anticoagulated patients, but the way the hematoma is enlarged, I think that's my understanding of it. Probably somebody else has a different opinion, but it's my personal opinion.

Dr. Steiner:
Yeah, and there's data on that. So they it is old. The oldest one is study from 2004 – 2001, sorry, and where you can see that when you compare patients with and without oral anticoagulation, they have the same baseline characteristics, but those with on anticoagulants just bleed longer, which is another hint towards that it is the underlying vascular disease that is the pathology, and then comes the change, or not, of the coagulation.

Dr. Gibler:
Hiren, do you want to answer the second question as it relates to mass?

Dr. Patel:
I understand STICH I and STICH II slightly differently. So STICH I essentially was a randomized trial with a view to looking at the effects of early surgery on all comers. And I think that the volumes were starting from 10 mL to 80. And they used quite a destructive approach to taking out hematomas in how we understand surgery now. And actually, the outcome was still slightly better in the surgical group, but it didn't achieve significance. So I think the first thing is that there was still considered a role for surgery, and that's where the subanalysis from STICH I led to STICH II, which is a primary lobar hemorrhage.

I think the slight difference between STICH II and ENRICH was that the inclusion criteria for STICH II were really tight. The patient had to be quite well, albeit with an intracerebral hemorrhage. And I think that the ENRICH trial, given that they go down to a GCS of 5, probably answers that in that they have big clots in people that aren't well. I think that in STICH II, you had to be localizing a GCS 14, you know, that's a that's a pretty well person, from a neurosurgical perspective, to have their clot taken out. I think perhaps what you're alluding to where surgery didn't show a benefit in STICH I is in patients in coma, and that's essentially what I was perhaps saying as well.

Dr. Gibler:
Thank you for your question. Dr. Kreitzer and then Dr. Seiffge. Do you have someone there?

Dr. Kreitzer:
Yes, we have a question back here.

Male #3:
So thank you very much. My question is regarding timing of surgery. When we look into ENRICH, medium time was about 16 hours. So what are your thoughts about the aiming goals of the upcoming trials this and EVACUATE within 8 hours of symptom onset?

Dr. Patel:
So my view on that is really a practical one in terms of, once you've made a decision to operate, how quickly can you get them into the operating theater? Because, as I said, the aim of surgery really is to remove mass effect. And I suppose the basic tenets of neurosurgery are that if you have mass effect in the acute setting, you should deal with it as soon as possible. I think, or I wonder whether the reason why time to surgery is long in the randomized trials is really because of the process of the randomization, that means that it takes a little bit longer for patients to get into theater.

Male Speaker:
The bleeding might be still ongoing, and that's make it difficult to do the surgery.

Dr. Patel:
Yeah, no I don't. And, you know, that's notwithstanding the fact that that is a worry, but it's something that hasn't happened. So you know, if it happens, I have to deal with it. David?

Male #5:
My question is regarding the anticoagulation reversal. So when you assess the time, do you check to make sure with the lab test the air when you get the first lab results. So there is an anti-hypercoagulation. And then do you need to check again to make sure you have reached the reversal? Or you just measure the time when you started?

Dr. Parry-Jones:
Yeah, so vitamin K antagonists, that's much easier. So you know, you can get a very quick INR, and you certainly would repeat. We do it at 30 minutes and 6 hours, and we'll give further treatment if it's not adequately normalized. But I'm glad you brought this point up for

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the DOACs, because we don't have a quick test that's going to tell us, you know, in minutes, that this patient's anticoagulated and they need treatment. And as we all know, there's often uncertainty about timings with these patients, so frequently you don't really know when they last took a DOAC. So a blood test that would tell you that would be amazing, and we'd all welcome that, I think, in our practice.

And secondly, you sometimes don't know the onset time, and that's, as I showed, it's really important in terms of the risk of hematoma expansion, which you should be weighing up in your mind regarding treatment.

So I think in practice, you just have to make a nuanced assessment of all of these uncertainties. So if you're reasonably confident they took the DOAC in the last 6-12, hours, I'd just go ahead and treat and I wouldn't wait for a lab test to come back, because you'd lose an hour potentially. And that patient, if that, you know, expansion happens in that time, that's a bit of a disaster.

