Guidance for the Oversight and Monitoring* of Direct Oral Anticoagulants (DOACs)
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Rationale

The direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban are currently on the VA National Formulary and are approved by the Food and Drug Administration (FDA) for various indications as outlined in Table 1. Compared to warfarin, DOACs have a shorter duration of effect, different drug-drug interaction profiles and varying administration considerations. DOACs undergo varying degrees of renal and hepatic elimination. With the widespread uptake of DOACs and preference over warfarin in most scenarios, anticoagulant use overall has increased significantly in the past decade. Coinciding with the increased use of anticoagulants is a rise in anticoagulant-related adverse drug events, including life-threatening bleeding and thromboembolic complications. Anticoagulants, including DOACs as major contributors, were the most frequently implicated class of medications associated with adverse events resulting in emergency department visits in a U.S. study from 2017-2019. With more predictable pharmacokinetic and pharmacodynamic profiles, the approach to monitoring DOACs differs from that of warfarin, yet appropriate oversight remains paramount given the aforementioned risks. Published literature has revealed that poor patient adherence to DOAC therapy may lead to increased risk for all-cause mortality and stroke. Within the Veterans Health Administration, about one-quarter of the DOAC patients were found to have sub-optimal adherence and a higher risk for all-cause mortality and stroke. [7] Another VA specific study showed that individual site-level variation in monitoring practices may also lead to decreased adherence. [8-9] In addition, off-label dosing, overdosing, and underdosing has been associated with an increased risk of adverse outcomes including major bleeding, stroke, all-cause mortality and cardiovascular hospitalizations. This information, when combined with the inherent risk associated with anticoagulation therapy supports the benefit of assessing appropriateness of therapy including agent choice and dosing, specialized patient education, and a plan for follow-up care. VA PBM recommends the following monitoring and oversight parameters for the use of DOACs with the goal to promote consistency and safe use of DOACs in VA.

Table 1
FDA Approved Adult Indications for Direct Oral Anticoagulants (DOACs)

	APIXABAN (ELIQUIS)	DABIGATRAN (PRADAXA)	EDOXABAN (SAVAYSA)	RIVAROXABAN (XARELTO)
Non-valvular atrial fibrillation	√	√	√	√
Treatment of DVT and PE	√	√ (After 5-10 days of parenteral anticoagulant)	√ (After 5-10 days of parenteral anticoagulant)	√
Reduction in the risk of recurrent DVT and PE following initial therapy	√	√		√
Post-surgical VTE prophylaxis following hip replacement surgery	√	√		√
Post-surgical VTE prophylaxis following knee replacement surgery	√			√
VTE prophylaxis in acutely ill medical patients				√
Cardiovascular risk reduction in patients with coronary artery disease (CAD)				√
Thrombotic vascular risk reduction in patients with peripheral arterial disease (PAD)				√

CAD=coronary artery disease; DVT = deep vein thrombosis; PAD=peripheral arterial disease; PE = pulmonary embolism; VTE = venous thromboembolism

Oversight

It is recommended that patients prescribed chronic therapy with a DOAC be initially assessed, educated, and followed by locally designated staff (e.g., anticoagulation management program or other designees)) able to provide specialized education to patients regarding their medical condition and proper use of their medication as well as periodic follow-up monitoring for continued appropriateness of therapy, dose reassessment, drug interaction assessment, adherence, bleeds, thromboembolic events, or other adverse events. Given these are commonly used and high risk medications, facilities should consider using decision support tools and/or anticoagulation management program staff or designees for efficient and thorough upfront review of drug requests to ensure that the patient is an appropriate candidate for a DOAC and receiving an appropriate agent and dose upon initiation of treatment

***Note:** Following initial evaluation as appropriate, patients prescribed short-term treatment with a DOAC (e.g., prophylaxis following hip or knee replacement surgery) or very low dose rivaroxaban (2.5 mg twice daily for CAD or PAD), patient education, monitoring, and follow-up should be similar to the use of alternative agents in this setting (e.g., low molecular weight heparin, fondaparinux, or other antiplatelet treatments).*

Laboratory Monitoring

Baseline tests:

- Serum creatinine (SCr) (to estimate creatinine clearance [CrCl])
  Note: In the pivotal clinical trials with the DOACs, CrCl was estimated using the Cockcroft-Gault equation using actual body weight in the dabigatran, edoxaban, and rivaroxaban trials. The Cockcroft-Gault equation was used in the trials for apixaban with no guidance on use of actual versus ideal body weight.
- Hemoglobin, hematocrit, platelets
- Liver function tests may be considered in patients with history or risk of hepatic insufficiency (e.g., cirrhosis, viral hepatitis, alcohol abuse, heart failure, etc.)
- Prothrombin time (PT)/partial thromboplastin (aPTT) may be useful to have for future reference in case of an emergency to detect presence or absence of DOAC effect.

