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Reducing the Risk of Cardiovascular Events in Patients With Chronic CAD/PAD

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

Dr Caudle:
Coronary artery disease, or CAD, and peripheral artery disease, or PAD, are progressive diseases as the result of plaque buildup in the arteries. Not only are they both related to one another, and are often diagnosed together, but they also take a significant toll on patients. In fact, CAD claims over 370,000 lives each year, and PAD affects up to 8.5 million people in the US alone. That's why today we'll be exploring how we can help treat our patients with these life-threatening diseases. This is ReachMD, and I'm your host, Dr Jennifer Caudle. Joining me to discuss a treatment option to help reduce the risk of major cardiovascular events in chronic CAD or PAD are Dr Matthew C. Becker, Chairman of Structural Heart Therapies, Director of the Cardiac Catheterization Laboratory, and President of Panvascular Consulting, LLC, at the Allegheny Health Network in Erie, Pennsylvania. And Dr Arthur C. Lee, Director of Peripheral Vascular Services at the Cardiac and Vascular Institute in Gainesville, Florida. Thank you both for being here today.

Dr Lee:
Thank you for having us. It's a pleasure to be here.

Dr Becker:
Thank you very much.

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

- XARELTO® (rivaroxaban) is indicated, in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular [or CV] death, myocardial infarction [or MI], and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

Before we discuss XARELTO®, let's review the BOXED Warning and contraindications.

- XARELTO® carries a BOXED Warning. The first part notes that premature discontinuation of XARELTO® places patients at an increased risk of thrombotic events. This is based on a higher rate of thrombotic events in the XARELTO® arm compared with the warfarin arm following the discontinuation of XARELTO® and a nonbridged transition to warfarin at the end of the ROCKET AF trial. If anticoagulation with XARELTO® must be discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant

- The second part of the BOXED Warning pertains to epidural or spinal hematomas. These have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture and may result in long-term or permanent paralysis
- Factors that can increase the risk of developing epidural or spinal hematomas in these patients include the use of indwelling epidural catheters, concomitant use of other drugs that affect hemostasis, a history of traumatic or repeated epidural or spinal punctures, or a history of spinal deformity or spinal surgery. Optimal timing between the administration of XARELTO® and neuraxial procedures is not known
- These patients should be monitored 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®

Dr Caudle:
Well, why don't we start with you, Dr Becker? So, you know, why does a dual pathway approach with XARELTO® make sense when treating patients with chronic CAD and/or PAD?

Dr Becker:
So, the anticoagulant XARELTO® is situated to address 2 distinct pathways of coagulation involved in thrombus formation. First, of course it inhibits factor Xa, which is going to decrease thrombin generation. Second, although XARELTO® has no direct effect on platelet aggregation, it does indirectly inhibit platelet aggregation induced by thrombin.

Dr Caudle:
Excellent. Now switching to you, Dr Lee, what can you tell us about the COMPASS trial that examined the use of XARELTO® in combination with aspirin therapy in patients with chronic CAD and/or PAD?

Dr Lee:
Yeah, sure. COMPASS was a randomized, double-blind, double-dummy trial with 3 treatment arms. One treatment arm with XARELTO® 2.5 mg twice daily plus aspirin 100 mg once daily, the second arm was rivaroxaban 5 mg twice daily alone, and the third arm was aspirin 100 mg once daily alone. Now, it is important to note that the COMPASS trial was ended early for efficacy of the XARELTO® 2.5 mg twice daily with aspirin 100 mg daily dose. And because the 5 mg dose alone was not superior to aspirin alone, only the data concerning the 2.5 mg of XARELTO® plus 100 mg of aspirin are discussed further in this podcast.

Now, patients were included if they met the criteria for chronic CAD, PAD, or both, and the primary efficacy outcome studied in the COMPASS trial was a composite endpoint of cardiovascular death, stroke, and MI.

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.

Now the modification part is that last part, where if you had bleeding and you lead to presentation to an acute care facility or hospitalization, it was counted as major, even if you weren't hospitalized overnight.

Dr Caudle:
So, Dr Becker, why don't we stay on the topic of the COMPASS trial? Can you provide some details on the efficacy results?

Dr Becker:
Well certainly. You know, this is really important to those of us that are taking care of folks with the chronic CAD and PAD. Because what we saw was that the 2.5 mg twice daily of XARELTO® in association with aspirin 100 mg was superior to aspirin 100 mg alone when it came to the composite reduction of cardiovascular death, stroke, and MI. And significantly, that was a 24% relative risk reduction. And I think that's really notable because these are patients that are already being very well managed, they're on good background therapy, and they're getting contemporary medical care that is the likes of which we provide in the United States and in places that you're probably listening tonight. Now, although it wasn't adjusted for multiple comparisons, the results were consistent with each of those endpoints, meaning that there was a 22% relative risk reduction in cardiovascular death, a 42% reduction in stroke, and a 14% relative risk reduction in MI. And that's really generated a lot of talk in the community about what a potent effect we can have on this vulnerable patient population.

So now importantly, XARELTO®2.5 mg twice a day with aspirin 100 mg a day had a reduction in the total or all-cause mortality, which is an important endpoint that we like to look at. And that again was in comparison with the aspirin 100 mg alone. So that's an 18% relative risk reduction. Again, you do have to remember that this endpoint was not adjusted for multiple comparisons, which is a statistical analysis that of course we like to mention in these types of discussions. If you want further detail on any of those COMPASS results, I would really encourage you to look at the XARELTO® Prescribing Information. It's full of information. It's full of details. And of course the New England Journal article by John Eikelboom has numerous supplemental appendix that go into a lot of detail about some of those endpoints.

