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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Meaningfulness of ISTH Chart Audit of In-hospital Mortality for ICH?

Announcer:
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Dr. Dobesh:
Hello, my name is Paul Dobesh. I'm a pharmacist and a Professor at the University of Nebraska Medical Center, the College of Pharmacy here at Omaha, Nebraska. And today I want to discuss the meaningfulness of the ISTH, or the International Society of Thrombosis and Hemostasis chart audit data that was presented on in-hospital mortality for intracranial bleeds comparing andexanet alfa versus a 4-factor prothrombin complex concentrate.

A little bit of background of why this study was done is that we know that factor Xa inhibitors such as apixaban and rivaroxaban, they're associated with many benefits over vitamin K antagonists like such as warfarin. And one of those benefits is less bleeding, especially severe bleeding, like fatal bleeding, intracranial bleeding. But while they're less than they are with vitamin K antagonists, the numbers aren't zero. And with the millions and millions of patients who are getting apixaban and rivaroxaban, we're going to see these types of bleeds.

Now, before andexanet alfa was approved, right, we kind of were scrambling for what to do when these patients presented. And one of the things that we kind of theorized probably might work would be some replacement with a 4-factor prothrombin complex concentrate. And we did this really with very limited data, as well as the fact that we really didn't have a pharmacologic mechanism for sure about why this would even work, if it would even work. And so since this time, there had been data that people - where people have looked at andexanet alfa versus the 4-factor PCC in these real-world analysis as far as clinical practice. But remember, there are a number of limitations to the data as they exist. These are things such as they're pretty small studies. They're, you know, single center, maybe single systems studies. You know, other limitations that are out there is that you know, if there are differences between the groups, which there probably are, there's no statistical, you know, a correction, whether it be propensity or multivariable logistical regression analysis to correct for different differences between groups. Rarely do we ever know the time from the last dose, so how much anticoagulant is suspected to even be there. And so, there's a lot of limitations to these data that we wanted to kind of, you know, try to correct for or provide data that didn't have the same limitations. So our objective was to compare in-hospital mortality overall in patients receiving andexanet alfa or 4-factor PCC, for treatment of a rivaroxaban or apixaban-associated major bleed. We also then looked at specifically at the subgroups of patients who had either intracranial bleeds or gastrointestinal bleeds, with intracranial bleeding data being the focus of our discussion here today.

Overall, the study design is a multicenter observational study conducted in 4,395 patients which is multifold bigger than anything that's been done before, hospitalized with a rivaroxaban or apixaban-associated major bleeding episode treated with either andexanet alfa or 4-factor PCC. We looked at data in 354 hospitals, collected our data in 42 different states. And our primary outcome here is in-hospital mortality, and also doing a multivariable logistic regression analysis to compare for differences between groups, especially if there are differences in issues that affect in-hospital mortality.

The data we collected, we looked at - we collected demographic data, comorbidities, we, you know, whether it was apixaban or rivaroxaban, and 60% were on apixaban, 40% rivaroxaban. We collected basically the time from arrival at the institution to actually receiving the management strategy for that related bleed, whether it be andexanet alfa or a 4-factor PCC. We also collect the data of time from last dose, which I said is really missing in a number of different studies. The location of a bleed, so was it intracranial bleeding, GI, critical compartment, something else? Specifically for the intracranial bleeds, we collected information, whether it was traumatic or spontaneous in origin, as well as intracranial bleeding, intracranial hemorrhage severity, and also information on the GI bleeds.

Like I said, when we look at the institutions that were here that we – that helped collect our data, like I said, 354 hospitals across the United States, 42 states, so a wide geographic representation. You can see most institutions were a comprehensive stroke center, you know, about 45% were a level 1 trauma center, and actually that number grows much higher if you look at level 1 and 2 trauma centers. Roughly about two-thirds of the institutions had both an andexanet alfa and 4-factor PCC on their formulary, about 10% had only andexanet alfa, and yet about 23% that had only a 4-factor prothrombin complex concentrate.

As far as the bleed location, the most common site of bleeding was GI, which is what we see in clinical practice. But we do see that about 30% of all the bleeds in our study were patients with intracranial bleeding, which is our focus here today.

So what you can see here, right, when you look at the bleeds, right? So we're looking at well over 600 patients in each group, in fact we're looking at about 1,300 bleeds collectively. In the intracranial, you can see as far as where the bleeds were, you know, with andexanet alfa versus a 4-factor PCC, the numbers are very similar, no differences here between the groups. We did have information on baseline Glasgow Coma scores. And that is shown here. And you can see some a little bit of vacillation in the groups here. But just realize that Glasgow Coma scores were not reported in about 50% of the patients. So not all patients had a Glasgow Coma score available, but this is the information for those where the information was available.

When we look at in-hospital mortality, our primary outcomes, especially in the intercranial group, what you can see here is a 10% absolute reduction in mortality, which is pretty powerful. Now, when you correct for differences between groups, especially things that may have impacted mortality in the multivariable logistic regression analysis, that is associated with a 45% lower mortality for patients getting andexanet alfa versus that of a 4-factor PCC. Now, like I said earlier, not all patients had a Glasgow Coma score. And Glasgow Coma score was not part of our initial logistic regression analysis, because remember, our analysis looked at patients' overall data, where it didn't matter where the bleed was, we looked at everybody. So we did a sensitivity analysis, where we included in the intracranial hemorrhage group, only those patients who had a Glasgow Coma score available. Right? So if there were, you know, concerns about the slight vacillations in those Glasgow Coma scores, all right, well, let's try to see what happens when you correct for that. And actually, what you still find is basically over - well over 38% reduction in mortality, statistically significant. So the data are very consistent whether you include the Glasgow Coma score in the analysis or not.

Now what else affected in-hospital mortality? I already mentioned that andexanet alfa was associated with a 45% significant reduction in mortality. Not surprisingly, impaired mental status or DNR orders did not - did increase mortality. Interestingly, whether it was a traumatic bleed or a spontaneous bleed, the mortality was very similar. As far as comorbid conditions, you can see that heart failure was associated with a higher bleed, right there. Time to treatment, so you know, a lot of that has been in the literature lately about hematoma expansion, and how detrimental that can be and how fast that can happen. And you can see here that if your door-to-treatment time was more than 30 minutes, that was associated with almost a 2.5-fold increase in mortality, regardless of what you got. So once again, the, you know, the time of treatment - to treatment in these patients definitely does matter.

So in conclusion, this is the largest study overall, observational, that's been done to date by several-fold the data comparing andexanet alfa versus a 4-factor PCC in clinical practice. In the overall population, looking at all types of bleeds, treatment with andexanet alfa in patients hospitalized with rivaroxaban or apixaban-related major bleed, was associated with a 50% lower odds in mortality compared to 4-factor PCC, in the logistic regression analysis. And what's interesting is when we look specifically at the patients with intracranial bleeds, that reproduction was very similar, 45%. So the data are very consistent. It really doesn't seem to matter where the bleed was. But the data are very consistent for this statistically significant, approximately 45% to 50% reduction in mortality, I think, which is a very important outcome for us to consider.

And so with that, I want to thank everybody for taking part and listening to this presentation, and I wish you a good day.

Announcer:
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