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What's the Best Available Evidence for Reversal of Life-Threatening Bleeds?

Announcer:

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Dr. Coleman:

Hello, my name is Craig Coleman. And I'm a Professor of Pharmacy Practice at the School of Pharmacy at the University of Connecticut. It's my pleasure today to talk to you about the best available evidence for reversal of life-threatening bleeds.

Now, at the moment, the best available evidence that we have in terms of reversing life-threatening or severe bleeds in patients receiving oral factor Xa inhibitors clearly come from the ANNEXA-4 trial. Here, they looked at andexanet alfa in major bleeding. And again, in patients receiving various types of factor Xa inhibitors. Patients had to have an acute major bleed within 18 hours, a factor Xa inhibitor administration. There was a safety population for an ANNEXA-4, where they included all patients but also an efficacy population, which was included where patients had to have a baseline anti-factor Xa activity level which was above a predefined threshold. And this was in order to assure that patients were actually - still had adequate anticoagulation and board worth reversing.

Now to get into the trial, patients also had to have a major bleed that met a modified International Society for Thrombosis and Hemostasis definition. A key aspect of the ANNEXA-4 trial was that major bleeding criteria, hemostatic efficacy, and thromboembolic events which were key outcomes in this study, were assessed by an independent adjudication committee, with the primary outcome being excellent or good hemostatic efficacy defined by a scale used in other previous reversal studies at 12 hours. And now you can see overall it was - and this is data coming from the most ANNEXA-4 publication and circulation 2023 by Milling and colleagues. And what we can see that of the 342 patients who were in the efficacy population, 274 patients achieve either excellent or good hemostasis, or 80% of patients overall. And interestingly, regardless of the site of bleed, whether it be an intracranial hemorrhage, whether it be a gastrointestinal bleed, or some other site of major bleed, again, the percent of patients having excellent or good hemostasis was very similar to the overall population around that 80% mark.

Now, while the ANNEXA-4 study is, I think in my opinion, by far the most convincing data we have about reversal of factor Xa inhibitors, there are other studies out there that are noteworthy and worth mentioning, say in our talk. I do want to talk about a study by Andrew Cohen and colleagues, which was published in the *Journal of American College of Emergency Physicians Open* in 2022. And here, they're looking at mortality at 30 days with andexanet alfa, compared to PCC in patients with life-threatening DOAC-related bleeding. Now, what's interesting about this study is actually a two-patient level data sets that were used. For the andexanet alfa population, it was drawn from the ANNEXA-4 study. For the control population, for those patients receiving prothrombin complex concentrates, these data from the ORANGE study, which was a prospective observational study of anticoagulated patients seen in UK hospitals.

In this study, in order to control for potential differences between the andexanet alfa and PCC patients, patients were propensity score matched based on very important and key demographic and clinical characteristics. Now, in total, there are 322 ANNEXA-4 patients treated, and they were matched to 88 patients from the ORANGE study, again, who were treated with PCC. And what we can see here

highlighted in the figure, if we look at the whole population of patients, so patients who had any type of severe or life-threatening bleed, andexanet alfa was associated with a 57% relative risk reduction of 30-day death compared to the PCC group. Right? So some very compelling evidence.

So an additional study that I'd like to talk about was presented by Paul Dobesh and colleagues at the most recent International Society of Thrombosis and Hemostasis Meeting in Montreal, Quebec. And they were, in their study, comparing in-hospital mortality with andexanet alfa versus 4-factor prothrombin complex concentrate. Now, what was nice about their study, it was a very large study. Data source included electronic medical records from over 350 U.S. hospitals. And these patients were identified between May of 2018 and September of 2022. Now to be included in this study by Dobesh and colleagues, patients had to be at least 18 years of age, be hospitalized for anticoagulant-related major bleeding, be receiving rivaroxaban or apixaban at the time of the bleeding event, be treated with andexanet alfa or 4-factor PCC during the hospitalization, and finally having complete or documented discharge disposition data. And what was demonstrated is that in over 2,000 andexanet alfa patients, the unadjusted mortality - in-hospital mortality rate was about 6%, compared to 10.6% in the 4-factor PCC population. Again, they had a sample size of a little over 2,200 patients. This resulted in an adjusted odds ratio of 0.50. Or in other words, saying andexanet alfa was associated with a 50% reduction in the odds of in-hospital mortality compared to 4-factor PCC. And, of course, this is very interesting data. But data also that lines up very closely with the data that we just discussed previously, from the Cohen and colleagues study, the slide previously.

And so with this data, I'd like to conclude by again, thanking you for your attention. And hopefully, this gives you a brief overview about what some of the best available evidence is, again, currently for the reversal of life-threatening bleeds.

Thank you very much.

Announcer:

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