Transcript Details

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Managing Thrombosis in Pediatric Patients

Announcer
You're listening to ReachMD.This medical industry feature, titled Thromboprophylaxis in Pediatric Patients With Congenital Heart Disease Who Have Undergone a Fontan Procedure and Treatment and Reduction in the Risk of Recurrence of Venous Thromboembolism in Pediatric Patients, is sponsored by Janssen Pharmaceuticals, Inc.

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Here's your host, Dr Jennifer Caudle.

Dr Caudle
Venous thromboembolism, or VTE, while more common in adults, is a blood clot that can still be a serious problem in children. Children may be at greater risk of blood clots when suffering from other conditions such as infectious diseases, active cancer, or after undergoing surgery, like a Fontan procedure, which is performed in children who have a single functioning heart ventricle to redirect blood flow from the lower body to the lungs.

This is ReachMD, and I'm your host Dr Jennifer Caudle. And joining me to explore the only direct oral anticoagulant, or DOAC, FDA-approved for primary prevention of clots in pediatric patients following the Fontan procedure, and the only DOAC in the U.S. to offer an oral suspension formulation for flexible body weight-adjusted dosing options for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients is Dr Marisol Betensky, Attending Physician of Hematology at Johns Hopkins All Children's Hospital and Assistant Professor of Pediatrics at Johns Hopkins School of Medicine in St. Petersburg, Florida. Thank you so much for being here today.

Dr Betensky
Thank you so much for the invitation. It's a pleasure to be here.

Dr Caudle
Well, we're happy that you're here. And before we dive into our discussion, let's take a moment to review some Important Safety Information, Boxed Warnings, and contraindications for XARELTO®.

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INDICATIONS

XARELTO® (rivaroxaban) is indicated for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.

XARELTO® is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

Let's review the Boxed Warnings and contraindications.

BOXED WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XARELTO® increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of XARELTO® and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

- Contraindications for XARELTO® include active pathological bleeding and severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

Please read full Prescribing Information, including Boxed WARNINGS for XARELTO®, at www.xareltohcp.com.

Dr Caudle
So, Dr Betensky, let's begin by discussing the EINSTEIN-Jr trial. What can you tell us about this trial?

Dr Betensky
EINSTEIN-Jr was a multi-center, open-label, active-controlled, randomized trial comparing the efficacy and safety of body weight-adjusted doses of XARELTO® with standard anticoagulation in pediatric patients from birth to 17 years of age with confirmed VTE. Patients received initial treatment with therapeutic doses of unfractionated heparin, low molecular weight heparin, or fondaparinux for at least 5 days. Patients were then randomized 2:1 to receive either body weight-adjusted doses of XARELTO® or a standard anticoagulant, heparin, or switched to a vitamin K antagonist. The main treatment period was 3 months; 1 month in children less than 2 years of age with catheter-related venous thromboembolism. The weight-adjusted doses of XARELTO® were intended to have exposures to match that of the 20-mg daily dose in adults. The primary efficacy outcome was symptomatic recurrent VTE, and the secondary efficacy outcome was a composite of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging. The principal safety outcome was a composite of overt major and clinically relevant non-major bleeding. Major bleeding was defined as clinically overt bleeding associated with a decrease in hemoglobin of at least 2 grams per deciliter, a transfusion of the equivalent of at least 2 units of packed red blood cells or whole blood in adults, bleeding at a critical site, or with a fatal outcome. Clinically relevant non-major bleeding was defined as clinically overt bleeding which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

This trial was not powered for non-inferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with the standard anticoagulants in children. Hence, there was no formal prior sample size calculation.

Dr Caudle
Now, you mentioned the efficacy outcomes for this trial, can you give us some information on the efficacy results?

Dr Betensky
Absolutely. Of the 500 patients in the EINSTEIN-Jr trial, the primary efficacy outcome occurred in four patients at a rate of 1.2% with XARELTO® compared to five patients for a rate of 3% for the comparator group. The hazard ratio was 0.4 and the 95% confidence interval was 0.11 to 1.41. Although not statistically significant, this was a 60% relative risk reduction and a 1.8% absolute risk reduction.

Additionally, the rates of the secondary outcome of symptomatic recurrent VTE or asymptomatic deterioration on repeat imaging were 1.5% with XARELTO® compared with 3.6% for the comparator group.

Lastly, complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 out of 335 children at a rate of 38.2% in the XARELTO® group compared with 43 out of 165 children at a rate of 26.1% in the comparator group.

Dr Caudle
Now, let's look at the safety results of the EINSTEIN-Jr trial. Dr Betensky, what can you tell us about that?

Dr Betensky
Well, there were similar rates of the composite of major and clinically relevant non-major bleeding between XARELTO® and the comparator with rates of 3% versus 1.8%, respectively. The hazard ratio was 1.58 with a 95% confidence interval of 0.51 to 6.27.

Taking a closer look at the components of the principal safety endpoint, the rates of major bleeding were 0% with XARELTO® compared with 1.2% for the comparator group. The rates of clinically relevant non-major bleeding were 3% with the body weight-adjusted doses of XARELTO® compared with 0.6% for the comparator group.

Dr Caudle
Thank you for that.

For those of you who are just tuning in, this is ReachMD and I'm your host Dr Jennifer Caudle. I'm joined today by Dr Marisol Betensky to take a look at some of the clinical data for a new treatment to prevent blood clots in pediatric patients who've undergone the Fontan procedure.

