Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/real-world-data-compared-to-clinical-practice-are-the-data-replicated-in-clinical-practice/15379/

Time needed to complete: 55m

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

Real-World Data Compared to Clinical Practice: Are The Data Replicated in Clinical Practice?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Dobesh:
Alright, so we'll get started here. So just as we start out, right, we talked about reversal versus replacement strategies. And so we know that with the use of Xa and direct Xa inhibitors, right, one of the beautiful things about Xa inhibitors compared to Warfarin is there's less bleeding. But we all know that the bleeding, even though it's less than intracranial hemorrhage, especially those is less, the number is not zero. And so there are still going to be events. And with the fact that there's about 8 million people in the United States alone getting oral Xa inhibitors, there's going to be a number of these bleeding events that happen. And so what do we do? How do we treat these?

So one approach is reversal. And that's where andexanet alfa comes in, as most of us know, is basically a decoy protein. It's a modified factor Xa molecule, it's not enzymatically active, it can't convert prothrombin to thrombin. But it can kind of act as a sponge and kind of gobble up the factor Xa that's in the circulation and bind it to it. It also does not insert itself into the prothrombinase complex.

Another approach that people have decided to take is what about just replacement? And what if we just give these in, you know - a four-factor PCC. In United States, that's usually Kcentra. I think in Canada, you guys have about three. I think there's about four or five of them in Europe. But there's a number of them that are out there. And basically, these are inactivated clotting factors II, VII, IX, and X. This is the approach that's really - that we want to use for warfarin reversal, obviously. And but - do we, you know, what is the role of it here in the area of factor Xa inhibitor reversal?

And so let's look at like the clinical evidence that exists as well as kind of then transition into real-world data. Most of us are familiar with these data. This is Deb Siegal's paper in New England Journal of Medicine, where people - patients got andexanet or placebo in a prospective manner. Placebo was kind of what's shown here in the black. And so they got a bolus dose of andexa, so you can see, bam, right, the anti-Xa levels go down immediately. And they stay down for the 2-hour infusion. And then over the next 2 hours after you stop the infusion, it doesn't matter if it's rivaroxaban or apixaban, they slowly make themselves back up.

Now as they go back up, there's been a number of people have looked at these graphs and said, ‘Well, I'm concerned about this go back up part.’ Right? You have to remember, it's not going back up to baseline; these numbers still here end up being a roughly about 40% reduction from the peak. But also remember, I think what's more important is the fact that if you look at like - the purpose of inhibiting Xa is to stop thrombin. Now we can debate on how much what thrombin generation means, but really what you can see here, then once again in the orange, I think that's orange, I'm a man, I've got like four colors in my wheel. Right? But you can see here, right, the thrombin generation definitely goes up. And after you stop the infusion rate, right, you basically have done enough to kickstart to thrombin again. Right?

That does not sail back down. And so the thrombin generation is basically maintained even after the infusion is stopped.

That leads us to more clinical evidence of ANNEXA 4, once again, a study most of us are familiar with. And so besides just looking at reversal of anti-Xa, which it did with 93 and 94% reductions for apixaban and rivaroxaban, respectively, there was also - they also looked at hemostatic efficacy. And they looked at hemostatic efficacy in 12 hours. I think that's important as we look at some of the data here in a minute, often in other studies, is time has been stretched out. And so once, you know, the anesthetic efficacy - and this is actually from the final report that was just published full in print just this last week, and you can see basically the hemostatic efficacy at 80%. Then it really - it was irrespective of what drug they got, it was irrespective of where they bled, whether it be GI or intracranial. And

it was irrespective of whether you've got low or high doses of andexanet. And so you know, while the low dose is used in about 80% of patients. So very consistent hemostatic efficacy there.

Alright, well, what do we know about four-factor PCCs? Right? We've got the clinical data or these prospective, randomized - not randomized, excuse me, prospective trials. So here's a retrospective review. Probably the largest one. There's many of these out there. There's a stack of literature like this. But this is probably the largest one that I've seen. This is actually published in circulation. So this is looking at intracranial hemorrhage, and they got basically different types - whoops, sorry, backup - they got different types of four-factor PCC. And what they found was a hemostatic efficacy that ran right around 80%. So that's pretty similar. But once again, there's some limitations to these data. And this is the problem with this retrospective data, is you don't know when the first scans are done. Since it's not prospectively evaluated, trying to figure out what hemo - and I think, you know, we're going to talk more about this later, but trying to figure out what hemostatic efficacy is retrospectively is extremely challenging. Right? Because you don't know what's happened even before the first scan was done. Okay? So they didn't have that. There are certain types of ICH.

