**Transcript Details**
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/dual-pathway-inhibition-a-different-antithrombotic-strategy-for-patients-with-cad-pad/11382/

**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

Dual Pathway Inhibition: A Different Antithrombotic Strategy for Patients With CAD/PAD

**Announcer:**
You're listening to ReachMD.

This medical industry feature, titled "Dual Pathway Inhibition: A Different Antithrombotic Strategy for Patients with CAD/PAD" is a promotional educational activity brought to you by Janssen Pharmaceuticals, Inc., and is not certified for continuing medical education. The consultants are paid speakers for Janssen Pharmaceuticals, Inc. The speakers are presenting on behalf of Janssen and must present information in compliance with FDA requirements applicable to Janssen.

Here's your host, Dr Jennifer Caudle.

**Dr Caudle:**
Current guidelines for thrombotic risk reduction in patients with chronic coronary artery disease, or CAD, and peripheral artery disease, or PAD, focus on platelets as a single target for inhibition, but is this enough? Or is it time to consider a different treatment paradigm? This is ReachMD, and I'm your host, Dr Jennifer Caudle, and joining me to discuss a dual pathway inhibition approach that uses XARELTO®2.5 mg twice daily plus low-dose aspirin once daily in patients with chronic CAD or PAD is Dr Sandeep Nathan. He is an associate professor of medicine at the University of Chicago Medical Center, he's a general and interventional cardiologist, and Medical Director of the Cardiac ICU and Co-director of the Cardiac Cath Lab at the University of Chicago. Dr Nathan, thanks so much for being here today.

**Dr Nathan:**
Thank you for having me. It's a pleasure to be here.

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

- XARELTO® is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (or 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 (or DVT)
- XARELTO® is indicated for the treatment of pulmonary embolism (or PE)
- XARELTO® is indicated for the reduction in the risk of recurrence of DVT and/or PE in 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 patients undergoing knee or hip replacement surgery
- XARELTO® is indicated for the prophylaxis of venous thromboembolism (or 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® 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:**
So, let's jump right in. Dr Nathan, can you start by helping us understand how atherosclerosis puts patients with chronic CAD or PAD at risk for cardiovascular events?

**Dr Nathan:**
Sure. So, atherosclerosis is a chronic inflammatory disease that can ultimately result in thrombosis. Thrombosis causes cardiovascular events depending on the site of blockage. For example, coronary artery disease often results in cardiovascular death, stroke, and/or myocardial infarction. Peripheral artery blockages can also cause the same event that I mentioned plus critical limb ischemia, acute limb ischemia, and/or amputation. Understanding how an arterial thrombus forms helps us to target it. We know it's composed of platelets, fibrin, and erythrocytes, and platelets can serve as a target for modulation. Thrombin is also a target and affects the synthesis of fibrin.

**Dr Caudle:**
Thank you for that overview, Dr Nathan. Can you tell us more about the current treatment paradigm for addressing thrombus formation?

**Dr Nathan:**
Definitely. I'd like to point out first that the current treatment paradigm addresses platelets, but not thrombin. With regard to CAD, the 2012 ACC/AHA Guideline recommends either single antiplatelet or dual antiplatelet therapy for thrombotic risk reduction. Single antiplatelet therapy can consist of taking aspirin 75 mg to 162 mg once daily indefinitely. If aspirin is contraindicated, clopidogrel is a reasonable alternative. Dual antiplatelet therapy might be reasonable in certain high-risk patients and consist of aspirin 75 mg to 162 mg once daily plus clopidogrel 75 mg once daily. With regard to PAD, the 2016 ACC/AHA Guideline on the management of lower extremity PAD recommends single antiplatelet therapy with aspirin alone in the dose range of 75 mg to 325 mg once daily or clopidogrel alone at 75 mg once daily to reduce myocardial infarction, stroke, and vascular death in patients with symptomatic PAD, and states that antiplatelet therapy is also reasonable in asymptomatic patients with PAD. Asymptomatic PAD is defined as an ankle brachial index, or ABI, of less than or equal to 0.9. Dual antiplatelet therapy may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization, but it's important to keep in mind that in patients with symptomatic PAD, the effectiveness of dual antiplatelet therapy to reduce cardiovascular ischemic event risk is not well established. Please note also that the 2012 and 2016 ACC/AHA Guidelines were developed prior to and do not include the results of the COMPASS trial.

**Dr Caudle:**
And as a follow-up to that, Dr Nathan, if patients are on antiplatelet therapy along with other medications recommended in the Guidelines, to what extent does it affect their cardiovascular risks?