Now, let's take a look at another trial. Dr Betensky, what can you tell us about the UNIVERSE trial?

Dr Betensky
UNIVERSE was a prospective, open-label, active-control, multicenter, two-part study designed to evaluate the single and multiple-dose pharmacokinetic properties of XARELTO® and to evaluate the efficacy and safety of XARELTO® when used for thromboprophylaxis in children 2 to 8 years of age with single-ventricle physiology who had the Fontan procedure. Using a 2:1 randomization, 98 patients received either body weight-adjusted doses of XARELTO® to achieve exposures to match that of the 10 mg daily dose in adults, or aspirin at approximately 5 mg/kg as thromboprophylaxis for 12 months. The primary efficacy outcome was any thrombotic event. The principal safety outcome was International Society of Thrombosis and Hemostasis, or ISTH, major bleeding events, defined as clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL, a transfusion of the equivalent of at least two units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. The secondary safety outcomes were clinically relevant non-major bleeding, which was defined as clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life, and trivial or minimal bleeding events. However, the UNIVERSE study was not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.

Dr Caudle
Now, keeping with the UNIVERSE trial, can you provide some details on the efficacy results?

Dr Betensky
Sure. In the overall UNIVERSE population, there were numerically fewer thrombotic events with XARELTO® compared with aspirin. For the primary efficacy outcome, one patient, or 1.6% of patients in the XARELTO® group experienced a thrombotic event compared with three patients, or 8.8% in the aspirin group.

Dr Caudle
And what can you tell us about the safety results from the UNIVERSE trial?

Dr Betensky
Overall, the UNIVERSE study demonstrated a similar safety profile between XARELTO® and aspirin. The rates of the principal safety outcome of ISTH major bleeding were 1.6% with XARELTO® compared with 0% of patients with aspirin. The rates of the secondary safety outcome of clinically relevant non-major bleeding were 6.3% with XARELTO® compared with 8.8% of patients with aspirin. The rates of another secondary safety outcome of trivial bleeding were 32.8% with XARELTO® compared with 35.3% with aspirin.

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The following is additional Important Safety Information for XARELTO®
WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue in patients with active pathological hemorrhage.
  - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
  - Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding: Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO® for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO® is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients with Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or end-stage renal disease (ESRD) on dialysis.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

- **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
- **Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Recent Lower Extremity Revascularization Due to Symptomatic PAD:** For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO® twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO® did not enroll patients with end-stage renal disease (ESRD) on dialysis.
- **Pediatric Patients:** There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2); therefore, avoid use of XARELTO® in these patients.

  There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile; therefore, avoid the use of XARELTO® in these patients.

- **Use in Patients with Hepatic Impairment:** No clinical data are available for adult patients with severe hepatic impairment. Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased. No clinical data are available in pediatric patients with hepatic impairment.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients with Prosthetic Heart Valves:** Use of XARELTO® is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO® compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO® have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO® is not recommended in patients with prosthetic heart valves.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (DOACs), including XARELTO®, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing to a pregnant woman.
  - Fetal/Neonatal adverse reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
  - Labor or delivery: The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.
  - There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants, including XARELTO®, should be assessed in females of reproductive potential and those with abnormal uterine bleeding.
- **Pediatric Use:** XARELTO® was not studied and therefore dosing cannot be reliably determined or recommended in children less than 6 months who were less than 37 weeks of gestation at birth, had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg.

  Clinical studies that evaluated safety, efficacy, and pharmacokinetic/pharmacodynamic data support the use of XARELTO® 10-mg, 15-mg, and 20-mg tablets in pediatric patients. For the XARELTO® 2.5-mg tablets, there are no safety, efficacy, and pharmacokinetic/pharmacodynamic data to support the use in pediatric patients. Therefore, XARELTO® 2.5-mg tablets are not recommended for use in pediatric patients.

  Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents.
- **Geriatric Use:** In clinical trials the efficacy of XARELTO® in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients.

OVERDOSAGE

- Overdose of XARELTO® may lead to hemorrhage. Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS

- Most common adverse reactions in adult patients with XARELTO® were bleeding complications.
- Most common adverse reactions in pediatric patients were bleeding, cough, vomiting, and gastroenteritis.

Please read full Prescribing Information, including Boxed WARNINGS for XARELTO® at www.xareltohcp.com.

Dr Caudle
Now unfortunately, we're just about out of time for today. But Dr Betensky, do you have any takeaways you'd like to share with our listeners?

Dr Betensky
In the EINSTEIN-Jr trial, although not powered for non-inferiority, XARELTO®, compared with standard anticoagulation resulted in a 60% relative risk reduction and a 1.8% absolute risk reduction in the rate of recurrent DVT/PE. In addition, there were similar rates of

major and clinically relevant non-major bleeding in patients receiving XARELTO® compared with patients who received a standard anticoagulation. In the UNIVERSE trial, although not powered for non-inferiority, patients who received XARELTO® had a similar safety profile and numerically fewer thrombotic events compared with patients who received aspirin.

Dr Caudle
Well, those are great takeaways, and I'd like to thank Dr. Betensky for helping us better understand this treatment option for thromboprophylaxis in pediatric patients age 2 years and older with congenital heart disease who have undergone the Fontan procedure, as well as an option for treatment and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age.

Dr. Betensky, it was great speaking with you today.

Dr Betensky
It was great speaking with you today, too. Thank you.

Dr Caudle
You're welcome. And I'm Dr Jennifer Caudle and thanks for listening.

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