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Summary of Real-World Data for Treatment of Oral Factor Xa-Related Major Bleeding

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Dr. Dobesh:
Hello, my name is Paul Dobesh. I'm a Professor at the University of Nebraska Medical Center College of Pharmacy. And today we're going to kind of summarize the existing real-world data regarding oral factor Xa-related major bleeding treatment.

When people use 4-factor PCC, this is typically the study that they reference. And realize this is a study that's conducted at a number of different hospitals, but only 430-some patients. You can see they have a hemostatic efficacy of about 82%, but actually, with the use of 4-factor PCC, it's actually slightly lower than that. What's interesting, though, is a number of limitations in the study. Remember, outcomes here are not adjudicated, timing of first brain scans not reported, excluded patients who probably had the most severe types of intracranial bleeding, time from last dose isn't collected. And actually, even though they might have had high hemostatic efficacy, only 24% of these patients actually went home. So that I would argue that while this is the study most often referenced, probably not the largest, the highest scale of evidence.

Now, when we look at prospective studies that have been done with the use of 4-factor PCC for this same thing, it's important to remember that everybody, instead of what we see in ANNEXA-4 or ANNEXa-I of a 12-hour hemostatic efficacy, these all use a 24-hour hemostatic efficacy. And you can see that the hemostatic efficacy is not quite what we see in an ANNEXA-4, which is about 80%, slightly lower, and this one having a higher mortality. Also, another study which does get close to that 85%, but realize that the time from last dose here was 18 hours on average. And so basically, right, I mean, most of these patients probably didn't have much drug in their system, an important point to bring out when you're evaluating these data.

Once again, another study with time from last dose of about 10 hours, but once again, a lot of patients not having adequate anticoagulation to reverse. And a hemostatic efficacy at 24 hours, not quite that of what we see in ANNEXA-4.

When we look at the comparative data, the biggest thing to remember here is that look at – is that once again, is hemostatic efficacy at 24 hours. And while many of these studies say, 'Oh, well, there's no difference,' the thing to remember is that collectively, all four of these studies is less than 200 patients. So, you know, what happens when you don't find a difference in a study with not a lot of people in it, patients in it, is that there's high risk of type 2 error. And that's clearly where we are with the existing data that exists here on this slide.

So, you know, when we look at the overall data here, right, there's a lot of limitations. Most of these are single center or single system studies, like I said, with a higher risk of type 2 error because of a lack of power. There's limited, if any, statistical adjustments for differences between groups; unclear differences of outcomes and no adjudication of the index bleeding event; variable use of accepted definition of hemostasis. So, what definition? What does - actually makes hemostasis? And many times, its clinical judgment was used. Did anything even show up in the chart? Inconsistent follow-up times. Right? So, is it in-hospital versus 30-day mortality? Is it in-

hospital versus 30-day thrombotic events? Is it hemostatic efficacy at 12 or 24 hours? And once again, inconsistent reporting of time from last dose. Right? If we're going to look and evaluate a, quote unquote, reversal or replacement strategy, the question is, is there anything in there to reverse? It almost always, very rarely I should say, that this is actually reported.

That leads us to another study, which is ANNEXA-Orange. And ANNEXA-Orange is a very interesting study in which, while it is a retrospective review of data, the data collected was all prospectively collected. So, what they used was the patients from ANNEXA-4 who got andexanet alfa, right, which is a prospectively done study. And they also looked at the data collected from the ORANGE registry. And if you're not familiar with the ORANGE registry, it's a database in the United Kingdom, in which they prospectively collect, you know, how and reversal or treatment of major bleeding with anticoagulants is managed. And so, what they did is they took out the basically the apixaban and rivaroxaban patients who were treated with a 4-factor PCC and then that's where this comparison comes from. They did - so there's about 410 patients here, propensity matched based on age, bleeding site, and a number of other things. But they were not able to match for things like bleeding severity or volume of bleeding; it just wasn't available. They had 322 patients from ANNEXA-4, 88 patients from the ORANGE registry. You can see that the mean age was fairly similar between the groups. Bleeding events was intracranial hemorrhage was pretty similar about 2/3 of the patients and GI bleeding between 25 and 30%.

