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Challenges, Evidence, and Treatment Options for Anticoagulation of Nonvalvular Atrial Fibrillation (NVAF) Patients with Obesity and Morbid Obesity

Approximately 40% of the US population has obesity and about 8% has morbid obesity.[1] Obesity increases the risk of NVAF by nearly half compared with non-obese patients and can reduce certain anticoagulant drug levels.[2-4] Many morbidly obese patients are treated with older anticoagulants, such as warfarin, which requires more laboratory monitoring than in patients of normal weight and also has many drug/food interactions, making management of treatment cumbersome.[5] In addition, morbidly obese patients are often underrepresented in phase 3 trials. In 2016 the International Society on Thrombosis and Haemostasis (ISTH) published a guidance statement recommending against direct oral anticoagulant (DOAC) use in morbidly obese patients (BMI >40 kg/m^2 or weight >120 kg). This recommendation was driven by limited clinical trial data in these patients and pharmacokinetic/pharmacodynamic (PK/PD) evidence for certain DOACs that showed a decrease in drug levels with increased body weight.[6] Information on PK/PD in patients with increased body weight, evaluation of clinical trial data, and new real-world evidence is now available to help fill this evidence gap and provide clinicians with an alternative option.

Understanding the obesity risk in NVAF patients

The obese population, including those who are morbidly obese, are at an increased risk for developing thrombotic events, with a 70% higher chance of suffering an ischemic stroke compared to patients with a lower BMI.[7] Obesity is a contributing risk factor for conditions where anticoagulant therapy is indicated, such as conditions which induce a prothrombotic and proinflammatory state.[3,8] NVAF patients with obesity typically present with comorbidities both caused and exacerbated by their weight, such as hypertension and diabetes mellitus.[8] Additionally, obesity may influence thrombotic risk through its effects on clinical pharmacology, potentially leading to under-coagulation, thereby increasing the risk for thrombotic events.[3]

Challenges of anticoagulation with warfarin in patients with NVAF and obesity

Warfarin can be challenging to use in normal weight patients with NVAF, and these challenges are increased in patients who are obese. One study demonstrated that with warfarin, it took up to 10 days for a morbidly obese patient to reach a stable international normalized ratio (INR), compared to only 6 days for an average weight patient.[5] Another issue, specifically with obese patients, can be dietary restrictions. Clinicians encourage obese patients to pursue a healthy diet, which can include increased green leafy vegetables that might alter patient response to warfarin therapy.

Fortunately, PK/PD data in this population, results from a subgroup analysis of obese patients within the ROCKET AF trial, along with the findings from the largest and only real-world study using claims in morbidly obese patients, may help provide more evidence in this patient population.

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Evidence for DOAC use in NVAF patients with obesity

PK/PD data

Kubitza et al conducted a randomized, placebo-controlled study in healthy subjects to evaluate the effect of extreme body weight (≤50 kg and >120 kg) compared to subjects of normal weight (70–80 kg) on the safety, tolerability, PK, and PD of rivaroxaban 10 mg. Twelve patients in the rivaroxaban subgroup reported mild or moderate treatment-emergent adverse events (AEs) and no AEs were reported in the placebo group. Its peak serum concentration was unaffected in subjects >120 kg (149 mcg/L) compared to those of normal body weight (143 mcg/L). The area under the curve was also unaffected by increased body weight (1,029 mcg•h/L for normal weight and 1,155 mcg•h/L for >120 kg). There was no difference in peak serum concentration or total drug exposure in obese patients compared to normal weight patients.[9] Upreti and associates conducted an open label, parallel group study of apixaban to measure the PK and PD impact in healthy subjects with extremes in body weight (≤50 kg and ≥120 kg) compared to patients with normal body weight (65-85 kg). The investigators found a 31% reduction (90% confidence interval [CI]: 18–41%) in peak concentration (144 ng/mL vs 207 ng/mL), 23% reduction (90% CI: 9–35%) in area under the curve (1,561 ng•mL/hr vs 2,024 ng•mL/hr), and a 34% reduction in peak anti-Xa activity (1.85 IU•mL vs 2.79 IU•mL) in patients weighing ≥120 kg compared to subjects with normal body weight.[4]