Now, with regard to limb events and this is important to Dr Lee and I who obviously deal a lot with that vulnerable patient population of chronic PAD, XARELTO® 2.5 mg twice a day plus aspirin 100 mg reduce the rate of acute limb ischemia with a relative risk reduction of 44%, and then the rate of major amputation, an important endpoint, was reduced with a relative risk reduction of 70% and that was compared to aspirin alone. These endpoints were also not adjusted for that multiple comparison.

Dr Caudle:
Absolutely. Um, you know, thank you for going through that. And—and—let's turn to the safety result. So, Dr Lee, can you share information with our listeners about some of the safety results of the COMPASS trial?

Dr Lee:
Sure. As you may recall from an earlier part of the discussion, the principal safety outcome was the rate of major bleeding defined by the modified ISTH criteria, and included, again, 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 COMPASS trial showed that there was a higher rate of major bleeding in the patients that received a combination of XARELTO® 2.5 mg twice daily plus aspirin 100 mg daily compared with patients who received the aspirin 100 mg daily alone, and those rates were 1.6% per year in the combination arm versus 0.9% per year in the aspirin alone arm.
Now, 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 the patients that received a combination of XARELTO® 2.5 mg twice daily plus aspirin versus aspirin alone.

There was a higher rate of bleeding that lead to hospitalization in the XARELTO® 2.5 mg twice daily plus aspirin arm compared to aspirin alone.

Dr Caudle:
So now that we know more about the COMPASS efficacy and safety results, Dr Lee, could you share the results that identified patients with a higher risk of recurrent vascular events?

Dr Lee:
Absolutely. An analysis of COMPASS used two methods to classify patients by risk of vascular events. The first method they used was the REACH Registry Risk Score and the second was something called the CART Survival Analysis. The REACH score analysis utilized published REACH registry scoring systems, with some adaptation to accommodate the COMPASS trial design. They used a cutoff score of 13 to identify high-risk versus low-risk patients. And the CART Survival Analysis was used to identify groups of high-risk individuals in the control arm where they were treated with aspirin alone. So when you apply these scoring methods—, of —with the REACH scoring method, there were 3 high-risk features that were identified. These were patients with a history of 2 or more vascular beds affected, patients with a history of heart failure, or patients with a low estimated GFR defined as less than 60 mL/min. The CART analysis also identified 3 high-risk features, and these were patients with 2 or more vascular beds affected, patients with a history of heart failure, and, in this case, patients with a history of diabetes. So there was overlap in the high-risk features identified by these 2 methods. And in summary, 4 distinct high-risk features were identified. Patients with 2 or more vascular beds affected or the polyvascular disease patient, patients with a history of heart failure, patients with a low eGFR defined at less than 60 mL/min, and patients with a history of diabetes. This analysis, does provide physicians some guidance in terms of assessing a patient's benefit and risk by looking at the overall risk and high-risk features, and this could assist them in deciding who in their practice should be considered for treatment with the combination of XARELTO® 2.5 mg twice daily with low-dose aspirin.

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, P2Y12 platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (or SSRIs), and serotonin norepinephrine reuptake inhibitors (or 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 (ie, spinal or 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 and/or 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 (for example, 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 (or ESRD) on dialysis.
  - **Treatment of Deep Vein Thrombosis (or DVT), Pulmonary Embolism (or PE), and Reduction in the Risk of Recurrence of DVT and of PE; Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery; 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 Chronic CAD or 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 of 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 (or ESRD) on dialysis.
- **Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use in patients with moderate (or 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.

- **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 and/or 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 (or DOACs), including XARELTO®, are not recommended in use in patients with triple-positive antiphospholipid syndrome (or 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 (example, 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 and/or 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:** Safety and effectiveness in pediatric patients have not been established.

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 IN CLINICAL STUDIES

- Most common adverse reactions with XARELTO® were bleeding complications.

Please visit www.xareltohcp.com for full Prescribing Information, including BOXED WARNINGS, for XARELTO®.

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Dr Caudle:
Now, unfortunately, we're just about out of time for today, but Dr Becker, what do you want our listeners to take away from our discussion?

Dr Becker:
So, XARELTO® 2.5 mg twice daily plus low-dose aspirin once daily significantly reduced a composite of cardiovascular death, myocardial infarction, and stroke in the COMPASS trial in patients with chronic CAD or PAD.

There was also a reduction in that all-cause mortality as we mentioned above. Now remember, in patients receiving XARELTO® in combination with aspirin, major bleeding was increased; however, again important to remember is that 97% of patients did not experience a major bleeding event.

Dr Caudle:
Excellent. And how about you, Dr Lee? What's your final takeaway?

Dr Lee:
Yeah, I think when deciding on which patients should be considered for XARELTO® 2.5 mg twice daily plus low-dose aspirin once daily, I think using the COMPASS analysis that identified 4 high-risk features is helpful. These were patients with a history of 2 or more vascular beds affected, patients with a history of heart failure, patients with low estimated GFR, glomerular filtration rate, defined as <60 mL/min, and patients with a history of diabetes. These are the patients with high-risk features that have the higher risk of recurrent vascular events and may stand to benefit from this dual pathway inhibition.

Dr Caudle:
Excellent. Well, those are really great takeaways from you both, and I'd like to thank you all who are my guests, for helping us better understand this treatment option for patients with chronic CAD and PAD. Dr Becker and Dr Lee, it was great speaking with you today.

Dr Becker:
Thank you very much.

Dr Lee:
Thank you so much. Thank you for having us.

Dr Caudle:
And I'm Dr Jennifer Caudle, your host for today. And thanks for listening.

Announcer:
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