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Released: 08/11/2023
Valid until: 08/11/2024
Time needed to complete: 1h 30m

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Newest Emerging Data from ISTH: Andexanet Alfa vs. 4F-PCC?

Announcer:
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Dr. Dobesh:
Hello, my name is Paul Dobesh. I'm a Professor at the University of Nebraska Medical Center at the College of Pharmacy, in Omaha, Nebraska. And today what I'm going to be talking about is the newest emerging data from ISTH, which is the International Society of Thrombosis Hemostasis. They had their annual meeting just back in June here of 2023, and data looking at andexanet alfa versus a 4-factor prothrombin complex concentrate.

Now a little background on why this project was done. As we know that, you know, oral Xa inhibitors, which is mainly apixaban and rivaroxaban. And they reduce ischemic events, and they have less bleeding compared to warfarin, right. But we do know that the bleeding rates aren't zero, right? So there are still some bleeding events, serious bleeding events that occur. And so – and before andexanet alfa was available, people were scrambling trying to figure out okay, well, how can we treat these bleeds? One of the things that clinicians kind of grabbed on to was the use of a 4-factor prothrombin complex concentrate, or a 4-factor PCC. And we really, you know, a lot of people did this without really, you know, any much evidence to support it, or even a real pharmacologic mechanism of action that supported it. But we're grasping at straws.

Well, now, you know, andexanet alfa has been available for several years. And so, kind of now that a lot of people have used 4-factor PCC people want to know, well, how was the comparative effectiveness between these two agents. So we basically conducted a study of data, you know, in this area, because what basically out there, while there are some studies that have compared these two, you have to remember these are very small studies, typically single-center, single-system studies, they don't have - there's no time from last dose, there's no correction for statistical comparison, you know, of differences between groups. And so, we wanted to take data and kind of collect data that was going to provide, you know, an advancement of the science in this area.

So overall, the study objective here is to compare the overall in-hospital mortality in patients with a major bleed from apixaban or rivaroxaban, and receiving either andexanet alfa or 4-factor PCC. We also then wanted to collect enough patients where we were able to do a subgroup analysis, specifically looking at patients with intracranial hemorrhage and gastrointestinal bleeds.

So is a multicenter observational study, it was conducted in several thousand patients, you can see 4,395 patients hospitalized with rivaroxaban or apixaban-associated major bleed. And like I said, treated with either andexanet alfa or a 4-factor PCC. You know, this is not single center, this is not single system. This is not, you know, just one geographic area. You can see we had 354 hospitals that contributed data to our study going across 42 different states. And like I said, our primary outcome was in-hospital mortality, also then doing a multivariable logistic regression analysis to compare the odds of in-hospital mortality between these two, and correct for any differences in baseline characteristics that may exist. information that was collected, obviously was demographics and comorbidities whether they got apixaban or rivaroxaban; 60% got apixaban, 40% rivaroxaban. Time from hospital arrival to actually getting their

reversal, and then of course time from last dose of their Xa inhibitor. We looked at the bleed characteristics such as its location, and like I mentioned intracranial hemorrhage, GI, but also critical compartment, and of course, there's a small percentage that fit into another. Especially for intracranial bleeds, was it traumatic or spontaneous? Severity, so things like Glasgow Coma score, and also GI bleed location was all collected as part of our analysis.

Like I said, 350 or more hospitals across the U.S., 42 states, most institutions were a comprehensive stroke center, a lot of more level 1 trauma center, and a pretty high percentage were level 1 or 2 Trauma Center. You can see that about two-thirds of centers had andexanet alfa and 4-factor PCC both on the formulary, about 10% had andexanet alfa only, and about a little over 20% had 4-factor PCC only, as far as formulary. So this is our overall population information.

The other thing I would also mention is that everything on this slide is really what was in the multivariable logistic regression analysis. The only things that weren't that you don't see here, was we also looked at whether it was traumatic or spontaneous. And once again, those numbers were very similar. We also looked at baseline blood pressure. So baseline blood pressure was about 134 millimeters of mercury systolic versus 130 in the andexanet alfa and 4-factor PCC, respectively. You can see the overall age patients are about 66 years old. You can see that, you know, most of the patients were male, with about 58% male. And it's again, time from last dose, and that these are very similar numbers between the groups. There was about 3.5% more patients who had - with the andexanet alfa group, who had their dose much, much more, more frequent - or more recent, which would be within the last 8 hours. And then outside of 18 hours, there were more patients numerically, not statistically, with 4-factor PCC in that group. Door-to-treatment time was about 2.5 hours between the groups. Once again, altered mental status, having a DNR order, different comorbidities like diabetes, heart failure, renal disease, and liver disease, were all very well matched within the groups. Once again, all of these things were within our analysis.

As far as the bleed locations, and so you can see here andexanet alfa in the blue colors, and 4-factor PCC in the red colors. So you know, the majority of our bleeds, or the most common type of bleed, was a gastrointestinal. And it's very common to what we see in practice. In fact, there were 2,467 GI bleeds in this. Intracranial bleeds was the next most common with being about 30%. And then there were about 10% that were compartmental or non-compressible, and about 2% that were other. As we look at the overall mortality analysis, just remember, the other bleeds are not included in that because they're very hard to quantify.

When we look at in-hospital mortality, our primary outcome what you can see here in patients who received andexanet alfa, there was actually - when you look at the raw data of 4.6% absolute reduction in in hospital mortality. When we then look at that through the multivariable logistic regression analysis, that basically corresponds to a 50% statistically significant lower mortality for patients getting an andexanet alfa versus a 4-factor PCC.

So in conclusion, this study is the largest observational study comparing andexanet alfa and a 4-factor PCC in clinical practice. To our knowledge, it is several-fold higher than anything else that's been done, which gives us some real power in correcting on limitations of other studies. And so, in this overall population, whether they andexanet alfa, hospitalized with rivaroxaban or apixaban-related major bleeding, it's associated with a 50% lower odds of in-hospital mortality when adjusted for identified risk factors of mortality.

So with that, I want to thank you very much for listening to this presentation.

Announcer:
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