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

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Clinical and Practical Viability of RWE – What Now?

Announcer:
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Dr. Coleman:
Hello, my name is Craig Coleman. I'm a Professor at the University of Connecticut School of Pharmacy. And it's my distinct pleasure to have my colleague and friend, Paul Dobesh, here. Paul is from the University of Nebraska Medical Center School of Pharmacy. Paul, thank you very much for taking the time today.

Dr. Dobesh:
Yes, thank you for having me. My pleasure to be.

Dr. Coleman:
So we were both at the most recent International Society for Thrombosis and Hemostasis meeting not too long ago. And you presented a very impactful and well-done study comparing the effectiveness of andexanet alfa to 4-factor PCC. Can you tell us a little bit about that study and what some of the key findings were?

Dr. Dobesh:
Sure, I'd be happy to. You know, like you said, I think it was a really impactful data to present. You know, basically, we presented this as a study looking at patients, so basically, you had to have a code for major bleeding, it had to be patient had to be on either apixaban or rivaroxaban prior to the bleed for this hospitalization, they had to get either andexanet alfa or 4-factor prothrombin concentrate for treatments, and then we had to know what their discharge disposition was. So you know, no loss to follow-up to information there. And so basically, we collected data in 354 hospitals, 42 states, and we had 4,395 patients. So to my knowledge, it's the largest real-world evidence collected by several-fold in this area. And we also did logistic regression analysis to correct for differences between groups. We also had time from last dose. And so with all that information, and through the regression analysis, demonstrated a 50% reduction in in-hospital mortality for patients getting andexanet alfa instead of that major bleed treated with a 4-factor PCC. What's also interesting is that 50% reduction mortality, those data were consistent when we were able to look at subgroups of patients with intracranial hemorrhage, as well as those with GI bleeding. And so, you know, with this larger database and some real power to make these types of findings, I think this is the ability to hopefully impact some practice going forward.

Dr. Coleman:
Oh, absolutely. And it sounds like there are a couple of really important or distinct strengths of this study that we really should reinforce. And again, one, it sounds like you had a very large sample size. And I know that you'll agree that if you look at the literature, we're talking a sample size many-fold larger than what you would typically see for either a single-arm study that a individual institution might be performing on either one or other agent, or even doing a comparative analysis. And I think that's very important.

I also think it's incredibly important that you implemented this multivariable logistic regression method. Right? So it's very important that

we control for potential confounders and that we adjust for those differences in patient populations. Because as you can imagine, there are going to be important differences between patients who receive one agent over the other just based upon physician gestalt, you know, how they go about, you know, making these decisions.

So, based on your data, what do you think this does in terms of - what are the current state of the guidelines? And maybe what do you think your study adds in terms of the guidelines for reversal of DOACs, and particularly oral anti-factor Xa inhibitors?

Dr. Dobesh:
Yeah, I think, you know - I think these data build on many of the limitations of the existing real-world evidence that you mentioned. You know, a lot of the real-world evidence is single center or single system. We're across 42 different states and 300 hospitals, right? Many of the existing real-world data that exists is very small. There are some studies that suggest there's no difference between these agents. But to my knowledge, the largest of those studies to date is 109 patients. And we are 40-fold times that. So there's clearly a power issue, right? A high risk of a type two error with these smaller studies and it shows that when you actually look at larger numbers of patients, we see some differences.

You know, we correct for the baseline variables. Most of these smaller studies don't do that. We have time from last dose, so we actually know that we're actually have something to reverse. Most of these other studies don't have that. So it really is building on this.

And one of the things too, Craig, that I know you and I have discussed, and maybe I'll throw this back to you, because you know, most of the existing data right now is in this that the comparative data was mainly looked at data with patients with intracranial hemorrhage. And what about, you know, GI bleeds? Because we actually had a lot of Gi bleeds in this study, I think we had 2,567. You know, I know you've reviewed these data, what have you found in the world of GI bleeding?

Dr. Coleman:
Absolutely. So there's a very large, or quite a paucity of literature in terms of the relative efficacy and safety, particularly in real-world settings of these agents in terms of treating gastrointestinal bleeds. It's very rare, if any, that you'll actually see a study that actually focuses specifically on looking at gastrointestinal bleeds. They do on occasion occur, you know, as a subset of some of the studies that have been out there in the past; however, we're usually talking about a small handful of patients, which really doesn't allow us to make any real or draw any real solid conclusions.

In addition, of course, you know, and this is something that we'll, you know, perhaps think about as future studies are done in gastrointestinal reversal in gastrointestinal bleeds is, you know, not all gastrointestinal bleeds are the same, right?

Dr. Dobesh:
Yeah.