And another big thing is the time from last dose is not reported. And it's not reported in most of these studies. Because we have to ask ourselves, right, so when did they get the last dose? Is there any actually Xa activity in there to be reversed? And we don't know that information from this.

Alright, well, what about are there prospective studies? And there are three that I'm aware of, these prospective studies, looking at a four-factor PCC, and its hemostatic efficacy. But realize all these - they're not looking at hemostatic efficacy at 12 hours, they're stretching it out to 24. So this is twice the timeframe. And so what you can see, though, is hemostatic efficacy here in the Majeed trial, right, it's about, you know, the average time for last dose is known. So that's good data, right, about 12 hours. It's actually very similar to what was seen in ANNEXA 4.

ANNEXA 4 is about 11.5 hours from last dose with a hemostatic efficacy of about 70%. And then, of course, when you go to Sam Schulman, and - but a mortality rate of 32%, which I think is pretty high in these types of studies. You know, here's another one. Now, this study here has 85% hemostatic efficacy. Well, that's really good. But look at the time from last dose. The average time from last dose was 18 hours. That's the average. That means that half of them, right, had time beyond that. And so how much anticoagulant is really being reversed in that setting? I don't think we know the answer to that with these studies. And then finally, another one. So time from last dose is good. Efficacy was 70%. But realize they had almost 20% of patients who had basically what you would consider subtherapeutic. I don't like therapeutic for Xa's, but let's just call it low levels of the factor Xa inhibitor. Right? So is that number 53%? Or is that number of 70%? Because if you don't have any - if you're not reversing anything, then, you know, that's not really contributing to your efficacy.

And we do have some head-to-head data. Once again, these are small. These are basically kind of almost like case series per se. So the head-to-head data here, we can see once again, thrombotic efficacy – or, excuse me, hemostatic efficacy at 24 hours. And you can see in the first study here, you can see that the efficacy, you know, 90% basically, versus 60. We don't know if that's different. Okay? And then finally, you know, we have this one over here, very similar. Very similar mortality, no different.

And these papers come to the conclusion, oh, it doesn't really matter what you do. But realize that none of these papers - you know, these papers rarely enroll over 100 patients. Okay? So there's very limited data. So there are larger databases. This is - so you never want to be second author on a paper, I think. Right? Because on all the slides, it always just shows the first author. Craig Coleman will always be - I'm the second author, no one ever knows, no one ever cares. Okay, I'm just kidding. So basically, what we did though, is we collected data from 45 hospitals in the U.S. and said, 'Okay, what do you guys doing for reverse?' Right? Now, there is no comparative statistics here. Alright? Disclaimer. Because we do not collect a bunch of data - a lot of the baseline data, and we did not basically - so we didn't - there was no way to adjust for differences. Alright? But what you do - what we did find is that when we look, you know, across the different agents here that get used, options, if you look at andexanet, four-factor PCC, the mortality rate for intracranial hemorrhage is one-third. And then the mortality rate actually for GI bleeds is about one-fourth of that. So andexa patients consistently had lower mortality.

And then finally, this is the largest, at least to my knowledge, the largest database ever collected. I was able to present this data at the ISTH meeting this past year; 184 hospitals, over 2,800 patients. And these are patients with a DOAC-induced bleed as well as enoxaparin bleeding. And basically what we saw - so these are all the things that went into the logistic regression analysis. And so after all that, basically, the use of andexanet alfa was associated with a 31 statistically significant percent reduction in the odds of in-hospital mortality. Okay? Other things that affected mortality as well, such as things you'd expect, ICH bleeds versus GI bleeds, and things like that. But using andexa significantly reduced mortality. And this is just a different slice of that data looking specifically at the ICH and GI bleeding. And basically, once again, about a 33%, very similar, statistically significant. And what you see is a very consistent impact of the event rates. That it doesn't mean - the benefit's not just in the ICH patients, the benefit seems to be there in the GI patients as well.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.