So currently, my view is that you have to sort of put all these uncertainties together, make your very best assessment of whether they're likely to need treatment and get on with it. And delaying a long time, thinking about it, consulting with others just adds to that. So if anyone else has any thoughts.

Dr. Gibler:
I wanted to ask a questionm just one step further with this, David, in your shop, or shops that you work at, and Natalie, as far as thromboelastography, viscoelastic testing, do you see there's – is there a role? Or does the audience feel there's a role in these patients, not to be any factor Xa levels, but instead, thromboelastic testing, is that something that you all use, or have seen used?

Dr. Kreitzer:
We haven't studied that. We do get TEGs in our trauma patients, and that's where it has been most studied. Trauma, obstetrics, and cardiac surgery are the three big ones for thromboelastography. The ultimate test for this is the anti-Xa, the PT/PTT are not going to be as helpful. So we at UC just recently have that available, actually to us. But at our other site, Westchester, our community site, we still don't have the test available. So it's very dependent on which institution you're in.

Dr. Gibler:
David, do you have a follow-up with that?

Dr. Seiffge:
Yeah, so we don't use thromboelastography in our center, because we get Xa levels quite quick. We are in the lucky situation that we get it quite fast, and we draw some blood samples from every patient coming in with a suspicion of stroke, and then we get the results within 45 to 60 minutes. Then if it is an ischemic stroke, we can use it for the decision of thrombolysis, for example. And if it is a hemorrhagic stroke, then we can use it for decision of reversal or not. But usually, if it is an ICH, we don't wait for the results if we are sure about the last intake, within the last 15 hours, for example, according to - in line with the protocol.

Male #6:
Thank you for a great talk. My question goes on the treatment as well with the PCC. As we understand, time is brain here as well with the expansion. But the treatment with PCC, how fast are you giving it? Because I see different protocols in different countries, how fast you infuse it, the infusion rate, because PCC is also given for other bleedings. And the general norm for, I'm from Denmark, we say 3 mL/minute for the first couple of minutes, and then – no 1 mL/minute for the couple of first minutes, and then up to 3 mL. And that that could take up to 30 to 40 minutes for full dose. But for ICH, I think, is there any different protocols for that?

Dr. Gibler:
Is that consistent with your all?

Dr. Parry-Jones:
It may differ by the product you use. So I think we use Beriplex, and we just follow the manufacturers recommended maximum rate of infusion, which, off the top of my head, I think, is 8 mL/minute. So that's the rate that we give it. So I think you just want to get it in as quickly as you possibly can, as you say. Yeah.

Dr. Gibler:
Well, doctors Kreitzer and Seiffge, if you'll come back up. With the last couple of moments, wanted to see if the panel had any final thoughts, our expert panel. We wanted to, obviously, thank you all for being here, but to see if you all had any parting words for us, if you will, as we close down our hour and a half.

Dr. Kreitzer:
I think for me, probably some parting words are to recognize that a lot of these things that we do that impact outcomes happen in the

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emergency department right when the patient is coming in. So involving your emergency medicine colleagues, and particularly your emergency medicine nurses, so that they are educated and have an understanding of all of this is critical. Oftentimes in the ICU will be day 2 or 3 of an ICH and debating the blood pressure goals. And I'm like, look, it just doesn't matter like it did 2 days ago. So that, to me, is probably the parting advice.

Dr. Gibler:
Well, we certainly want to thank everyone for being here today, and it was absolutely a pleasure to have you here. I want to thank our panel. You all did a wonderful job, and it was, I feel like we're in a – did you have something, Adrian, you want to say? I feel like, you know, we're in a great place now, with all these amazing trials such as ANNEXa-I that are coming out, that hopefully this will inform the guidelines for ESO in a great way and help produce better care for our patients. So thank you all again. We appreciate you being here. Thanks for beautiful Switzerland. This is amazing. And have a great afternoon and evening.

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