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What Therapeutic Options Are Currently Available for Post-acute Anticoagulation Therapy To Prevent Recurrent VTE in Pediatric Patients?

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Dr. Kumar:
Hello, thank you for tuning in. My name is Riten and I'm a pediatric hematologist at Boston Children's Hospital. We are going to talk today about secondary thrombo-prophylaxis in children. Now, as the incidence of venous thromboembolism in children has steadily and significantly increased in the last two decades, so has the use of anticoagulant agents. Anticoagulation may be used in children for primary prophylaxis, for treatment of venous thromboembolism, and for secondary thrombo-prophylaxis. And today, we are going to focus on secondary thrombo-prophylaxis.

Now, while talking about secondary thrombo-prophylaxis, the anticoagulants that are used most commonly in children include Vitamin K Antagonists, which have been around for about seven decades, low molecular weight Heparin, and Fondaparinux, which have been used in children for about 20 to 30 years, and Direct Oral Anticoagulants of which Dabigatran and Divaroxaban were only approved for children in the last two years. Vitamin K Antagonists inhibits an enzyme known as Vitamin K epoxide reductase, and decreases the hepatic activation of factors two, seven, nine, and 10. Warfarin is taken orally and is monitored using a laboratory assay known as the INR. Reversal agents for warfarin include four-factor thrombin complex concentrates, fresh frozen plasma, and Vitamin K. The biggest advantage of warfarin, is the fact that it can be used orally, and the fact that we have a vast clinical experience using these agents. Warfarin unfortunately has a lot of disadvantages. It has a very narrow therapeutic index, which results in high risk of bleeding. In addition, warfarin has numerous drug interactions and is affected by the Vitamin K content of food. This is particularly problematic in infants and toddlers who have rapidly changing diet, which alters their Vitamin K consumption. Given its therapeutic index, patients on Vitamin K Antagonists, require frequent lab draws to monitor their INR. And lastly, even though Vitamin K can be taken orally, a liquid formulation is not available. In smaller children, we often end up crushing the tablets, which results in inconsistent dosing.

Now, coming to low molecular rate Heparin, Enoxaparin and Dalteparin are the two low molecular weight Heparins, that are available for use in the United States. I will point out that Nadroparin, Tinzaparin, and Reviparin are not available in the United States. Both Enoxaparin and Dalteparin are derived from unfractionated heparin, but have a much shorter polysaccharide chain, which results in more profound factor 10 a inhibition. These agents are typically given subcutaneously and are usually dosed twice a day. I will point out that once a day dosing for secondary Thrombo-prophylaxis has been used in several centers including our center at Boston Children's Hospital. They're monitored using a laboratory assay known as anti-factor 10 a. They're eliminated renally and the reversal agent protamine sulfate only partially reverses low molecular weight heparin. The biggest advantage of low molecular weight heparin are, is a very stable pharmacokinetic, which results in a predictable drug dose response. Additionally, unlike warfarin, low molecular weight heparins do not have any food or drug interaction. The disadvantages of low molecular weight heparin, include a risk of major bleeding. It does require subcutaneous administration, which can be difficult in small childrens and toddlers. It also requires lab draws to monitor

the anti-factor 10 a activity, though, I will point out that at several centers, including us, we do not require anti-factor 10 a monitoring for kids on prophylactic dosing.

There is a small risk of Heparin Induced Thrombocytopenia with low molecular weight heparin. And while I'm not aware of pediatric studies, there is in vitro and in vivo data to suggest a negative impact of low molecular weight heparin on bone health. Fondaparinux is a synthetic antithrombin-dependent inhibitor of factor 10 a. It has been studied systematically in children. It is given subcutaneously and does require a chromogenic factor 10 a assay, which is calibrated specifically for Fondaparinux. The biggest advantage of Fondaparinux, is its longer half-life compared to low molecular weight heparin, which allows for once a day dosing. Additionally, there is no risk of heparin-induced thrombocytopenia or osteoporosis with the use of Fondaparinux. The disadvantages of Fondaparinux, include the fact that major bleeding was reported in about 2.5% of patients on the Fondaparinux study. It is renally excreted, just like low molecular weight heparin and does remain dependent on antithrombin for its anticoagulant effect. Lastly, the chromogenic 10 a assay used to monitor Fondaparinux is not routinely available and is only done by very specialized labs. Low molecular weight heparin, Fondaparinux, and warfarin have several limitations. Low molecular weight heparins, require subcutaneous administration and have a potential risk of HIT and osteopenia.

Warfarins, on the other hand, have a very narrow therapeutic index, have multiple food and drug interactions, and require frequent laboratory monitoring. So the question we ask ourselves is, are direct anticoagulants the answer? Now, direct oral anticoagulants were approved for use in adults with venous thromboembolism about 10 years ago. We've had the luxury of studying these agents extensively in children. Rivaroxaban has been studied for treatment of venous thromboembolism in the EINSTEIN Junior studies, which are now published. Rivaroxaban was also studied in a phase two, phase three randomized trial in children with single ventricle physiology, who had undergone a Fontan procedure. In this particular trial, Rivaroxaban was compared to aspirin and showed a similar safety profile with fewer thrombotic complications compared to aspirin. Apixaban is being studied in children with venous thromboembolism. A study that looked at prophylactic apixaban in children with leukemia and lymphoma, getting asparaginase therapy was recently completed and the results are expected shortly. Another study called the SAXOPHONE trial looked at apixaban prophylaxis in children with congenital and acquired cardiac disease. Again, this trial was recently completed, and the results are expected shortly.

Dabigatran has been studied both for treatment and for secondary prophylaxis of venous thromboembolism in the diversity trials, and edoxaban is being studied in children with venous thromboembolism, and in children with cardiac indications for anticoagulation. Rivaroxaban and apixaban, are direct antithrombin independent inhibitors of factor 10 a. They can be taken orally. With regards to dosing. the dosing of Rivaroxaban is weight based and I would refer you to the package insert. Most patients on these agents, do not require laboratory monitoring, though chromogenic anti 10 a assay calibrated to rivaroxaban and apixaban are available. Both rivaroxaban and apixaban are excreted renally and hepatically, and the reversal agent for rivaroxiban and apixaban is a Andexanet Alfa, which hasn't been systematically studied in children. We can also use four-factor, prothrombin complex concentrates. Dabigatran, on the other hand, is a direct inhibitor of factor two a. Again, the dosing of dabigatran is weight-based and I would refer you to the package insert. It is excreted renally, and Idarucizumab is a monoclonal antibody, that's used as an antidote for dabigatran. Again, this agent has not been systematically studied with children. So in summary, DOACs have several advantages over low molecular weight heparins and Vitamin K antagonists.

These agents can be taken orally. They have extremely stable pharmacological profile, do not require constant monitoring, have decreased food and drug interactions compared to Vitamin K antagonists, a rapid onset and offset of action, and their safety and efficacy is similar to low molecular weight heparin in the phase three clinical trials, that have recently been concluded for Rivaroxiban and Dabigatran. Thank you for your time, and for watching this educational program.

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