**Dr Nathan:**
I'm glad you brought that up, Dr Caudle, because I want to highlight that these patients still have residual CV risk even with high use of standard medications and treatments. I'll share some data we have from the REACH registry, which was a large global observational registry of approximately 68,000 patients in 44 countries. These patients had documented cerebrovascular disease, coronary artery

disease or peripheral arterial disease, or 3 or more atherothrombotic risk factors. Patient enrollment spanned December 2003 to December 2004. There were over 53,000 patients eligible for one-year evaluation, nearly 40,000 patients eligible for three-year evaluation, and the registry collected data on rates of major cardiovascular events in patients with symptomatic disease. Major cardiovascular events were defined as myocardial infarction, stroke, vascular death, or rehospitalization for a vascular event other than the ones stated. The majority of symptomatic patients were taking guideline-recommended medications—92% of patients were on at least 1 antithrombotic drug at both baseline and 3 years, 91% of patients on at least 1 antihypertensive drug at both baseline and 3 years, 73% and 76% were on at least 1 lipid-lowering drug at baseline at 3 years respectively, 68% and 72% on a statin at baseline and 3 years respectively, and in the diabetic patients, 87% and 85% were on at least 1 anti-diabetic medication at baseline and 3 years, respectively. The data show that despite the high use of standard medications and treatments, the rates of major cardiovascular events at 1 year were 15.2% for CAD patients and 21.1% for PAD patients. Then, at 3 years, the risk nearly doubled to 29.7% and 40.4% for each respective group. I think, you know, there's 2 very important points that residual risk continues to persist in these patients and, in fact, upward trending from year one to year three. In the patients with PAD who were on statins and of which the majority of them were on medications consistent with guideline recommendations, the risk of limb events at 4 years was 18.2% and 3.8% for any peripheral revascularization and amputation, respectively.

**Dr Caudle:**
Thank you for sharing that data, Dr Nathan. As I understand it, those numbers paint a compelling picture of cardiovascular risk for patients with chronic CAD or PAD who are receiving standard medications and treatments. Is there an additional therapy healthcare providers could consider in these patients to help reduce this residual cardiovascular risk you described?

**Dr Nathan:**
You're correct, Dr Caudle. That's why it's important to consider addressing both platelets and thrombin in these patients. In this type of treatment paradigm—dual pathway inhibition—both of these clotting mechanisms are targeted at once, and that's exactly how XARELTO® 2.5 mg twice daily plus low-dose aspirin once daily works. More specifically, XARELTO® inhibits factor Xa and addresses thrombin while aspirin addresses platelet aggregation. Additionally, XARELTO® indirectly inhibits platelet aggregation induced by thrombin. Please note that the clinical significance of this mechanistic information has not yet been established. XARELTO® 2.5 mg twice daily plus aspirin 75 mg to 100 mg once daily is indicated to reduce the risk of major cardiovascular events defined as a composite of cardiovascular death, myocardial infarction, or stroke in patients with chronic CAD or PAD and, in fact, XARELTO® is the only DOAC with this indication.

**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 (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; for the Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery; for the 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 a 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 to read full Prescribing Information, including BOXED WARNINGS, for XARELTO®.**

**cp-62551v7**

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

**Dr Nathan:**
Well, I'd like to reiterate that patients with chronic CAD/PAD who are taking standard medications and treatments remain at a high risk for cardiovascular events. A CV event may be caused by arterial thrombus, which is composed of platelets, fibrin, and erythrocytes, and

that the current treatment paradigm recommended by the Guidelines consist of either antiplatelet monotherapy or dual antiplatelet therapy and addresses platelets, but fails to address thrombin. A different treatment paradigm vis-à-vis dual pathway inhibition using XARELTO® 2.5 mg twice daily plus low-dose aspirin once daily addresses both of these mechanisms simultaneously. Although, in full disclosure, the clinical significance of the mechanistic data that I've shared with you has not been established, but we do know that it works in this capacity and that XARELTO®is the only DOAC that's actually indicated for reducing the risk of major cardiovascular events in patients with chronic CAD/PAD.

**Dr Caudle:**
Well, with those takeaways in mind, I'd really like to thank my guest for taking us through dual pathway inhibition in patients with chronic CAD or PAD. Dr Nathan, it was wonderful speaking with you today.

**Dr Nathan:**
Thanks so much for having me, Dr Caudle. It was a pleasure.

**Announcer:**
This program was sponsored by Janssen Pharmaceuticals, Inc. If you missed any part of this discussion, visit ReachMD.com/dual-pathway-inhibition. This is ReachMD. Be part of the knowledge.