When we look at the mortality here overall, though, what we see is pretty drastic differences, right? We see an absolute reduction of almost 20% in mortality with patients who got andexanet alfa instead of a 4-factor PCC. And that's actually consistent with the intracranial group, as well as the GI bleeding group. Now what's very interesting is like this almost consistent 50% relative reduction across these groups. It's there for GI bleeding, but once again, the GI bleed group is, you know, only about a quarter of the overall group. So once again, it's going to lose some statistical power there and it obviously did not meet statistical significance, but the same magnitude of change.

That then just leads us to another real-world study done in U.S. veterans, recently published just this year, which compared andexanet alfa versus 4-factor PCC, collecting data over 6 years, ending up with about 250 patients. Once again, a larger number of those patients getting 4-factor PCC than andexanet alfa. Data collected, like I said, from the VA. They did do some statistical corrections, they did propensity score-weighting Cox Model. And what they found here, as you can see in the bar graphs, the blue represents the in-hospital mortality and 30-day mortality with andexanet alfa, the red bar represents 4-factor PCC. And you can see some dramatic, once again, you know, in-hospital mortality reduced by over 50%, 30-day mortality reduced by about a third, and then the propensity score-weighting Cox model. You can see here that the significant reductions when doing those corrections, the bar graph represents the raw data.

And then finally, we've got the largest real-world study that's been conducted to date, really dwarfs that of anything else that's been conducted. You can see here that there's almost 4,400 patients hospitalized with a rivaroxaban or apixaban-associated major bleeding event, treated with either andexanet alfa or 4-factor PCC. You can see that, you know, this is not single center or even one geographic region, right, 354 hospitals, 42 different states. Statistical corrections were done and adjustments were done with a multivariate logistic regression, as well as a sensitivity analysis to make sure that the model was good with propensity weight-scoring. Primary outcome here is in-hospital mortality between the agents.

And when we look at the overall population, we can see a 4.6% absolute reduction in in-hospital mortality with andexanet alfa. And when we put that into the logistic regression model, that gives us a 50% statistically significant lower odds of mortality for the patients getting andexanet alfa versus a 4-factor PCC.

With so many patients, we were actually able to do some subgroup analysis. And so, when you look at the intracranial hemorrhage patients in this study, you're looking at over a 10% absolute reduction in mortality. And when you put that into the regression model, you can see that is associated with a 45% lower statistically significant reduction in in-hospital mortality.

And then in the GI subgroup, and it's important to remember, this is actually the only GI database that pretty much exists, there are 2,567 GI bleeds in this study. You can look at the overall mortality rate, yes, their mortality is not as high as it is in intracranial hemorrhage, but there's a lot of these bleeds that happen, so there is a significant mortality associated. And once again, when you put that in the regression model, you can see over a 50% reduction in in-hospital mortality for patients who got andexanet alfa versus that of a 4-factor PCC.

So in summary, real-world data is complementary to prospective clinical trials, it helps confirm what we already know. But it also answers questions not achievable, per se, in prospective clinical trials. Because remember, the process of randomization takes time, and in acute care that can also change what we might see. Initial real-world evidence suggesting similar outcomes between the agents are plagued by several limitations, right, small size, small scope, no time from last dose, no statistical correction between groups, and inconsistent outcome evaluations. Then I would argue that the more recent well-designed real-world comparisons, once again still with limitations, but much stronger, consistently demonstrate a significantly lower in-hospital or 30-day mortality. And the numbers, the

magnitude of that benefit is actually very consistent at about 50%.

So, with that, hopefully this quick review of where we are today with real-world clinical data will be helpful for you in your practice.

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