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Direct Anticoagulants in Children: Application of Clinical Trial findings in Practice

Announcer:
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Dr. Young:
Hello, my name is Guy Young. I'm a professor of pediatrics at the University of Southern California Keck School of Medicine and the director of the Hemostasis and Thrombosis Center at Children's Hospital, Los Angeles. And I'm here to give you a little short talk on direct oral anticoagulants in children. First of all, what did we have or do we still have before we had DOACs as I'll call them, the direct oral anticoagulants? Well, we have warfarin and we have parenteral drugs. When it comes to warfarin, it's only available in pill form. So, not really useful in younger children. It cannot be compounded to a liquid.

You know that there are numerous drug interactions and it has a narrow therapeutic window, which means there's increased risk for bleeding and also with a low INR increased risk for thrombosis, and it requires frequent laboratory testing. We have injectable subcutaneous drugs for long-term use, low molecular weight heparins and fondaparinux. These actually have been quite useful. They're generally safe and effective although not really extensively studied prospectively as the DOACs have, and they have a longer half-life and minimal note drug reactions but, they do require injections and parents and patients don't really enjoy having to do those injections repeatedly.

So, let's take a look at the coagulation cascade. First of all, Warfarin is a vitamin K dependent antagonist and so it interacts with the vitamin K dependent molecules. We do have the factor 10a inhibitors, so you recognize those. They have an Xa in the middle and they inhibit factor 10a or Xa. And we're going to talk about rivaroxaban today because it has the most data so far. We're also going to talk about dabigatran. Dabigatran is a thrombin inhibitor. There's sort of a TR in- well, there is a TR in there almost like a THR, and that will help you to recognize that it is a thrombin inhibitor.

So, let's take a look at rivaroxaban. It was studied extensively over a period of 10 years, and this is the pivotal publication published a couple years ago or three years ago now at Lancet Hematology, comparing rivaroxaban with standard anticoagulants for the treatment of acute venous thromboembolism in children phase three trial. Here is the study design. Basically, it was an open label, two to one randomization to give a 20 milligram equivalent dose. In other words, a dose that would be equivalent to 20 milligrams in an adult for pediatric patients. And there was a lot of work done behind the scenes to figure out what exactly the dose would be for each of those. And those are published in phase one and two studies that you could find online. So this study had 500 children they're randomized during day one through nine. They would start the study drug day six through nine. So they did receive a standard anticoagulant for five days. And then you can see the number of patients who got rivaroxaban versus the comparator. Typically, again, heparins may be vitamin K antagonists. Low molecular heparins are fondaparinux. So there's the two to one randomization. Repeat imaging was done at the end of three months. This was sort of the key pivotal endpoint. And you can see that this trial took a long time to do.

And here is the types of thrombosis treated by age group. You'll see, interestingly, quite a lot of cerebral venous sinus thrombosis. Almost half of those patients between two and 12. You see a lot of catheter related thrombo- venous thromboembolism in the younger

children, not surprisingly, and non-catheter related in the older children. And there's the symptomatic patients. Most of the patients were symptomatic. Some of these were found incidentally. And, for almost all of these, it was the first episode of venous thromboembolism. We had a tablet, of course, as used in adults, but, a pediatric formulation a suspension was made for children. So, you can see here's the ratio of the total patients. Obviously, the younger children used the suspension. As we got to the older children, we used more tablet.

But, overall, in the pediatric study you can see about two thirds of the patients ended up using the suspension and one third the tablets. As far as risk factors for VT across the age groups, you can see that there were a fair number that were provoked by a persistent risk factor, many provoked by a transient risk factor, and some provoked by both. So, these were mostly provoked thrombi. These are the number of provocations. In other words, the number of risk factors, one, two, and three. So most patients had one, a fair number had two and some even had more than two. You see the types of patients here. These are patients with cancer. A fair number of patients, about 10% overall, had active cancer. And here's the outcome. So, we're looking at all the different outcomes here. Rivaroxaban versus the comparator. Bottom line here is the primary efficacy outcome, which was recurrent venous thromboembolism was exceptionally low, only 1% in the rivaroxaban arm. Only 3% in the comparator was not statistically significant, those differences. The bottom line is that rivaroxaban performed very very well at preventing recurrent venous thromboembolism, which was the primary efficacy outcome. And then, for those patients who had deterioration on repeat imaging, not just recurrence, but deterioration you could see again, it's very, very low, only 1% on the rivaroxaban arm.

As far as bleeding another primary efficacy outcome measure, this time, safety. Only 1% had major bleeding who were on rivaroxaban compared to 4%. That was, as you can see, statistically significantly higher for those on the comparator. Very few only, one patient in the whole trial, died. So, I don't think we could make much of that, and that was a cancer related death. Again, as far as safety, breaking it down further major or clinically relevant non-major bleeding was very low and similar between the two arms. So again, only 3% of patients had major or clinically relevant non-major bleeding. In fact, you can see, below no patients on rivaroxaban had major bleeding and we had 3% that had clinically relevant but non-major bleeding. You see the locations below that. So, let's take a look at dabigatran. This was the phase 2b/3 study that was done looking at patients also for the treatment of acute venous thromboembolism. Here's the flow chart of the patients, which I won't really get into very much, other than to say it was also a two to one randomization between dabigatran and standard of care. And here the primary efficacy endpoint, which was a composite endpoint of complete thrombus resolution, freedom from recurrent venous thromboembolism and freedom from venous thromboembolism related death. So, they did a composite endpoint. And, you can see that there was basically, similar between the two groups, 42% and 46%.

Here's the freedom from venous thromboembolism recurrence. This is a Kaplan-Meier plot. As you can tell, you can see that the dabigatran performed very well in the red, even a bit better than the standard of care, and that was statistically significant. So, you could see that that, well over 90% of the patients did not have recurrent venous thromboembolism. In the- actually over 95% in the dabigatran arm at about 93% in the standard of care arm. This is looking at freedom from any bleeding. You see that the majority of patients, close to 80% have no bleeding in either arm and those were similar. Last comment is about reversal agents. Just, if you start using these drugs, rivaroxaban or dabigatran, be aware that there are reversal agents commercially available. Idarucizumab is a monoclonal antibody that specifically binds to dabigatran. You can see in the top, you've got dabigatran bound and deactivating thrombin, then the anti-dabigatran fab or monoclonal antibody, that's Idarucizumab in the red.

If you add that in, it preferentially binds to dabigatran, essentially blocking it from being able to form a bond with thrombin. So in other words, thereby reversing the effect and allowing thrombin to be active again. And then for rivaroxaban and other 10a inhibitors, there's andexanet alpha. This is basically what factor 10a normally looks like and the factor 10a inhibitor in the red pizza pie there in the upper right corner is where the blocking happens. Andexanet alpha is designed to look just like factor 10a but it does not have a catalytic domain so it doesn't function like factor 10a. It's just really an inactive version of factor 10a but it has a strong binding feature for a factor 10a inhibitor, so the rivaroxaban binds, as you see there, and it basically just moves it from the circulation this way.

So, the take home messages are there are five DOACs licensed for various uses in adults. All of them have or are being studied in children. And in fact, rivaroxaban and dabigatran are now licensed for children. A pediatric friendly suspension is available for rivaroxaban. And, I think there will be capsules or a little sprinkles, I should say, available for dabigatran. Data on the other 10a inhibitors apixaban, edoxaban, and betrixaban are all still being developed for pediatrics. And, I would say, that DOACs certainly are going to replace warfarin and probably low molecule weight heparin and fondaparinux for most uses in children in the coming few years. So with that, I'll stop. Thank you.

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