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Anticoagulant-Associated Major Bleeding Is a Significant Problem: How Do I Address?

Announcer:
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Dr. Siegal:
Hi, I'm Dr. Deborah Siegal. I'm a Hematologist in Ottawa, Canada. And it is my pleasure to present to you today on anticoagulant-associated major bleeding, which is a significant problem. And I'm going to address how we manage this in patients who are receiving direct oral anticoagulants, or DOACs.

I'm sure that the audience is well aware that bleeding complications limit oral anticoagulant use, and although we're fortunate now to have access to direct oral anticoagulants, or DOACs, which have substantial benefits for patients, including improved rates of intracranial hemorrhage, major bleeding, compared to warfarin, we do see that there may be an increased risk of gastrointestinal bleeding, dependent on the type of drug but they have not been compared head to head. So that jury's still out on that aspect.

Bleeding remains an important problem. So again, even in the era of DOACs, we're seeing major bleeding rates of around 2 to 4% per year. And then an additional 10 to 12% of patients experience clinically relevant non-major bleeding. And of course, these rates vary by indication and patient population and comorbidities. But still, the point here is that bleeding remains an important complication of anticoagulant use that our patients experience.

This slide summarizes just how severe anticoagulant-related bleeding complications can be. And here we're showing the risk of death associated with different types of bleeding complications. On the left, you see, hemorrhagic stroke, which is associated with a 27-fold increase in the risk of death and compare it to patients without that complication, subdural bleeding, 7-fold increase in the risk of death and also extracranial bleeding, perhaps surprising to some, is also associated with an increased risk of death of about 5-fold. This includes a site outside of the cranium.

So it's not just intracranial bleed the matter a lot to patients; other types of bleeds matter too. And here, this slide shows a bleed management framework, which summarizes some of the important features of management, including prevention. And this really does start with the initiation of oral anticoagulant therapy in our patients. And of course, it's really important to implement the principles of stewardship, you know, right patient, right drug for the right indication at the right time, and to manage that going forward. Unfortunately, some patients experience complications of bleeding while on anticoagulants. And the important piece here is to refer those patients for early supportive measures, and interventions such as procedures or surgeries, which will ultimately definitively stop the bleeding. Of course, anticoagulants make bleeding worse, they don't cause bleeding themselves. And often that procedure is required, if it's available, to stop the bleeding.

Reversal is indicated for severe bleeding complications. In the absence of the availability of reversal agents, hemostatic therapies may be also administered for patients who are having bleeding complications. And then finally, once bleeding has resolved, reassessing

anticoagulants is extremely important. And then again, we're back to the prevention piece. Secondary prevention is really important, including minimizing or modifying risk factors for future bleeding complications.

And so the first step of bleed management is really to assess the severity of the bleeding because ultimately, this is what guides management going forward. On the left hand of this slide, you can see non-major bleeding complications. And these would be things like self-limited epistaxis, or for example, self-limited hemorrhoidal bleeding, for which anticoagulants may be continued. In the era of DOACs, remember, these drugs are much easier to start and stop, they have short half-lives, and they also have a short time to peak concentration. So these actually can be you know, start and stop; therefore, it's much easier to continue anticoagulants in the DOAC era. Local measures can be helpful. Monitoring can be important, particularly if a patient has recurrent non-major bleeding complications and therefore, you know, really just reviewing the drug that they're receiving. Are they taking it correctly? Are there any new medications that could be interfering? And here, we have some examples of comedications. And then just making sure basic blood work is stable.

As we progress on to the right-hand side you can see, you know, major bleeding that is either - that may or may not be life, limb, or organ threatening. And certainly, general measures with compression and volume replacement are important. Definitive interventions are also here. And then finally, reversal or hemostatic therapies, and we'll get into this a bit more in the subsequent slides, will be appropriate. Of course, for major bleeding complications, at this point, we are interrupting oral anticoagulant therapy because of the severe outcomes that can occur with ongoing bleeding complications. We want to optimize hemostasis for the patient who is having an acute bleed.

There is a lot of discussion these days about the use of tranexamic acid in various populations and it has been shown to decrease bleeding in many patient populations. We do not have robust data in anticoagulated patients, and a recent trial has shown that there may be harm with a lack of benefit in GI bleeding. So these treatments can be used but shouldn't be used appropriately for the right patients.

So for patients who have severe or life-threatening bleeds, reversal or hemostatic agents are indicated, but these drugs need to be used judiciously, which means using them for the right patient at the right time. And that starts with an assessment of whether the DOAC is present in a, quote, significant quantity. And that can be because it's clinically suspected based on the time they last took their dose and the known clearance of the drug or half-life, in conjunction with the patient's hepatic and renal function, or because they had a measurement of the – a quantitative measurement of the drug, and that drug level is consistent with a clinically significant level. There is some controversy about this because, of course, we don't have an established threshold for clinically relevant hemostatic effect or anticoagulant effect. However, if a patient has taken their DOAC within the previous 24 hours, it's likely that they have a significant circulating DOAC, and that a reversal or hemostatic agent could be administered. So patients for whom this would be appropriate are those with severe life-threatening bleeding, critical organ bleeding, such as brain or spinal cord, or ongoing bleeding despite measures to control, perhaps a less common indication of bleeding with an expected long delay in achieving hemostasis, also, you know, less common or for an urgent surgery that cannot be done safely on anticoagulants.

