

Sticky Issues: What APs Need to Know About Anticoagulants and Patients With Cancer

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Abstract

During the JADPRO Live Virtual 2020 conference, Val R. Adams, PharmD, FCCP, FHOPA, BCOP, discussed how to determine which patients with cancer should be treated with direct oral anticoagulants (DOACs), the similarities and differences between the DOACs, and recent data on the prevention and treatment of cancer-associated venous thromboembolism.

Both CHEST and National Comprehensive Cancer Network (NCCN) guidelines can help advanced practitioners determine which patients with cancer should be treated with a direct oral anticoagulant (DOAC), but optimizing the risk-to-benefit ratio must still be done at the individual patient level, according to Val R. Adams, PharmD, FCCP, FHOPA, BCOP, of the University of Kentucky in Lexington.

During JADPRO Live Virtual 2020, Dr. Adams discussed the factors involved in making benefit-to-risk decisions in unclear situations, described the similarities and differences between DOACs, and evaluated the use of DOACs for the prevention and treatment of cancer-associated venous thromboembolism (VTE).

VTE RISK IN CANCER PATIENTS

In trying to balance the benefit vs. the risk of anticoagulation in patients with cancer, providers generally categorize risk based on clot history (positive or negative) and inpatient or outpatient. Clot history–negative patients who are ambulatory can be the most challenging to assess for VTE risk, said Dr. Adams, who noted that a model called the Khorana Score is used to determine that risk (Khorana et al., 2008).

In this model, stomach cancer and pancreatic cancer are considered “very high risk” (score of 2), while lymphoma, gynecologic malignancies, bladder, lung, and testicular cancer are considered “high risk” (score of 1). Other characteristics, such as prechemotherapy platelet count ($\geq 350,000/\mu\text{L}$), hemoglobin

level (< 10 grams/dL) or use of erythropoietin stimulating factor, and white blood cell count (> 11,000/ μ L), are factored in as well.

“We’re looking for markers of inflammation, which we know increases the risk for a blood clot,” said Dr. Adams, who noted that a body mass index of 35 or more also puts a patient at risk.

Patients who score a 0 on the Khorana scale have a less than 1% chance of developing VTE, but those with a score of 3 or higher carry a risk between 7% and 10%.

“Even in the ambulatory setting, it makes sense to intervene with an anticoagulant and decrease the risk of VTE in high-risk patients,” said Dr. Adams.

As Dr. Adams explained, all inpatients without a contraindication should receive prophylaxis with unfractionated heparin, low-molecular-weight heparin, or fondaparinux in the inpatient setting (Table 1).

In the outpatient setting, patients with a positive clot history should receive anticoagulation, and patients who are clot negative but have a high Khorana risk score (> 2) should be considered for prophylactic anticoagulation.

Patients with either lymphoma or multiple myeloma who are on immunomodulatory drugs (e.g., lenalidomide) are generally considered high risk, but recently have been further evaluated and categorized to be high risk or low risk with the utilization of the IMPEDE or SAVED scoring systems. High-risk patients can receive full anticoagulation, while low-risk patients will generally receive aspirin (81–325 mg daily) to prevent thrombosis.

DOACs: POTENTIAL FOR DRUG INTERACTIONS

Dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Lixiana) are the four current DOACs. While dabigatran is a direct inhibitor of IIa, the remaining DOACs work by inhibiting Xa (Table 2).

Unlike warfarin, said Dr. Adams, these agents do not need to be monitored on a regular basis; however, there is potential for drug interactions with CYP3A4 and P-glycoprotein inhibitors/inducers.

Although tuberculosis is not too common in patients with cancer, said Dr. Adams, rifampin is a CYP3A4 inducer and can interact with the Xa inhibitors. Providers should also watch out for natural products like St John’s wort.

Enzalutamide (Xtandi), a prostate cancer drug, is a strong inducer that accelerates clearance of rivaroxaban or apixaban, which philosophically impairs efficacy. Unfortunately, patients often receive these medication concurrently, said Dr. Adams.

With respect to inhibitors, providers should be cautious about administering high-dose fluconazole or voriconazole for a long duration with anticoagulants, and for patients with lymphoma or AIDS-related diseases, protease inhibitors can be problematic, he added.

THE NEED FOR REVERSAL

If patients experience bleeding problems, a reversal agent may be needed, said Dr. Adams, but it’s important to consider standard of care first.

“Reversal agents are very expensive—in the tens of thousands of dollars,” he said. “The finan-

Table 1. Anticoagulation for Different Patient Situations

Negative clot history	Inpatient	Prophylaxis with UFH, LMWH, or fondaparinux unless contraindicated	
	Outpatient	Low risk (Khorana < 2)	No prophylaxis
		Moderate risk–high risk (Khorana \geq 2)	Consider prophylaxis
		High risk (IMiD)	Prophylaxis: low risk or high risk
Positive clot history ^a	Inpatient and outpatient	Therapeutic anticoagulation unless contraindicated	
		<ul style="list-style-type: none"> • DOAC • LMWH • Warfarin can be used 	

Note. DOAC = direct oral anticoagulants; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; IMiD = immunomodulatory drug. Information from NCCN (2020).

^aDepending on clot location, symptoms, extent of clot.

