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Reducing the Risk of Major Thrombotic Vascular Events in Patients With PAD

Announcer Introduction
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Here's your host, Dr Jennifer Caudle.

Dr Caudle
Peripheral artery disease, or PAD, is a progressive disease resulting from plaque buildup in the arteries that often goes undiagnosed, and can lead to gangrene, amputation, and death. Today, we'll be exploring how we can help treat our patients with this life-threatening disease.

This is ReachMD, and I'm your host, Dr Jennifer Caudle. And joining me to explore a treatment option to help reduce the risk of major thrombotic vascular events in patients with PAD is Dr Vamsi Krishna, Interventional and Endovascular Cardiologist at Ascension Seton Heart Institute, and Medical Director of the Cardiac Catheterization Laboratory and the Cardiac Rehabilitation Center at Seton Medical Center Hays in Austin, Texas.

Thank you for being here today.

Dr Krishna
Thank you.

Discussion
Before we dive into our discussion, let's take a moment to review some important safety information, Boxed Warning, and contraindications for XARELTO®.

Announcer:
In our discussion today, we will focus on the clinical profile of XARELTO® (rivaroxaban).

- XARELTO® (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF).
- There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
- XARELTO® is indicated for the treatment of deep vein thrombosis (DVT). XARELTO® is indicated for the treatment of pulmonary embolism (PE). XARELTO® is indicated for the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.
- XARELTO® is indicated for the prophylaxis of DVT, which may lead to PE in adult patients undergoing knee or hip replacement surgery.

- XARELTO® is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE, and not at high risk of bleeding.
- XARELTO®, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in adult patients with coronary artery disease (CAD).
- XARELTO®, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in adult patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.
- XARELTO® 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.

Before we discuss XARELTO®, 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 Krishna, let's begin by focusing on combination therapy. What can you tell us about the impact of a dual pathway approach with XARELTO®?

Dr Krishna
First, XARELTO® inhibits FXa, decreasing thrombin generation. Second, although XARELTO® has no direct effect on platelet aggregation, it does indirectly inhibit platelet aggregation induced by thrombin. Aspirin also addresses platelet aggregation. So therefore, this dual pathway inhibition with XARELTO® plus aspirin targets both clotting mechanisms at once.

Dr Caudle

Dr Krishna, what can you tell us about the VOYAGER PAD trial?

Dr Krishna
VOYAGER PAD was a randomized, double-blind, double-dummy, placebo-controlled, event-driven trial comparing the efficacy and safety of XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily with placebo plus aspirin 100 mg once daily in patients undergoing a lower extremity revascularization procedure due to symptomatic PAD.

The primary efficacy outcome was a composite of myocardial infarction, or MI, ischemic stroke, cardiovascular, or CV, death, acute limb ischemia (or ALI), and major amputation of vascular etiology.

The principal safety outcome was TIMI major bleeding and defined as: patients with intracranial hemorrhage, a ≥5 g/dL decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or a fatal bleed.

It's important to note that concomitant clopidogrel was allowed for up to 6 months after revascularization at the discretion of the investigator; however, the median duration in the trial was 31 days. Patients were not formally randomized or controlled based on clopidogrel usage.

Dr Caudle
You mentioned the primary efficacy outcome. Can you give us some information on the efficacy results from the VOYAGER PAD trial?

Dr Krishna
Absolutely. XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily was superior to placebo plus aspirin in reducing the rate of primary composite endpoint of MI, ischemic stroke, CV death, ALI, and major amputation of a vascular etiology.

Of the 6,564 patients in the VOYAGER trial, the Kaplan-Meier incidence of a primary outcome event at 3 years was 17.3 percent for the XARELTO® 2.5 mg twice daily plus aspirin group compared with a 19.9 percent for the placebo plus aspirin group. This resulted in a 15 percent relative risk reduction and a 2.6 percent absolute risk reduction. The hazard ratio was 0.85 and the 95 percent confidence interval was 0.76-0.96.

The number needed to treat was 39 at 3 years.

There were also several secondary efficacy endpoints that were tested for superiority in a prespecified hierarchical order. Of note, there was a significant reduction in unplanned index limb revascularization for recurrent limb ischemia and a significant reduction in hospitalization for a coronary or peripheral cause of a thrombotic nature in the XARELTO® 2.5 mg twice daily plus aspirin group compared with the placebo plus aspirin group.

Dr Caudle
Thank you for that. Let's look at the safety results of the VOYAGER PAD trial. Dr Krishna, what can you tell us about that?

