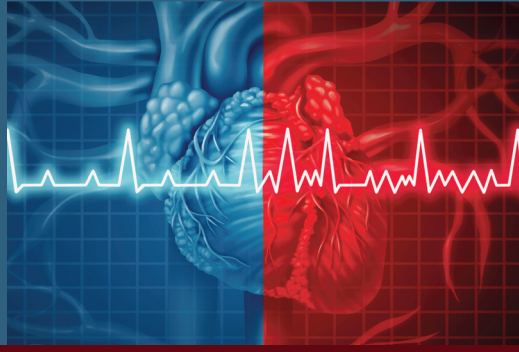
Perspectives for Pharmacy Practice:

Examining All the Evidence to Facilitate the Effective and Safe Use of Direct Oral Anticoagulants in Patients With NVAF Who Are Obese



Frequently Asked Questions

What is the right laboratory parameter for a clinician to monitor to determine if a patient is on the right drug dose with a Factor Xa agent?

If laboratory monitoring is appropriate, the recommendation is to monitor peak/trough drug concentrations, which are technically not drug concentrations but rather chromogenic factor X levels that have been generated on a specific factor Xa inhibitor scale. Published expected ranges are available for apixaban and rivaroxaban.

What is the target reference range of apixaban?

The expected ranges that are in the apixaban label and have been published are from modeled population PK data from the ARISTOTLE trial, the pivotal phase III trial of apixaban versus warfarin and patients with atrial fibrillation. Population PK modeling was done based on a single PK sample that was drawn at visit two in several thousand patients. The ranges are the 95 percent confidence interval of what is expected from that model. That's very not the same as a target range. We don't know that that expected range is correct. And that higher levels or lower levels wouldn't have efficacy and safety. This is just what was observed using 5 mg twice a day in a broad population of patients with atrial fibrillation, with the dose reduction to 2.5 milligrams twice a day in selected patients (as seen in the apixaban label). If a patient has a lower-than-expected level, the clinician could either increase the dose of the DOAC to one that is off-label or switch the patient to warfarin.

Of note, the issues are not comparable between apixaban and rivaroxaban regarding comparative potency or target ranges. There isn't much discussion regarding comparative potency of apixaban vs rivaroxaban – rivaroxaban is dosed once daily at a higher dose, 20 milligrams, once daily for atrial fibrillation and has a different expected range developed the same way from population PK parameters from the ROCKET AF trial. Consequently, rivaroxaban ranges might be different, but it has the same kinetic issues that apixaban does.

When do you recommend drawing a peak or trough?

The recommendation is to draw a peak two to four hours after a dose is taken and draw the trough level just before a dose is taken. The patient should be in a steady state when the levels are assessed. As the half-lives of these DOACs are between 8 and 18 hours (depending on the agent), the peak or trough levels can be assessed after at least a week into therapy. It can be difficult or impractical to draw both on the same day, as that would require the patient staying in the office for a few hours to get the peak level after taking the dose. While there is no gold standard choice regarding which of the two levels to draw first, a trough is generally more useful in obese patients because we want to ensure that the patient has consistent exposure over the course of a 24-hour period to their level of anticoagulation. One could then obtain a peak level at a future visit.

At what BMI do you recommend drawing drug levels to make sure that you're in the expected range?

The ISTH guidelines selected a BMI of >40 as their cut-off for DOACs. It is possible to use DOACs with close monitoring for patients with a BMI between 40 and 49 whose weight is stable and who have consistent/stable renal function. However, it is reasonable to measure levels in patients with a BMI over 50.

Are the peak and trough levels of DOACs available with major commercial labs?

Unfortunately, these are not readily accessible labs that have quick return. Consequently, it can take between two to seven days, depending on the lab that you're using to obtain these levels. I will say that at the large labs that most clinics and hospitals will use it as a possibility to get these levels, but please note that it will not be a rapid turnaround time

When switching from warfarin or LMW heparin to a DOAC, do you automatically switch to the maintenance dose of apixaban or do you do 10 milligrams twice a day for seven days and then five milligrams twice a day?

If the DOAC is for stroke prevention in atrial fibrillation, the initial higher dose of rivaroxaban or apixaban is unnecessary. I would go to the traditional dose of 5 mg twice a day of apixaban or 20 milligrams once a day of rivaroxaban with the largest meal of the day - assuming renal function is stable and is above the cut points.

When should we recommend a lower DOAC dose (such as apixaban 2.5 mg BID)?

The apixaban dose reduction strategy requires a patient meets two out of the following three parameters: age over 80, weight less than 60 kilograms, or serum creatinine more than 1.5 milligrams per deciliter. You'll recognize these are the variables that go into creatinine clearance, Patients who only have one of those three should be using the standard five milligrams twice a day dose of apixaban. That's a relatively low dose for apixaban. And the benefits over warfarin, both on bleeding and thromboembolic events, look like they extend well into the elderly patients, the patients with low body weight, and the patients with renal insufficiency. There is good evidence from RELY and from the ENGAGE AF programs suggesting that lower doses of oral anticoagulants are associated with higher rates of stroke. As such, under-dosing apixaban in patients with only one characteristic is not something that should be encouraged.

What is the optimal antiplatelet agent to use in a patient who requires an oral anticoagulant?

This seems to come up quite frequently in discussion of dual versus triple therapy. If the patient undergoes coronary stenting and they have an indication for an oral anticoagulant such as atrial fibrillation, we typically try to use one antiplatelet drug, typically a P2Y12 inhibitor, with an oral anticoagulant. From trials like AUGUSTUS, we learned that a DOAC (like apixaban or rivaroxaban) plus a P2Y12 inhibitor, without aspirin, likely has the best risk / benefit profile.