Table 2. DOAC Overview for VTE in Cancer Patients

	Dabigatran	Rivaroxaban^a	Apixaban	Edoxaban
Indication/dose acute VTE	150 mg twice daily ^b	15 mg bid × 21 days, then 20 mg daily	10 mg bid × 7 days, then 5 mg bid	60 mg daily ^b
Primary prophylaxis	N/A	10 mg daily	2.5 mg bid	N/A
Mechanism of action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Half-life normal and moderate renal fxn ^c	7-17 hr 17-20 hr	7-11 hr 7-11 hr	8-12 hr 8-12 hr	10-14 hr
Onset of action	1-3 hr	1-3 hr	1-3 hr	1-3 hr
Drug interaction(s)	P-gp inducers	P-gp and 3A4 inhibitors/ inducers	P-gp and 3A4 inhibitors/inducers	P-gp inducers/ inhibitors
Antidote	Idarucizumab	Andexanet	Andexanet	Andexanet ^d
Measuring effect	aPTT or dilute TT or hemoclot	PT/INR Anti-factor Xa	PT/INR (minorΔ) Anti-factor Xa	Anti-factor Xa

Note. See drug prescribing information and NCCN guidelines for additional details.

^aTake with food.

^bInitial therapy with low-molecular-weight heparin or unfractionated heparin for at least 5 days.

^cModerate renal function: CrCl 30-49 mL/min.

^dOff-label use.

cial toxicity of these reversal agents is hefty, and it's hard to get reimbursed for them.”

Thus, although highly effective, reversal agents are reserved for major bleeding and emergent surgery. If the surgery is not urgent, said Dr. Adams, providers should wait for the patient to clear the anticoagulant, and NCCN has guidelines based on the half-life of the agent.

“The general rule of thumb is to wait 3 days from the last dose of DOAC or 4 to 5 days for major surgeries,” said Dr. Adams, who noted that every institution should have their own policy.

“When patients are reversed, they return to a hypercoaguable state and may have increased rates of VTE,” he cautioned.

NCCN CATEGORY 1 RECOMMENDATIONS FOR PATIENTS WITH A VTE EVENT

Based on result of the Caravaggio trial, which compared dalteparin to apixaban in over 1,100 patients, apixaban is an NCCN Category 1 recommendation (Agnelli et al., 2020). Although the study was a noninferiority design, said Dr. Adams, mortality on apixaban was slightly reduced vs. dalteparin, and it's administered orally vs. subcutaneously.

A similar trial was conducted of dalteparin vs. rivaroxaban (Young et al., 2018). Although the rivaroxaban demonstrated reduced thromboembol-

ic events and slightly lower mortality, this was not a large noninferiority study (N = 406). Nevertheless, said Dr. Adams, the performance of rivaroxaban certainly warrants consideration.

Finally, data from a study comparing dalteparin vs. edoxaban in over 1,000 patients showed a benefit in the prevention of deep vein thrombosis with edoxaban but an increase in major bleeding and mortality as well (Raskob et al., 2018).

NCCN guidelines currently list the following Category 1 recommendations:

- Apixaban 10 mg po bid × 7 days, followed by 5 mg po bid
- Low-molecular-weight heparin or unfractionated heparin for at least 5 days, then switch to edoxaban 60 mg daily
- Dalteparin 200 units/kg SC daily × 30 days, then 150 units/kg daily.

“The major disadvantage with dalteparin is that it's an injection, whereas the other DOACs are oral tablets or capsules,” said Dr. Adams.

PRIMARY PROPHYLAXIS FOR HIGH-RISK AMBULATORY PATIENTS

In 2019, two studies of primary prophylaxis for high-risk patients were published. In the first study, patients deemed to be high-risk were randomized apixaban vs. placebo (Carrier et al.,

2019). According to Dr. Adams, however, 91% of patients had a Khorana score of either 2 or 3 and most patients had a gynecologic malignancy or lymphoma, which are not indicative of high risk.

Although results showed a statistically significant decrease in rates of VTE with apixaban vs. placebo, rates of major bleeding increased by more than twofold. Mortality was also higher in patients receiving apixaban.

A similar study conducted with rivaroxaban vs. placebo showed protection against rates of deep venous thromboembolism with primary prophylaxis but again doubled the rate of major bleeding vs. placebo (Khorana et al., 2019). However, mortality was slightly lower at 6 months with rivaroxaban.

“Although the vast majority of these patients had a Khorana score of 2 or 3 as well, they also had pancreatic and gastric cancers, which are high-risk tumors,” said Dr. Adams.

In summary, clot-negative, ambulatory patients with a Khorana score of 2 or greater should be considered for anticoagulation; benefit with a half dose of either apixaban or rivaroxaban can be seen, but major bleeding rates will still be doubled.

Patients receiving an IMiD (e.g., lenalidomide or thalidomide) should be further classified for risk with the use of a tool like IMPEDE or SAVED. For high-risk IMiD patients, Dr. Adams recommended full anticoagulation with a low-molecular-weight heparin or warfarin. Providers can consider apixaban 2.5 twice daily, he added, but the data are limited for that approach.

For low-risk IMiD patients, aspirin or no intervention is recommended, particularly in the maintenance setting without high-dose steroids.

The duration of anticoagulation depends on the situation. For patients with a positive clot history, Dr. Adams recommended indefinite an-

ticoagulation with active cancer. When cancer is presumed cured, he said, providers should then follow standard treatment guidelines. ●

Disclosure

Dr. Adams had no conflicts of interest to disclose.

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