Dr Krishna
There were similar rates of TIMI major bleeding between the XARELTO® 2.5 mg twice daily plus aspirin group and the placebo plus aspirin group, with rates of 0.96 percent per year and 0.67 percent per year, respectively. The hazard ratio was 1.43 and the 95 percent confidence interval was between 0.97 and 2.10.

The most common site of bleeding was gastrointestinal.

There were numerically identical rates of fatal bleeding and a numerical decrease in the rates of intracranial bleeding in the XARELTO® 2.5 mg twice daily plus aspirin group compared with the placebo plus aspirin group.

There was a higher rate of bleeding defined as clinically overt signs of hemorrhage with a drop in hemoglobin of ≥5 g/dL or a drop in hematocrit of ≥15% in the XARELTO® 2.5 mg twice daily plus aspirin group compared with the placebo plus aspirin group.

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

Dr Krishna
COMPASS was a randomized, double-blind, double-dummy, event-driven trial with 3 treatment arms: XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily plus placebo, and placebo plus aspirin 100 mg once daily in patients with stable CAD and/or PAD.

COMPASS ended early for efficacy of the XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily dose.

Because the 5 mg dose of rivaroxaban plus placebo was not superior to placebo plus aspirin, only the data concerning the 2.5 mg dose of XARELTO® plus aspirin are discussed further in this podcast.

The primary efficacy outcome studied in the COMPASS trial was a composite of CV death, stroke, or MI.

The principal safety outcome was the rate of major bleeding defined by modified ISTH criteria and will be discussed further in a few minutes.

Dr Caudle
Staying on the COMPASS trial, can you provide some details on the efficacy results for the overall population as well as the PAD population?

Dr Krishna
In the overall COMPASS population of 27,395 patients, XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily was superior to placebo plus aspirin 100 mg once daily in the reduction of major adverse cardiac events, or MACE, defined as a composite of CV death, stroke, or MI. There was a 24 percent relative risk reduction and a 1.3 percent absolute risk reduction in MACE. The hazard ratio was 0.76 and the 95 percent confidence interval was 0.66 to 0.86.

For the COMPASS PAD population, the results for the primary efficacy endpoint were consistent with the overall COMPASS population. Please note, the results for the PAD population were not adjusted for multiplicity.

In addition, when looking at the efficacy results for the COMPASS PAD population expressed as the primary efficacy endpoint from the prespecified VOYAGER PAD trial, ie, a composite of MI, ischemic stroke, CV death, ALI, and major amputation of vascular etiology, the results for the COMPASS PAD population were consistent with VOYAGER PAD. These endpoints were also not adjusted for multiplicity.

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

Dr Krishna
The principal safety outcome was the rate of major bleeding defined by the modified ISTH criteria and included fatal bleeding; symptomatic bleeding into a critical organ; bleeding into a surgical site requiring reoperation; and bleeding that led to hospitalization, including presentation to an acute care facility without an overnight stay.

The results of the overall COMPASS trial population showed that there was a higher major bleeding rate in the XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily group compared with patients who received placebo plus aspirin 100 mg once daily, with rates of 1.6 percent per year versus 0.9 percent per year, respectively.

There was a numerical increase, but not a statistical difference in the rates of fatal bleeding, symptomatic bleeding into a critical organ, or bleeding into a surgical site requiring reoperation in patients receiving XARELTO® 2.5 mg twice daily plus aspirin versus placebo plus aspirin therapy.

There was a higher rate of bleeding leading to hospitalization in the XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily group compared with the patients who received placebo plus aspirin 100 mg.

Announcer:
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.

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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 Krishna, do you have any takeaways for our listeners?

Dr Krishna
In the VOYAGER PAD trial, XARELTO® 2.5 mg twice daily plus low-dose aspirin once daily demonstrated a superior reduction in the composite of MI, ischemic stroke, CV death, acute limb ischemia, or major amputation of a vascular etiology.

There were similar rates of TIMI major bleeding in patients receiving XARELTO® in combination with aspirin compared with patients who received placebo plus aspirin.

The overall COMPASS trial demonstrated a superior reduction in the composite of stroke, MI, or CV death.

The efficacy results for the PAD population were consistent with the overall COMPASS population.

Major bleeding in the overall COMPASS population was increased; however, approximately 97% of patients taking XARELTO® did not experience a major bleeding event compared with about 98% of patients taking placebo plus aspirin.

Dr Caudle
Well, those are great takeaways, and I'd like to thank Dr Krishna for helping us better understand this treatment option for patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD. Dr Krishna, it was great speaking with you today.

Dr Krishna
Thank you, Dr Caudle.

Dr Caudle
I'm Dr Jennifer Caudle and thanks for listening.

Announcer Close
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