ROCKET AF trial subgroup analysis

ROCKET AF is a blinded, double-dummy, randomized, controlled study in which 14,264 patients with NVAF at moderate-to-high risk for stroke were assigned to a 20 mg daily dose of rivaroxaban or dose-adjusted warfarin. In the ROCKET AF trial, 37% of enrolled patients were qualified as being obese. These obese patients in a subgroup analysis of the ROCKET AF trial demonstrated a 31% relative risk reduction of stroke or systemic embolism (SE) compared to normal weight patients. This analysis combined rivaroxaban and warfarin into one subgroup; but a similar trend was shown with rivaroxaban alone and warfarin alone suggesting that obese patients experienced lower rates of stroke regardless of treatment with rivaroxaban or dose-adjusted warfarin.[10] While there was no significant difference in the rates of major bleeding between the rivaroxaban and warfarin groups (3.6% and 3.4% respectively), rates of intracranial hemorrhage were lower in the rivaroxaban group than in the warfarin group (0.5% vs 0.7% per year). Major bleeding from a gastrointestinal site was more common in the rivaroxaban group (3.2%) compared to events in the warfarin group (2.2%).[11] These safety results were consistent regardless of the weight of the patient. Overall, these findings provide clinicians with evidence of the utility of rivaroxaban in patients with NVAF and obesity.

Real-world evidence study

Rivaroxaban was also studied in the largest and only real-world claims analysis (n=7,126) of patients with NVAF and morbid obesity. This real-world study used data from 2 US healthcare claims databases to identify patients initiating treatment with rivaroxaban or warfarin, who had an atrial fibrillation diagnosis plus a diagnostic code for morbid obesity or BMI ≥40 kg/m^2. Rivaroxaban and warfarin patients were 1:1 propensity score matched, and a total of 3,563 matched pairs of morbidly obese NVAF patients treated with rivaroxaban or warfarin were identified. Conditional logistic regression was used to compare stroke/SE and major bleeding risk, and generalized linear models were used to compare healthcare resource utilization and costs.

The authors of this study found that morbidly obese patients treated with rivaroxaban had a comparable risk of stroke/SE (1.5% vs 1.7%) and major bleeding (2.2% vs 2.7%) to those treated with warfarin. Once again, demonstrating comparable efficacy and safety with the use of fixed-dose rivaroxaban compared to adjusted-dose warfarin in morbidly obese patients. Interestingly, patients receiving rivaroxaban demonstrated a lower total healthcare resource utilization and costs. Total healthcare costs including medication costs per patient per year were significantly lower with rivaroxaban compared to warfarin ($48,552 vs $52,418). This difference was driven primarily by a lower hospitalization rate (50.2% vs 54.1%), shorter length of stay (7.5 vs 9.1 days), and less outpatient service utilization (86 vs 115 visits per patient per year) with rivaroxaban.[12]

As a reminder, morbidly obese patients tend to be treated with warfarin, which requires more laboratory monitoring than in those with normal weight, and morbidly obese patients are often underrepresented in phase 3 studies.[5,6] It is impactful to see results for these patients in a large RWE study. There are of course limitations to real-world studies that need to be considered. Data from these types of observational studies are retrospective and rely on accurate coding, and confounding cannot be completely accounted for despite propensity score matching. It should also be noted that using diagnostic codes to identify obesity may underestimate this population, however height and weight were not available in claims data to confirm BMI status.

Summary

With the PK/PD data in patients weighing >120 kg, the ROCKET AF trial obesity subgroup analysis, and new real-world evidence in patients with NVAF and morbid obesity, rivaroxaban demonstrates consistent drug concentration, a demonstrated efficacy and safety profile, as well as a reduction in healthcare resources utilized and costs. In light of the aforementioned datasets, it is time to reconsider the ISTH guidance recommending against DOAC use in NVAF patients with morbid obesity. In summary, based on the evidence reviewed, rivaroxaban can be an alternative to warfarin in patients with NVAF and obesity or morbid obesity.

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IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

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 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 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.
- **Use in Patients with Hepatic Impairment:** No clinical data are available for 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.
- **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).

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Please read accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO®.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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 these 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.
- **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 read accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO®.

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