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https://reachmd.com/programs/cme/repletion-or-reversal-optimizing-specific-therapy-for-direct-oral-anticoagulant-doac-related-life-threatening-bleeding-using-real-world-experience/15633/

Released: 06/20/2023
Valid until: 06/20/2024
Time needed to complete: 1h 34m

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Repletion or Reversal? Optimizing Specific Therapy for Direct Oral Anticoagulant (DOAC)-Related Life-Threatening Bleeding Using Real-World Experience

Announcer:
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Dr. Gibler:
Hi. I would like to introduce our first speaker. And Dr. Natalie Kreitzer is Associate Professor of Emergency Medicine in Neurocritical Care at the University of Cincinnati, in Cincinnati, Ohio. And Natalie is an Emergency Physician immediately with first training, subsequently doing 3 years of neurocritical care, and also stroke. So she's on the Greater Cincinnati Stroke Team. And Dr. Kreitzer is also a National Institute of Health funded investigator. And so she does research primarily in the area of traumatic brain injury. But we would like her today to speak with us about Repletion or Reversal? Optimizing Specific Therapy for Direct Oral Anticoagulant-Related Life-Threatening Bleeding Using Real-World Experience. Dr. Kreitzer.

Dr. Kreitzer:
Well, good morning. Thank you very much for coming in. And thank you, Dr. Gibler. Well, as he mentioned my name is Natalie Kreitzer. And I'm an Associate Professor of Emergency Medicine Neurocritical Care and part of the University of Cincinnati Stroke Team. I'm going to talk today a little bit about reversal versus repletion, and optimizing that specific therapy for patients who are on direct oral anticoagulant-related bleeding.

Now, before we get started, I want to point to this slide. And this is the reason that we provide anticoagulation reversal or repletion to these patients is to try to decrease the chance of hemorrhage expansion or hematoma expansion. Now, this certainly can happen in patients with spontaneous ICH who are not anticoagulated. But we know that that risk increases in patients who are anticoagulated. And this is the reason that we want to provide that reversal strategy.

I do want to show the coagulation cascade briefly. Certainly, this is something that we all learn and probably forget over time, but I do want to point it out to show how these different agents work. So when we think about vitamin K antagonists, warfarin, those are factors that are vitamin K dependent, factors II, VII, IX, and X. And we can see how that activates down into the pathway, activating Xa and to thrombin, and then fibrinogen into fibrin, which then leads to that clot formation. Now when we think about the anti-Xa inhibitors, which is certainly the most common type of oral anticoagulant that is being used in the United States, those directly inhibit factor Xa, which then allows for thrombin to turn fibrinogen and fibrin. And then less commonly, the direct thrombin inhibitors, such as dabigatran, work directly on the thrombin formation, thus preventing the fibrinogen to become fibrin.

Now repletion and reversal are two different strategies. So when we think about reversal, specifically, we think about those patients who are on a direct oral anticoagulants such as a factor Xa inhibitor or direct thrombin inhibitor. Those patients are not deficient in any of those factors II, VII, IX, and X. They certainly have enough of that in their plasma at any given time. So reversal is what we call agents

such as andexanet alfa or idarucizumab in the case of direct thrombin inhibitors, such as dabigatran. Repletion is utilized for those patients who are deficient in those factors is vitamin K dependent factors II, VII, IX, and X. Traditionally with prothrombin complex concentrates or fresh frozen plasma, and I'll talk a little bit about those two strategies in some further slides. Now, these are agents approved for warfarin repletion, and can be used off label - off FDA label in the United States for DOAC reversal.

Now I'll dive in just a little bit about the FFP versus PCCs, and go into some of the data behind that. But just as a little bit of background about what each of these two strategies do. FFP contains all the factors in the blood. And in order to reverse a patient who's on a vitamin K antagonist, it requires large volumes 10 to 15 cc's per kilogram, a lot of time to prepare and administer, and there's a risk of fluid or volume overload in those patients, as well as transfusion reactions.

Prothrombin complex concentrates, on the other hand, are either 4-factor or 3-factor activated or inactivated. Oftentimes institution specific as to what you might carry. And the dose is either fixed or based on the INR and the weight. This results in faster reversal, less volume, but at the cost of an increased price.

Now, when we think about reversal strategies, again, these are for patients who are not deficient in those factors, and they need that direct reversal of their DOAC. These are the two main studies, both published in *The New England Journal of Medicine* describing those agents. And I believe David is going to go into further depth about these particular studies within his slides. But just for review, dabigatran reversal is - sorry, idarucizumab for dabigatran reversal, idarucizumab is a monoclonal antibody that binds to that dabigatran, may be needed if the last dose was in 12 to 24 hours. And then the labs to follow with those patients can be the PTT and thrombin time, that dose being 5 grams. Now that's not as common of a DOAC agent. The one that is the more common is the factor Xa inhibitors such as rivaroxaban or apixaban. And andexanet alfa, or Andexxa as it's called in Europe, can be used for reversal for those patients. This is a recombinant modified human decoy factor Xa protein may be needed if the dose was within 18 hours. And again, David's going to speak to why that 18 hours may not be the very best marker. And the lab to follow and those patients is an anti-Xa level, although this is not available to most hospitals, sometimes the academic centers but most community sites are not going to have access to this. And if they do, it can take quite a while to come back. And then the dose is going to be based on the factor Xa inhibitor dose that the patient is on and the time since they've taken that medication.

And David is going to describe this study in a little bit more depth, but one of the endpoints of the ANNEXA-4 study which was a study that looked at patients who had active ongoing life-threatening bleeding, and were given andexanet alfa was those percent of patients who had excellent or good hemostasis. Now in the setting of ICH, that was deemed to be less than 35% hematoma expansion which was measured by serial CT scan that was done at 12 hours.

Now one of the criticisms of that study has been that there was not a control group looking at what you would do in a patient where you did not have andexanet alfa available to you. For that reason, that study is ongoing. But for now, we have two propensity matched real-world data types of analyses. This is one of the first ones. This is Costa which was published in *Critical Care*. And in this cohort, patients they looked at hematoma expansion and compared the andexanet alfa cohort from ANNEXA-4, propensity matched them to a group who received 4-factor PCCs. And the overall cohort analysis showed statistical significance when they looked at hematoma expansion in the group with andexanet alfa on board.

And likewise, this propensity study that was done by Huttner published in *Stroke* in 2022, demonstrated similar findings and the group with andexanet alfa, again propensity matched to those who had usual care, which was generally PCCs, demonstrated a significant difference when they looked at ICH expansion. And hospital mortality was close to a significant finding, but as you are well aware of and is oftentimes the case, that as an endpoint is just a little bit messier, just given all of the things that can happen in the hospital to a patient.

Announcer:
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