Reducing the Risk of Stroke in Nonvalvular Atrial Fibrillation Patients With Obesity

Announcer:
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And now, here’s your host, Dr Caudle.

Dr Caudle:
As the obesity epidemic continues to grow, it’s important that we take a look at how this health threat can impact other common conditions our patients are living with—conditions like atrial fibrillation, or AFib. In fact, not only does obesity increase the risk of developing AFib by 50%, but it also plays a role in increasing the risk for thrombotic events in these patients.

This is ReachMD, and I’m your host, Dr Jennifer Caudle. Joining me to discuss a treatment option to help reduce the risk of stroke in nonvalvular atrial fibrillation, or NVAF, is Dr Uszenski. Dr Uszenski is a clinical cardiologist at the Novant Health Heart and Vascular Institute in Huntersville, North Carolina. Dr Uszenski, thank you for being here today.

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

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:
Absolutely, so let’s begin by discussing the important health risks associated with obesity. Can you tell us about the impact of obesity in the United States, particularly its impact on atrial fibrillation, or AFib?

Dr Uszenski:
Yes. It’s well known that obesity is a problem in the United States with approximately 70% of people being overweight or obese. Furthermore, about 8% of people have morbid obesity. Now, please keep in mind that the CDC defines obesity as a BMI of 30 kg/m² or higher, and morbid obesity as 40 kg/m² or higher. About 2 to 3 million people have AFib in the US. Importantly, being obese has some negative impacts on atrial fibrillation. First, obesity increases the risk of developing atrial fibrillation by 50%. Second, obesity can induce a prothrombotic and proinflammatory state. Third, obesity can reduce the levels and the effects of certain medications. These factors can increase patient risk for thrombotic events, such as stroke.

Dr Caudle:
Thank you, Dr Uszenski. And now let’s switch gears and discuss XARELTO®, a treatment option to reduce the risk of stroke in
patients with nonvalvular atrial fibrillation, or NVAF. Additionally, we'll discuss the impact of obesity on the management of NVAF patients. But before we get too much further, we need to level-set our audience, and discuss the ROCKET AF pivotal trial. So, Dr Uszenski, what can you tell us about this trial?

Dr Uszenski:
Well, ROCKET AFib was a randomized, double-blind, double-dummy trial that examined XARELTO® and dose-adjusted warfarin for the reduction in the risk of stroke and non-CNS systemic embolization in patients with nonvalvular atrial fibrillation. The nonvalvular atrial fibrillation patient population included were at moderate-to-high risk of stroke. This elevated risk was indicated by a history of stroke, transient ischemic attack, or non-CNS systemic embolization; and at least 2 other CHADS risk factors, including heart failure or left ventricular ejection fraction of less than or equal to 35%, hypertension, age 75 years or older, diabetes mellitus, and prior stroke. Patients in ROCKET AF had mean CHADS score of 3.5. These patients were randomized to receive either XARELTO® 20 mg once daily with the evening meal or warfarin at an international normalized ratio, INR, target of 2.0 to 3.0. Patients with a creatinine clearance of 30 to less than 50 mL/minute received a lower 15-mg dose of XARELTO® once daily to account for the reduced renal clearance. The primary efficacy outcome studied in ROCKET AF trial was stroke or non-CNS systemic embolization, and the principal safety outcome was the rate of major and clinically relevant nonmajor bleeding.

