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What Future Studies Are Out There on the Meaningfulness of Reversal in ICH?

Announcer:
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Dr. Crowther:
I'm going to do the next little bit of this. So what future studies are out there on the meaningfulness of meaningfulness of reversal in intracranial hemorrhage?

So again, we're in the stage of the use of andexanet alfa in the real world where we're trying to collect as much data as possible so we can better understand this product. We're going to collect a very small amount of data in the clinical trials environment. The large bulk of the data is going to be collected in real-world data. So to do this, I divided - I looked at the clinicaltrials.gov, to look at studies that are ongoing.

In general, when you're talking about real-world data, you can divide them into two groups, the ones that are registered in central registries, such as clinicaltrials.gov, and then the unregistered ones. And unfortunately, the unregistered ones vastly outweigh the registered ones, because most of the real-world data, as Paul identified, is going to come from small studies done in individual centers where an individual PharmD or nurse practitioner or physician or another healthcare practitioners decided this is something that is of interest to them, and they're going to make it a summer project. And you're going to get a project with 58 patients from a single center.

As previously noted, the range of outcomes that can be directly addressed in large real-world studies is limited, since they're always restricted to the data at hand that is collected in the data sweep. So if you're going to do a prospective or retrospective multicenter real-world data study, you're likely going to register it because that's a lot of work. It's going to be expensive, because you're going to need to talk to people at multiple centers. You're going to need to collect data from multiple centers. You're going to develop common ways for the data to speak to one another. You're going to need to be able to do the analysis on that data. And so the multicenter registered real-world data studies are the ones that have the most value, but are the ones that are done least frequently.

Single center or small studies, which I would encourage you all to do, because it's the kind of an individual commitment we can all have to build the dataset, often can contain more data, because you're going to spend your summer looking in patient records. And you can get more granular data out of your personal review of the EPIC record than is a real-world multicenter thing, where they're going to try and get common data elements out of multiple different hospitals or data systems.

So here's some of the ongoing large studies. This is andexanet alfa and four-factor PCC in patients hospitalized with anticoagulant-related major bleed, it's an electronic medical record review of patients who received either AA or four-factor PCC, examining outcome and mortality - including mortality and length of stay. And it's reported to be coming out very shortly. Final primary completion date was December of 2022. And so it should be available to assume. It has been accepted at ISTH. There you go. It'll be out in a few months. So if you want to travel to Montreal, feel free to go listen to it. Trial of andexanet alfa in intracranial hemorrhage patients receiving an oral factor Xa, prospective randomized, multicenter clinical trial, this is the one I was talking about yesterday. It's to compare the efficacy of andexanet alfa against usual standard of care in patients presenting with acute intracranial hemorrhage, and in a baseline CT scan that goes within the window, within an estimated 15 hours of taking the oral factor Xa inhibitor. And we're anticipating recruiting around 900 to 1,200 patients, I'm indirectly involved in this patient - with this study. And then here's some of the other kinds of study. Remember I said the single center small study, and Paul focused on a couple of these earlier. So you know, you have these very complicated algorithms, because this is how things are actually rolled out in hospitals. And it's looking at the use of ICH management in patients who are on anticoagulants, be that vitamin K-associated or DOAC-associated ICH. And this is the protocol that's being followed. All I'm going

to say about this study is that this is extraordinarily useful if you're looking at how individual centers implement these kinds of designs, but they're not really going to speak to the issue of how well these interventions work when you apply them to broad populations in multiple different centers.

And here's a case series. And this is the problem with these small studies. So this is a - this I just picked this one out randomly, as Paul said, there's a stack this thick of them. It's looking at optimal reversal for factor Xa inhibitors. There's a lot of sort of qualifications to the study. But the problem in the bottom line is, if you look at the fourth bullet on the left-hand side, patients received four-factor PCC prior to an andexanet alfa. There were five patients. It's hard to draw any conclusions from five patients. If you look on the right-hand corner, some of the issue – right-hand side, some of the issues I identified, four-factor PCC doses ranged over a twofold and were administered over a long, 1.5 to 4 hours prior to andexanet alfa. So you might think, well, you know, what can I extract from this paper? Unfortunately, it's very useful because it's the first study that I think of to answer the question that was raised in the earlier session about giving andexanet alfa after four-factor PCC, but I don't think you can take very much from this. And so I apologize if the person who did this as in the audience. It's really focused on the specific way that these things were given in an individual center. And it's really, really hard to tease out the various bits and pieces of this. They say at the bottom, increased thrombotic risk associated with combination use. So that means, oh my goodness, should we not give an andexanet alfa after four-factor PCC? And I don't think the study like this, it helps us to think about it, but it doesn't provide us with any kind of definitive numbers. Tiny, tiny numbers of patients. But more importantly, as Paul said, you know, these patients are on anticoagulants for a reason. So they have enhanced thrombotic risk. They've got a major bleed, which is going to turn on their coagulation cascade. There's lots of reasons why this particular study, although I have no doubt was a lot of work for the investigators, really doesn't add an enormous amount to the literature.

Announcer:
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