***Note:** The timeframe where a laboratory test (CBC and SCr) may be considered an acceptable "baseline" value and reflective of the patient's current status is ultimately determined by the provider using his/her clinical judgment. Reasonably, baseline lab values (hemoglobin, hematocrit, platelets, and SCr) drawn within the prior 1 to 3 months may be used, although this may vary (accepting a shorter or longer threshold of time) depending on the age and health status of the patient and any comorbid conditions.*

Follow-up monitoring:

- SCr (to estimate CrCl) as clinically appropriate; SCr should be monitored at least annually and considered more frequently if the results may lead to change in agent, dose, or risk-benefit of therapy (e.g., CrCl < 60 ml/min, concomitant illness that may lead to worsening renal function, or who are 75 years of age or older,
- Hemoglobin, hematocrit, platelets should be monitored at least annually or more frequently as the clinical situation dictates.
- Liver function testing may be considered in patients with underlying liver disease or when the clinical situation dictates.

Patient Education

Initial and periodic follow-up patient and caregiver education should be provided. At a minimum, education should include:

- Capsule or tablet identification
- Proper storage of medication (as applicable, e.g., dabigatran)
- Indication for therapy
- Risks and benefits of therapy
- Anticipated duration of therapy

- Daily dose, including dosing changes (e.g., loading doses in acute VTE)
- Administration considerations as applicable (e.g., rivaroxaban with meal)
- Drug interactions
- Monitoring requirements
- Importance of medication adherence
- The management of missed doses or extra doses
- Signs and symptoms of bleeding and thromboembolic events
- Avoidance of medications known to increase risk of major bleeding (e.g., non-steroidal anti-inflammatory drugs and antiplatelet agents) unless specifically instructed to take
- Non-bleeding adverse events
- Risks associated with falling and what to do in the case of a fall
- How to obtain supply of medication
- Importance of notifying providers about DOAC therapy before procedures for appropriate peri-procedural management
- Contact information for the anticoagulation or designated provider
- Gender-specific considerations for women of childbearing age (e.g., menstrual difficulties, pregnancy, contraception)

Adherence

Patients should be monitored for adherence, appropriate refill history, and tolerance of medication, which are expected to be particularly important at the beginning of therapy. Sites may use different approaches to monitor adherence, depending on the need and available resources (e.g., population management tool, telephone follow-up, face-to-face visit, secure messaging, or a combination of these methods).

Follow-up

Within 2-4 weeks of initiation of therapy

- In addition to the initial evaluation and education provided to patients at the start of therapy, it is recommended that patients receive a follow-up point of contact by locally designated staff within 2-4 weeks of initiation of therapy (or sooner if clinically indicated) to assess for tolerance, bleeding, thromboembolic events, other adverse events (e.g., gastrointestinal intolerance), adherence, correct dosing (e.g., patients being treated for acute VTE and transitioning from higher intensity initiation dosing), duplicate therapy (e.g., patients previously on warfarin previously who may have leftover supply) and reinforcement of educational points as needed.

Periodic, long-term follow-up

- Follow-up care should include reassessing adherence, screening for drug interactions, and monitoring lab-work as needed. Most VA facilities utilize the population management tool to follow-up care.
- The specific time points, the method (e.g., population management tool, phone, face-to-face, secure messaging, patient letter, or a combination of these methods), and the staff responsible (e.g., anticoagulation therapy management program or other designee) for providing periodic follow-up care should be determined locally and in coordination with VHA Directive 1108.16(1).

Quality Assurance

It is recommended that DOACs be incorporated into the ongoing quality assurance plan to evaluate safe anticoagulation practices in alignment with VHA Directive 1108.16(1). , Staff are to report adverse events as designated by local protocols and the P&T Committee. Adverse events are to be entered into the VA Adverse Drug Event Reporting System (VA ADERS) at https://vaww.cmop.med.va.gov/MedSafe_Portal/ .

The Product Information should be consulted for detailed prescribing information. Also, visit the VA PBM website for more information at: PBM Formulary Management - Home (sharepoint.com) or VA Formulary Advisor

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