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Meaningfulness of ISTH Chart Audit of In-hospital Mortality for GI Bleeds?

Announcer:
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Dr. Dobesh:
Hello, my name is Paul Dobesh, PharmD. I'm a Professor at the University of Nebraska Medical Center College of Pharmacy, which is located in Omaha, Nebraska. And today what I want to discuss with you is the meaningfulness of the ISTH chart audit data that was presented looking at in-hospital mortality and specifically looking at the patients who had gastrointestinal bleeding.

A little background about why the overall study was done. We know that oral factor Xa inhibitors such as apixaban and rivaroxaban, they have advantages over vitamin K antagonists in efficacy and safety. There's less bleeding with these agents, especially less fatal bleeding, and things like that. But we do know that the bleeding rates are not zero. And with a large number of patients, millions of patients who are getting these agents, we know we're going to see these factor Xa-related major bleeding episodes.

Now, before andexanet alfa became approved for the treatment of these major bleeds, or the management of these major bleeds, we really were kind of scrambling as clinicians to figure out what to do. Right? And so one thing that people started to kind of utilize was the use of a 4-factor prothrombin complex concentrate, or a 4-factor PCC. And we did this really with very limited data. And really, without a real pharmaco – a known pharmacologic mechanism of action. We had some suspicions, but we really kind of really did - we were kind of just trying something. And so there have been studies since andexanet alfa got approved, some very small studies, that have been compared andexanet alfa to 4-factor PCC in routine clinical practice, kind of these real-world analysis. But they're really primarily based on kind of small, single-center or single health system studies. They have many other limitations as well, such as there's no correction for baseline differences and characteristics. Time from last dose is almost never known. So we don't really know how much anticoagulation might even – anticoagulant might even be in the system. And one of the things in our discussion today is there's very few data; I mean, literally could probably count them on my fingers, of patients who where we have data comparing these agents in the setting of gastrointestinal bleeding.

So our objective was to basically compare the overall in-hospital mortality in patients who received the other andexanet alfa or 4-factor PCC for treatment of their rivaroxaban or apixaban-associated major bleeding episode. We also then wanted to have enough patients that we could look specifically at some subgroups, such as those with intracranial bleeding, as well as those with gastrointestinal bleeding, which is kind of our focus here right now.

Our study design overall, it's a multicenter observational study conducted in over – in 4,395 patients. So very large database. Hospitalized with rivaroxaban or an apixaban-associated major bleeding episode, like I said, and treated with either andexanet alfa or 4-factor PCC. So we were not a single center or even, you know, single system, you can see we had 354 hospitals in over 42 states. And our primary outcome is in-hospital mortality. And once again, correcting for any differences in baseline characteristics. We did conduct a multivariable logistic regression analysis in patients getting these two agents.

As far as the data we collected, obviously, like I said, we have demographics and comorbidities. We had the type of Xa inhibitor, and so, you know, 60% were getting apixaban, and 40% were getting rivaroxaban. We have time from hospital admission or basically arriving in the hospital to actually receiving their management strategy. We also have time from last dose of their Xa inhibitor has been collected. Location, where was the bleed? Was it intracranial bleed? Was it gastrointestinal bleeding? Was it a critical compartment bleed? And there's a small number of patients that would have fit into this other category. Now, as far as intracranial bleed, we looked at traumatic versus spontaneous. We looked at ICH severity, and of course GI bleeding location.

Like I said, when we look at the institutions that were here, that we - helped collect our data, like I said, 354 hospitals across the United States, 42 states, 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% had only a 4-factor prothrombin complex concentrate.

As far as our bleed locations, and our focus being in gastrointestinal bleeds, that was really the majority of our bleeds. You can see basically it made up about 57% of our overall bleeding. That gives us well over 2,000 gastrointestinal bleeds to look at. So let's take a look at those.

As far as the bleed characteristics, you can see here once again at the numbers at the top. Once again, like I said, we're talking about well over 2,000, well over 1,000 each group, you know, it's basically looking at 1,567 major bleeds. And so you can see that the most common was the upper GI bleeding, which ran about 40%, lower bleeding at about 32%. And let's face, GI bleeding lots of times, we don't know where it's really coming from. And that's also what we found, as far as documentation in the patient record. And so that was about 27%. And these were very similar, and there's no differences here between these groups. An AIMS65 score was collected, if available, and about 70% of our GI bleeds did have these data available. Okay? And you can see here that the, you know, how they line up the andexanet alfa in the blue colors, and 4-factor PCC in the red colors. Once again, no statistical differences between those.

For our outcome of in-hospital mortality, specifically just in those 2,567 GI bleeds, you can see that the mortality rate was significantly reduced, the raw data there 2.5 versus 4.3, which is basically almost a 2% absolute reduction in in-hospital mortality. When that's put into the multivariable logistic regression analysis, basically what you see is a 51% lower mortality for patients getting andexanet alfa versus that of a 4- factor PC scene that was statistically significant.

Now, an AIMS65 score was not part of the initial multivariable logistic regression. Because remember, we were going to – we were looking at the total population, right. And so we did actually did a sensitivity analysis for - in the GI bleeding subgroup of the patients who were - that only had that data available. So you know, we all we know what their AIMS65 score in, like I said, in 70% of these bleeds. And actually when we do that, and we adjust for the AIMS65 score, the in-hospital mortality of andexanet alfa versus a 4-factor PCC is actually associated with a 55% reduction in mortality, so 51, 55, same thing. But really, the data really, really what it shows is the data is overall consistent in this setting.

We also looked at factors that were associated with in-hospital mortality. So you can see the fact the factors that are highlighted in red were the ones that were statistically significant. And so andexanet alfa, while, like I already mentioned, was associated with a significant reduction in in-hospital mortality. Age, so older patients, the older the age was, was associated with a small but statistically significant increase in in-hospital mortality. Not surprisingly, patients who presented with impaired mental status or a DNR order, that was associated with increased mortality. Patients with a history of liver disease, chronic kidney disease, or heart failure, all of those were associated with higher mortality.

And the last one I'll just kind of mention is down at the bottom, this door-to-treatment time, you can see a very wide confidence interval there. But still crossing one. So time to treatment was not associated with a significant increase in in-hospital mortality or, you know, a delay in treatment, I should say, in that setting.

So in conclusion, this is the largest study, observational study, conducted to date comparing andexanet alfa with a 4-factor PCC in clinical practice. Like I said, we had over 4,395 patients overall. And on our GI subgroup, this is the biggest collection of data in the GI population, probably by 50-fold, if not bigger, right. And so we just swarm - this is much, much more data we have than in any other area, looking at GI gastrointestinal bleeds. So the overall population looking at all the types of bleeds, treatment with andexanet alfa in patients hospitalized with a rivaroxaban or apixaban-related major bleed was associated with a 50% statistically significant reduction in in-hospital mortality, compared to a 4-factor PCC when adjusting for the factor, for when adjusting and multivariable logistical regression analysis. It’s interesting, when we look significantly in the GI bleed group, that reduction in mortality is very consistent to the overall study population with a 51% significant reduction.

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

Announcer:
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