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https://reachmd.com/programs/cme/pharmacy-perspectives-real-world-management-of-factor-xa-inhibitor-associated-bleeding-across-45-us-hospitals/14860/

Released: 03/31/2023
Valid until: 03/31/2024
Time needed to complete: 56m

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

Pharmacy Perspectives: Real-World Management of Factor Xa Inhibitor Associated Bleeding Across 45 US Hospitals

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Dr. Dobesh:
Welcome, everybody. And my name is Paul Dobesh, I'm a Professor at the College of Pharmacy at the University of Nebraska here in Omaha. And today I'm going to be presenting a journal club from the pharmacy perspective on some real-world management of factor Xa-associated bleeding.

My disclosures are shown here, you can see those.

A little bit of background, as most of us know, right, direct factor Xa inhibitors have been steadily increasing over the last several years. As you - if you look back to 2012, almost 99% of patients were getting a VTE treated with warfarin, where you jump ahead now just 5 years to 2017, and you can see that only about 1 in 5 patients are being treated with warfarin. So we've seen a dramatic shift. And a lot of that use of new anticoagulants as with rivaroxaban and apixaban, which account for about 80% of all use. And readily, as the numbers continue to grow, we're looking at about 7 million patients in the United States right now getting a direct factor Xa inhibitor.

And while the main advantage of these oral direct Xa inhibitors is that they provide less bleeding, significantly less bleeding than warfarin. The amount of bleeding is not zero. And so there are still going to be bleeding events that occur. And when you're talking about millions of patients that are getting the drugs, really management strategies are something we have to consider. And things that people have looked at, obviously four-factor prothrombin complex concentrate, which I'll just refer to as four-factor PCCs, which is really a nonspecific kind of platelet replacement, or they're not - and we andexanet alfa, which is actually a targeted reversal agent.

So the paper I'm presenting today is one by - where Craig Coleman is the lead author. I'm also part of this manuscript. But it's the real-world management of oral factor Xa-related bleeds with reversal of replacement agents, including andexanet alfa and four-factor prothrombin complex concentrate in a multicenter study. And this paper was published just a couple of years ago in 2021 in the journal, *Future Cardiology*.

The methods of this paper basically, it's a multicenter retrospective use of electronic medical records. Data came from 45 different U.S. hospitals. How did you get into the study? Well, basically, we use ICT billing codes. And so, you had to have a code for hemorrhagic disorder with extrinsic circulating anticoagulants, which kind of captures a lot of that. We also kind of gathered a few patients from an adverse effect of an anticoagulant or anti-thrombotic, or the use of andexanet alfa if not captured in that initial ICD-10 code. And of course, you had to be getting a direct Xa inhibitor prior to the admission.

We collected some baseline demographics, not extremely detailed, but mainly information on age and gender. We collected information on bleeding type, so kind of GI bleeds, intracranial bleeds, compartmental bleed, whether they are traumatic or not, the reversal

management. So what did they get as far as the reversal strategy. And of course, then we collected, as an outcome, in-hospital mortality.

This was purely descriptive analysis. So we're looking at the prevalence of the use of each reversal agent, and then the mortality associated with that. So we did no inferential comparisons, comparing like Group A versus B and having P-values and things like that. Like I said, very descriptive.

So what we found, like I said, we use 45 U.S. hospitals, the average size of our hospitals was a little over 450 beds. We had a really good mix, we had some larger hospitals, about half of them over 500 beds, you know, with about as many with less than 500 beds, about two-thirds were advanced primary stroke centers, 64% were trauma centers of at least level 1 and 36% level 2.

Overall, we collected data on over 14,000 hospitalizations for major bleeding between January of 2016 and September of 2019. And they basically, those that are associated with oral Xa inhibitor was about 21% of that total, which gave us a total number of patients of 3,030. Interestingly enough, the number of these percent of the hospitalizations related oral Xa bleeds was about 18% when we started the study in 2017, and rose to 21% in 2019, which is very reflective of the increased use of the oral direct Xa inhibitors. As you would imagine, most of the use was with rivaroxaban and apixaban, with a small number of patients getting the other oral direct Xa inhibitors. The average age of the patients was about 67.5 years, and just under 50% were female.

This table here just kind of gives you some of the demographics as well as the treatment strategies. So you can see the total sample of the andexanet alfa, four-factor PCC patients also managed with fresh frozen plasma, and kind of everything else. And everything else is kind of what could be a three-factor PCC, recombinant factor VII, an activated four-factor PCC, tranexamic acid, vitamin K, all those were included. And there were also patients who got no reversal agents. And so you can see that the age of the patients across the board, there was a little fluctuation but very similar, especially between andexanet alfa and four-factor PCC. The male-female split, once again, very consistent across the management strategies. The drug - the factor Xa that was used, once again, very similar. Most of the – the most common bleed, I should say, was GI bleed, meaning about almost 50% and numbers of 40 to 41% with andexanet alfa and four-factor PCC. That, of course, followed by intracranial bleeds, compartmental bleeds, and traumatic bleeds. And you can see that the number of bleeds there, you know, that numerically once again, no statistical comparison, so numerically, maybe more compartmental bleeds with four-factor PCC were more traumatic bleeds with andexanet alfa.

One of the things that you'll notice is that too, when we look at them how they were managed, of all the bleeds, these numbers add up to more than 100%, because these - the use of an agent, it was not mutually exclusive. Now, if you look at the bottom of the table where it says the single agent, right here, and so this is the percent of patients that that's all they got, right? So 83% got just andexanet alfa, 72% of people - I should say, 72% of patients who got four-factor PCC, that's all they got. Where about half of the patients who got fresh frozen plasma got something else for their management strategy, whether that be transfusions or something along those lines.

But we can see here that the - how the bleeds were managed, where about 10% of Gi bleeds were in given andexanet versus 13% of ICH. Once again, the numbers here are different because, of course, the ends of the above. It's the percent of the total number of bleeds within that, that got that individual agent.

We collected in-hospital mortality. And so, a lot of bars on this graph, which are okay, but the bleeds are basically broken down. If you look across the X axis at the bottom, all bleeds, GI bleeds, intracranial, critical compartment, and trauma, of course, and the others. And of course, the different colors of the bars represent their management strategy. And so one of the things that is quite obvious is that you can see obviously, intracranial bleeds carried the highest mortality, really, irrespective of what they - what reversal agent they got, where GI bleeds, obviously, that was much lower. One of the other things is very noticeable here, at least numerically, there are no statistical comparisons, is that it doesn't matter where the bleed was, there was always less mortality, lower mortality of patients that got andexanet alfa versus anything else, which I found pretty fascinating in this.

So in summary, kind of what we see here, the strengths of this paper, I think, are obviously multicenter, like I said, 45 different hospitals across the country, different sizes, types, over 3,000 patients. We looked at multiple reversal strategies, not just four-factor PCC and andexanet, but we included others as well. Like I said, it's a descriptive analysis, now no statistical comparisons, and we didn't yet get information on the severity of bleeding, which is one of the reasons that we didn't - couldn't balance the patients, per se, by severity. That's why we didn't feel it was appropriate to do statistical comparisons.

So in conclusion, what we have here is a large sample of hospitalizations for direct Xa inhibitor-induced major bleeding and how it's associated with in-hospital mortality and the reversal or the replacement agent used. And like I said, one of the major takeaways I took from the paper was that andexanet alfa was associated with the lowest in-hospital mortality across all the different bleeding types.

So with that, I want to thank everybody very much for your attention today.

Announcer:
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