So it's important to then again reflect on whether or not the DOAC is likely to be present in significant quantity. And the point of this slide is really just to show how limited - how the limited utility of most of our tests are for assessing the presence of DOACs. So routine coagulation tests that we're all familiar with are poorly sensitive and poorly specific for these drugs. You can see here for rivaroxaban, rivaroxaban may increase the PT, the INR, or prolong the PT, but not always. And this is dependent on the type of assay that's available. Similarly, dabigatran may prolong the APTT, but this is also dependent on the assay. More reliable are things like the dilute thrombin time or Ecarin clotting time to measure dabigatran, or calibrated anti-Xa assays, which provide a quantitative measure of the factor Xa inhibitor anticoagulants. But again, you know, in routine clinical practice, I think the important point is here, we're assessing patients based on their clinical presentation. So if they have a severe bleed, if they - if there was reason to believe that the DOAC is present in significant quantity again, either it's because we know when they took their last dose, and we know what the half-life of the drug is, so usually around 12 hours, we can say reasonably for certain that there is drug left in their system. And in reality, if a patient has taken their DOAC within the previous 24 hours, it's likely that they have a clinically significant level circulating. So these are present, of course, if these criteria are fulfilled, then reversal is warranted.

So there are two agents which reverse DOAC effect. Idarucizumab is a monoclonal antibody against dabigatran, and it's indicated for urgent surgery or procedures, or life-threatening or uncontrolled bleeding in patients receiving dabigatran.

Andexanet alfa is a human recombinant factor Xa variant molecule which is used to reverse the anticoagulant effect of factor Xa inhibitor anticoagulants and it's indicated for the reversal apixaban or rivaroxaban for life-threatening or uncontrolled bleeding. And the dosing is, as you can see here, 5 grams intravenously for idarucizumab, and that comes in two 2.5-gram vials. And then for andexanet, the dosing is dependent on the type of factor Xa inhibitor that was taken and the timing of the last dose.

So again, we mentioned treatments for major bleeding for factor Xa inhibitors. We have andexanet alfa if it's available, dosed according

to the type of factor Xa inhibitor and the last ingestion. In the absence of specific reversal agent, if a reversal agent is required, 4-factor PCC can be given. Some sources or experts recommend a fixed dose of 2000 units, or a weight-based dose of 25 to 50 units per kilogram, although there's uncertainty about the ideal dose in this setting. And it's also uncertain about whether or not there should be a maximum dose administered as a single dose. Other, you know, treatments might be activated charcoal, if given - if taken within the last 2 hours, although practically speaking, this is, you know, pretty rarely done.

Guidelines for intracranial hemorrhage again have a similar approach. If we focus here on the factor Xa inhibitors, in this box here in the middle, you can - and for dabigatran as well, you can see that it's important to determine when the last dose was taken. Again, activated charcoal if it was within the last 2 hours, also a challenge, not usually the case. And if the specific reversal agent is available, so in this case, either idarucizumab or dabigatran, or andexanet alfa for factor Xa inhibitors, then those specific reversal agents are recommended. In the absence of specific reversal agents, we're looking at coagulation factor replacement with either 4-factor PCC, factor Xa inhibitors, or perhaps even activated PCC for idarucizumab. Uncertainty, again about the types of - the doses that are available for those.

These guidelines discuss the timing of resumption of anticoagulation after a bleed. Again, there's a lot of uncertainty because of really limited data in this space. The data here are focused on patients with nonvalvular atrial fibrillation who have spontaneous intracranial hemorrhage. And really, the decision around resuming anticoagulation depends on a balance of the, you know, expected or benefits versus the harms. And so if the balance is thought to favor treatment, as opposed to withholding treatment, then that can be considered but you know, again, low quality evidence here. In patients with spontaneous intracranial hemorrhage, in whom the decision is made to restart, here they're discussing 7 to 8 weeks after intracranial hemorrhage. Now again, I think this is - there's, you know, really not very high-quality evidence indicating that that is the case. Of course, without anticoagulation patients are at risk of stroke and systemic embolism. So this is a discussion that really needs to happen with neurologists and perhaps neurosurgeons and perhaps hematologists, as well. And then finally, you know, patients who are deemed too high risk for anticoagulation, we may consider approaches like left atrial appendage occlusion, in order to reduce the risk of thromboembolic events.

So this slide summarizes just this approach, I think, for any type of bleeding complication. It's important to at first assess whether or not bleeding has stopped. That's really key. You know, one of the rules, or cardinal rules of anticoagulation and thrombosis medicine is that you can't anticoagulated bleeding patient, or we say, you know, it's important to treat the problem that's in front of you. You know, managing a patient for a theoretical risk of thrombosis when they're actually having a life-threatening bleeding is not sensible. And so that, of course, requires, you know, rapid follow-up. But ultimately, it's important to withhold anticoagulation if that is what's right to do for the patient's current clinical status.

It's also important to assess whether they still need an anticoagulant. And if they do, then to assess the thrombotic risk and the bleeding risk. Sometimes very challenging, and so really should be done in a multidisciplinary framework. And including patients and their caregivers. Patients and their families, you know, are keen to be involved in these types of decisions. Ultimately, they are challenging, and there's limited evidence about how to manage, so they should really be engaged. And then of course, if we're resuming anticoagulants, this should really be done with a stewardship mindset, making sure that everything is optimized for safety.

So I'll just end with this slide by saying that I hope that I've convinced you that anticoagulant-related bleeding remains an important problem for our patients, even in the era of DOACs. That prevention is the first step. That you know early supportive measures and interventions should be sought to reduce bleeding at the site. Reversal of course is important for severe bleeds. Hemostatic therapies can also be used if reversal agents are unavailable. And then finally, anticoagulation needs to be reassessed after bleeding is resolved, and a plan in place to do that.

I'll end there and thank you for your attention.

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