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Which Pediatric Patients With Venous Thromboembolism Are at Risk for Recurrence?

Announcer:

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Dr. Raffini:

Hello, my name is Leslie Raffini, and I'm a pediatric hematologist from the Children's Hospital of Philadelphia. This topic is "Which Pediatric Patients With Venous Thromboembolism Are At Risk For Recurrence?" When we think about this topic, and look at the literature, there are a couple things to consider. What is the patient population? Are these all-comers or just a cohort of neonates or adolescents? Were the clots provoked or unprovoked? What proportion were related to catheters or antiphospholipid antibody syndrome? What is the duration of follow-up of these patients? When do the recurrent events occur? And can we identify those at highest risk of recurrence, to then target interventional studies designed to reduce recurrent thrombosis?

So how common is recurrent VTE in children? If you look at population-based studies, we have the Canadian registry and the national registry from the Netherlands following patients for 2 to 2.5 years and reporting recurrent rates of 18.5% in the Canadian registry, which did not include neonates, and only 7% in the registry from the Netherlands, which did include neonates, and actually a high proportion of neonates in this study. In contrast, if you look at a large database study of pediatric VTE, in this case the PHIS, or Pediatric Health Information System Database, one study captured 11,000 patients and a subsequent study, nearly 40,000 patients. The reported rate of recurrent thrombosis in these studies was 13 and 18%. Now it's important to note that recurrent events were not validated in these studies and were likely overestimated to some extent.

What if we shift to look at some of the large high quality randomized multicenter clinical trials that have been published in the last couple of years. The Diversity Trial enrolled 267 children, from birth to 18 years, with venous thrombosis and randomized them to dabigatran or standard of care. Patients were followed for only three months. Symptomatic recurrent thrombosis occurred in 4% in the dabigatran arm and 8% in those receiving standard of care. In the Einstein-Jr Trial, where there were 500 children, ages birth to 17 years, randomized to rivaroxaban or standard of care, followed for three months, symptomatic recurrent thrombosis was reported in 1% in patients on rivaroxaban and 3% of those on standard of care. And lastly, the Kids-DOTT Trial, which randomized 417 children to six weeks versus three months of anticoagulation for a provoked thrombosis and followed them for one year, reported very low rates of recurrent thrombotic events. It's important to note that this was a very select group that made it into this cohort. So patients could not have active malignancy. They could not have lupus or antiphospholipid antibodies. And at six weeks they had to have an ultrasound that demonstrated a non-inclusive thrombosis. This study suggests that we really can identify a low risk group of patients.

Moving on to a few cohort studies of specific pediatric VTE populations. There have been several studies to look at the risk of recurrent thrombosis in children and adolescents with antiphospholipid antibody syndrome, all confirming very high rates of recurrent events from 27 to 32%. What about specific VTE locations? Cerebral sinovenous thrombosis, for example. A multicenter multinational study of nearly 400 children with sinovenous thrombosis followed for a median of three years reported a recurrence rate of 6%. And factors associated with recurrence in this cohort included age over two years at the index event, persistent occlusion and absence of

anticoagulation. What about children with genetic thrombophilia? Well, it probably depends a bit, depending on the thrombophilia and also the thrombosis. Was it a provoked or an unprovoked event? A multicenter study from Germany looked at 85 children with deficiencies in protein C, protein S or antithrombin, what many have classified as strong thrombophilias, and reported that 19% had a recurrent event with a survival curve shown here on the right. On the top in blue are the patients less than 18 years of age and below them are the adult patients. You can see the recurrence rate was even higher in the adult patients. Other studies have also demonstrated that the risk of recurrences is higher with strong thrombophilias and not surprisingly, patients who have more than one thrombophilia have the highest risk. On the bottom, is a study that looked at children with unprovoked or spontaneous thrombosis, which is actually relatively rare in pediatric thrombosis cohorts. In this study, 301 children with spontaneous VTE were followed for a median of seven years and the recurrence in this cohort was 21%. Patients with thrombophilias had a higher rate of recurrence, shown in this Kaplan-Meier curve. And patients with two thrombophilias in the lowest line had the highest rate of recurrence.

And lastly, but very important, is the large group of patients with central venous catheters. As many of you know, children with chronic illnesses often require multiple catheters. And what has become increasingly clear, reported now in several studies, is that a prior catheter related thrombosis is associated with a recurrent event in patients who require subsequent catheters. Two large single center studies reporting that 27 or 34% of patients who required a new catheter developed a recurrent event. Several studies which have confirmed that thrombophilia does not appear to be associated with recurrent catheter related thrombosis, but age, younger age, cardiac disease, and parental nutrition are additional risk factors. Two of these studies identified that the rate of recurrent catheter thrombosis was lower in patients on anticoagulation.

In summary, rates of recurrent thrombosis vary widely across the studies I've shown you from 1 to 34%. Patients at highest risk are those with a prior CVC thrombosis who need another catheter, those with unprovoked thrombosis and those with antiphospholipid antibody syndrome. Importantly, we can also now identify a group that has a very low risk of recurrence based on the Kids-DOTT Trial. Future studies should focus on evaluating safety and efficacy of extended duration of treatment in high risk patients, particularly now that we have availability of direct oral anticoagulants, which are generally much better options than what we've had in the past. Thank you for your attention.

Announcer:

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