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Andexanet Alfa Is Associated With Lower In-Hospital Mortality Compared to 4-Factor Prothrombin Complex Concentrate in Patients With Factor Xa Inhibitor–Related Major Bleeding

Announcer:
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Dr. Dobesh:
My name is Paul Dobesh, I'm a Professor at the University of Nebraska Medical Center at the College of Pharmacy and Omaha, Nebraska. And on behalf of my colleagues, I would like to present to you as a part of a presentation that we presented at the International Society Thrombosis and Hemostasis meeting in late June of this year, 2023. And so this is andexanet alfa associated with lower in-hospital mortality compared to a 4-factor prothrombin complex concentrate in patients with factor Xa-related major bleeding. And what I'll be presenting to you today is some of our subgroup analysis.

So the objective of the overall study was to compare the in-hospital mortality with andexanet alfa versus a 4-factor PCC, the treatment of rivaroxaban or apixaban-associated major bleeding, but as well as to look specifically for the patients in our study who had intracranial bleeds or GI bleeds, and to see what the impact was on those patients as well in terms of in-hospital mortality. You can see that the GI bleeds were the most common bleeds, in fact that there are a large number of these bleeds. There were 2,567 GI bleeds, which makes us the largest database on GI bleeds by several-fold compared to anybody else. There's also a little less than a third of the patients had intracranial bleeds with a kind of a smattering of other types of leads after that. And so the GI and intracranial bleeds are kind of the focus of this discussion.

So we look at the ICH subgroup, the clinical characteristics here. So this is over 1,700 intracranial hemorrhages. You can see as far as the location of the bleeds, they're very well matched. When you look at the baseline Glasgow Coma score, you can see a little bit of vacillation there. So based on the severe versus the moderate and the mild between the patients who had a 4-factor PCC or andexanet alfa. When we look at the in-house mortality, the raw data shows a in-hospital mortality with andexanet alfa of 12.6% versus 23.3% for 4-factor PCC. Realize that as over a 10% absolute reduction in mortality from. Now when we do the multivariable logistic regression, you can see that the adjusted odds ratio is 0.55, which really then reflects a statistically significant 45% reduction in in-hospital mortality for the patients with intracranial hemorrhage. Now, I will tell you in the original logistic regression model, Glasgow Coma scales were not part of that model, because we didn't have that information in everybody. But in a sensitivity analysis where we only included patients where we had the Glasgow Coma scores, because you could say, well, there's a little vacillation there between the groups. But when we do look at it and include that in the regression model, you can see that there is still a statistically significant reduction in in-hospital mortality for patients getting andexanet alfa versus a 4-factor PCC.

As far as what impacted mortality and intracranial hemorrhage groups, once again, the use of andexanet alfa versus a 4-factor PCC had that significant reduction, lower mortality. Other things like if a patient had impaired mental status at baseline or a DNR order, those things were associated with higher mortality, as would be expected. Patients with chronic kidney disease and heart failure were also

associated with higher mortality. And time-to-treatment, right, this is why you've got to treat these patients early. We're trying to prevent hematoma expansion. And so if you were - if we treated those patients within 30 minutes or really what the graph shows here, if a patient's treatment was more than 30 minutes after they came in, that was associated with almost a 2.5-fold increase in in-hospital mortality. And so this is just kind of showing you what impacted the in-hospital mortality in those patients.

As far as the GI group, the clinical characteristics are here, once again, like I said, 2,567 patients here, whether it was upper lower or not sure where it was, you can see very similar between the groups. We did have patients, about two-thirds of them had an AIMS65 score and so a little bit of vacillation there between the scores but once again, very similar. When we look at the results, while in-hospital mortality with GI bleeding happens significantly less often, it was definitely still reduced by over 50% with the use of andexanet alfa versus that of a 4-factor PCC. And once again here while an AIMS65 score was not part of our original logistic regression model, we did a sensitivity analysis where it included patients who did have that information. And once again, the magnitude of benefit and the statistical significance is still there for the reduction in in-hospital mortality for patients getting andexanet alfa versus that of a 4-factor PCC.

As far as the things that affected mortality in the patients with GI bleeds, they're a little bit different. Some of them some of them are similar, some of them are different, compared to that of intracranial bleed. Once again, you can see andexanet alfa associated with the over 50% reduction and in in-hospital mortality. Here, increased age obviously was associated; didn't see that in the intracranial group. Impaired mental status, DNR orders are still associated with increased mortality. Chronic kidney disease and heart failure, much like the intracranial hemorrhage patients, associated with increased mortality. But in these patients, a presence of liver disease was also associated with in-hospital mortality. And once again, the door, you know, basically the time to treatment, the magnitude is there, but, you know, once again, didn't quite meet statistical significance and very wide confidence interval in that setting.

This is not a randomized controlled trial, right, it's retrospective. So there's going to be obviously limitations to these types of data from a non-randomized study design. And so, you know, we, you know, obviously, through the regression model, we've corrected for as many things as we could, but obviously, there's going to be things that don't necessarily - that we're not aware of that maybe we should have corrected. And obviously, the data in is going to be as significant as the, you know, as is their output. So, right, it's the accuracy of the information is kind of based on what I was put in.

As far as future data, right. Most of us are probably aware now that the randomized controlled ANNEXA-I study has recently been stopped by its Data Safety Monitoring

Board after achieving a prespecified clinical criteria for hemostatic efficacy with andexanet alfa versus usual care in patients with intracranial hemorrhage. So once again, kind of a multitude of data here kind of showing very similar thing.

So in conclusion, this study represents the largest observational study of data comparing andexanet alfa and 4-factor PCC, and it's actually bigger by several-fold. The overall population, andexanet alfa, demonstrated about a 50% reduction in in-hospital mortality when correcting for confounders compared to that of a 4-factor PCC. And then when we looked at the subgroups, like we did just now, we can see that that magnitude of benefit of approximately a 50% reduction is consistent and statistically significant for both the intracranial hemorrhage and the GI bleeds.

Thank you very much.

Announcer:
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