Dr. Coleman:
Upper gastrointestinal bleeds, lower gastrointestinal bleeds, variceal bleeding, right? And so those are important things to consider. And we know that there are, for instance, risk scores that are associated with trying to assess what the outcomes of these patients are. And I believe, and correct me if I'm wrong, is in your study, that there were some attempts to assess some of those risk scores for gastrointestinal bleeds. So at least when we say that you adjusted for potential confounders, some of that was factored in, even within the gastrointestinal bleed subset.

Dr. Dobesh:
Yeah, we - about 70% of our GI bleeds, has an AIMS65 score, which actually wasn't part of the original analysis, because we looked at everybody, right, and, and so not everyone collects those data. But, you know, we had 70% of patients had an AIMS65 score. We actually did a separate analysis to just look at those patients to make sure in case there were differences between those scores, they look very similar, but just to make sure we're comparing apples to apples, and that 50% reduction in mortality holds consistent, actually grew a little bit, but you know, but yeah, it's very consistent.

And, you know, just to go back to what you are asking me about the guidelines, I think there's a huge misinterpretation of the guidelines as they're written even today. Right? The guidelines today, right, will say, andexanet alfa, right? That's the treatment for these Xa-related bleeds. And then it says, if not available, consider a 4-factor PCC. And I think that this has been manipulated, right? The reason that if not available is there, is because when the drug first came out, when andexanet alfa first came out, right, it was very limited supply. And so most patients, most places, could not physically get the drug in their hospital. And so if you didn't have it, the thought here is, ‘well, if you’ve got nothing else, you can try 4-factor PCC.’ It is not, right? The way a lot of people are using this is, the not available is not because you chose not to put it on your formulary. Right? It's not because of our decision not to have. It’s because we couldn't physically get it. And so our decision not to have it is not acceptable as if not available, because I decided not to make it available. Everybody now can get it.

And that is the guideline recommendation of this therapy. And so I, you know - and I think also, you know, will this change guidelines? It's hard to say It's real-world evidence, but I think, you know, you combine our very large study in the magnitude of reduction in in-hospital mortality, and you combine that with the ANNEXA-I, we're not going to know exactly what that is, but you know, it's probably at least a 10% benefit in hemostatic efficacy, right? So we've got data now from a randomized controlled trial. And we've got a very large real-world trial looking at mortality.

The argument to continue to use a 4-factor PCC is really thin, right? I mean, I guess, you know, whenever you're looking at this, right, you stack up your best data for andexanet alfa, and you stack up your best data for a 4-factor PCC, and this is not really a fair comparison, right? We have randomized control. We have prospective data and other studies. We've got study of over 4,000 patients, right, real-world evidence, and I think the best data over here for 4-actor PCC is like a single-center, 109 patients comparative and like another study that looked at - a single-arm study looking at hemostatic efficacy retrospectively. I mean, those are not apples and apples, right? This is a completely different – there's just completely different landscaping in the evidence that's available and we just have to really be honest with ourselves as clinicians about this is where this applies.

Dr. Coleman:
Yeah, absolutely. I think those are some very astute observations about the guideline and how they're being applied, you know, kind of generally. And of course, we also have to remember, you know, even within the discussion of using

PCCs or 4-factor PCC, right, that there's even within the guidelines, controversies there, for instance, dosing, right? So, you know, do you use the high dose? Do you use the low dose?

Dr. Dobesh:
Fixed dose.

Dr. Coleman:
Guidelines suggest that, you know, or at least some of the guidelines suggest that we should be using a 50 international unit per kilogram dose. But at the same time, when you look at the real-world evidence, all these studies, we're talking probably 3 dozen studies at this point, looking at real-world 4-factor PCC at individual institutions, and a good, probably the majority of patients, are still receiving a lower dose of 4-factor PCC. So another example of how we're not necessarily following what the guidelines suggest. And so it's, it's definitely a situation or there's room for additional research. But I absolutely agree with you, with studies like yours, which again, I want to compliment you on. I think it was an excellent study, and very well done, very impactful with what we're about to hopefully find out fairly soon about ANNEXA-I. Again, you summarized it very nicely. We don't know much, but what we do know for sure, is that it was stopped early because there was at least a 10% absolute benefit in hemostatic efficacy with andexanet alfa over standard of care. Not exactly sure what standard of care means, but we'll hopefully find out more details soon. But with all this data adding up, it's becoming increasingly, in my opinion, as well, more difficult to justify a 4-factor PCC strategy only.

So with that, Paul, I'd like to thank you very much for taking the time today to have this little roundtable discussion about your study and the guidelines and where we are in terms of reversal of oral factor Xa inhibitors in patients who are having major bleeds, and again, in particular, intracranial hemorrhage, but also gastrointestinal bleeds. Thank you very much for your time.

Dr. Dobesh:
Yep. Thank you, and I appreciate the invitation. It's always good to work with you, Craig. Thank you.

Dr. Coleman:
Thank you.

Announcer:
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