In ROCKET AF, XARELTO® was proven effective for reducing the risk of the composite of stroke or non-CNS systemic embolization in patients with nonvalvular atrial fibrillation. There was a 12% relative risk reduction in the composite efficacy endpoint with XARELTO® compared with warfarin. Noninferiority to warfarin for the primary composite endpoint of time to first occurrence of stroke or non-CNS embolization was demonstrated, but superiority to warfarin was not demonstrated in the ITT population. There are limited data on relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolization when warfarin therapy is well controlled. Consistent results were reported across secondary endpoints. Secondary endpoint number 1 was a composite of stroke, systemic embolization, and vascular death; while secondary endpoint number 2 was a composite of stroke, systemic embolization, vascular death, and MI. The ITT analysis included events occurring in all randomized patients between the time of randomization and the end of the study site notification. This analysis included events occurring on-treatment, as well as those occurring during open-label therapy in approximately 24% of patients who discontinued study drug early. A superiority analysis was conducted in the safety population during treatment. This is called the safety-as-treated population, which included patients who received at least 1 dose of the study drug and were followed for events while they were receiving treatment or within 2 days after discontinuation. XARELTO® demonstrated noninferiority versus warfarin in the ITT population, but superiority was seen in the safety-as-treated population with a 21% relative risk reduction in the composite endpoint. The conventional method for establishing superiority is the ITT population. Using data from all patients who are randomized to treatment, this analysis did not support superiority of XARELTO® over warfarin.

Now, let's discuss the bleeding rates in ROCKET AF. The rates of major bleeding were comparable overall, with rates of 3.6 events per 100 patient years versus 3.5 events per 100 patient years for XARELTO® and warfarin, respectively. There were differences in the event rates by category of major bleeding between the XARELTO® and the warfarin arms of ROCKET atrial fibrillation. There were fewer fatal bleeding and intracranial hemorrhages, or ICH events, in the XARELTO® arm compared with the warfarin arm, with fatal bleeding rates of 0.2 events per 100 patient years versus 0.5 events per 100 patient years, respectively; and intracranial hemorrhage rates of 0.5 events per 100 patient years versus 0.7 events per 100 patient years, respectively. There were significantly more GI bleeds in the patients receiving XARELTO® than warfarin, with rates of 2.0 events per 100 patient years versus 1.2 events per 100 patient years, respectively. There was no difference in fatal GI bleeds versus warfarin.

Dr Caudle:
So, Dr Uszenski, now that we've discussed the pivotal ROCKET AF trial results, let's discuss the results of the subanalysis of ROCKET AF patients who were obese. Can you tell us a little bit about those patients?
Dr Uszenski:
Sure. In ROCKET AF, 37% of the patients were obese and 13% had a BMI more than 35 kg/m\(^2\). In a subgroup analysis of ROCKET AF, efficacy and safety results were generally consistent among patients regardless of BMI. For the primary efficacy endpoint of the composite of stroke and non-CNS systemic embolism, there was a hazard ratio of 0.77, 0.93, and 0.99 in patients with a BMI of less than or equal to 25 kg/m\(^2\), greater than 25 to less than or equal to 35 kg/m\(^2\), and greater than 35 kg/m\(^2\), respectively. In the same BMI categories for the principal safety endpoint of major and nonmajor clinically relevant bleeding, there was a hazard ratio of 0.98, 1.08, and 0.93, respectively.

Dr Caudle:
So, what about the efficacy and safety data in NVAF patients with obesity in the real-world studies? Dr Uszenski, can you share this information with our listeners?

Dr Uszenski:
Yes. There was a retrospective cohort study using data from Truven MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases from December 1, 2010, through December 31, 2016. In fact, this is the largest real-world evidence trial in nonvalvular atrial fibrillation patients with morbid obesity. Patients identified were those who were initiated on XARELTO\textsuperscript{®} or warfarin, and who had 1 or more medical claims with an AFib diagnosis during the past 12 months, prior to or on the index date, and 1 or more medical claims for morbid obesity. Morbid obesity was defined as a BMI of 40 kg/m\(^2\) or more. These patients were 1:1 propensity matched. The primary endpoint was composite risk of ischemic stroke and systemic embolism; secondary outcomes included major bleeding risk. The real-world evidence for this study in AFib patients with morbid obesity was consistent with the rates of stroke and major bleeding observed in the ROCKET AFib trial. There was a relative risk reduction of 12% for the composite of ischemic stroke and systemic embolization for XARELTO\textsuperscript{®} compared with warfarin. There was a relative risk reduction of 20% for major bleeding for XARELTO\textsuperscript{®} compared with warfarin. Please keep in mind that due to differences in study design, patient populations, definition of outcomes, data collection methods, the results of real-world studies are not intended for direct comparison with clinical trials. Also please keep in mind that this real-world study has some limitations. The study was a retrospective claims analysis with inherent limitations, and its clinical significance is unknown. The use of administrative claims data may have been coded incorrectly or inconsistently. A claim for a prescription does not necessarily indicate that the medication was taken. The use of diagnosis codes to identify patients who have obesity may have been underestimated as height and weight were not available to confirm BMI status.

Dr Caudle:
Dr Uszenski, are there any other considerations with other anticoagulants that healthcare providers should be aware of in this population?

Dr Uszenski:
Yes. Warfarin, regardless of whether a patient is obese or not, has some challenges. These challenges include, number 1, time to therapeutic range fluctuation; number 2, need for continuous INR monitoring; and number 3, potential dose adjustments leading to individualized maintenance dosage. There are also challenges with warfarin that are specific to obesity and the management of nonvalvular atrial fibrillation. For example, patients with obesity and morbid obesity required a longer time to achieve therapeutic INR compared with normal-weight patients; 8 and 10 days versus 6 days, respectively. Patients with obesity in therapeutic INR range at discharge required up to a 50% higher daily dose of warfarin compared with normal-weight patients, and dietary recommendations for weight loss may conflict with warfarin restrictions. Obesity had varied effects on drug levels and activity in studies of direct-acting oral anticoagulants, or DOACs. In a PK/PD phase 1 study in healthy individuals, XARELTO\textsuperscript{®} demonstrated consistent drug levels and activity in subjects who have obesity compared with normal weight. With regards to apixaban, there are some pharmacokinetic/pharmacodynamic, or PK/PD data, that have demonstrated decreased drug levels and activity in subjects with obesity compared with normal weight. Apixaban showed a mean reduction in C\textsubscript{max}, a reduction in the AUC, and a mean reduction in
anti-factor Xa activity in patients with obesity versus normal-weight patients. Obesity was defined as more than 120 kg in these studies. With regard to dabigatran, a subgroup analysis of RE-LY demonstrated an inverse relationship between trough concentration and weight, with mean dose normalized trough concentrations that were lower for the high body weight group of greater than 100 kg, compared with subjects whose weight was between 50 and 100 kg. No studies examining the effects of obesity on edoxaban are publicly available. It is important to keep in mind that it is not known how PK/PD translates into clinical outcomes. These PK/PD studies were conducted in healthy volunteers; these trials were conducted with different designs and evaluated in different populations.

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 (i.e., 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 III 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 (e.g., 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.

- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

OVERDOSE

- 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®.

Dr Caudle:

Now, unfortunately, we're just about out of time for today, but Dr Uszenski, what do you want our listeners to take away from our
Dr Uszenski:
With regards to the pivotal clinical trial, ROCKET AF has extensive efficacy and safety data in patients with nonvalvular atrial fibrillation. XARELTO® has a proven safety profile. XARELTO® also has the convenience of once-daily dosing, taken with the evening meal, for stroke risk reduction in patients with nonvalvular atrial fibrillation. With regards to nonvalvular atrial fibrillation patients with obesity, XARELTO® has data from a post-hoc analysis and a large real-world evidence study.

Dr Caudle:
Excellent. Well, those are really all certainly great takeaways from our discussion today. And with those thoughts in mind, I’d like to thank you, Dr Uszenski, for joining me to talk about this treatment option for the reduction in the risk of stroke in nonvalvular atrial fibrillation patients and to discuss the impact of obesity on the management of NVAF patients. It was really great speaking with you today. Thank you.

Dr Uszenski:
Well, I’m very honored that you had me on your show today, and I’m very happy to bring this data to our listeners.

Announcer:
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