Direct Oral Anticoagulants (DOACs)
Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), and Edoxaban (Savaysa)
Criteria for Use for Treatment of Venous Thromboembolism (VTE)
April 2020
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria
If the answer to ANY item below is met, then the patient should not receive a DOAC.

- Mechanical heart valve
- Active endocarditis
- Antiphospholipid syndrome (APS), particularly those who test triple positive (lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies) – data are lacking in single or double positive states
- Active pathological bleeding
- Severe renal impairment: Estimated creatinine clearance (CrCl) less than 30 mL/min (for apixaban, CrCl less than 25 mL/min or serum creatinine greater than 2.5 mg/dL)
- Known significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis, liver function test elevations greater than 2 to 3 times the upper limit of normal, Child-Pugh B or C, any hepatic disease associated with coagulopathy)
- Pregnancy (e.g. known pregnancy or positive pregnancy test)
- Breastfeeding
- Increased bleeding risk: medical condition or history of major bleed that would be considered a contraindication to anticoagulation

Inclusion Criteria
The answers to ALL of the following must be fulfilled in order to meet criteria.

- Acute VTE (deep vein thrombosis or pulmonary embolism) or history of VTE
- Assessment of renal function (CrCl) and complete blood count (CBC)*

*Additionally, liver function testing may be considered in patients with a history or risk of hepatic insufficiency

Additional Criteria
For newly diagnosed acute VTE treatment, one of the following criteria must be fulfilled:

- For dabigatran or edoxaban: For acute VTE: Patient will/has receive(d) an initial 5 to 10 days of therapy with an injectable anticoagulant (e.g., enoxaparin) BEFORE starting dabigatran or edoxaban
- For rivaroxaban or apixaban: For newly diagnosed, acute VTE: Patient will/has receive(d) the appropriate oral loading dose of rivaroxaban (15 mg twice daily for 21 days) or apixaban (10 mg twice daily for 7 days) BEFORE starting the maintenance doses of rivaroxaban or apixaban
If applicable, the answer(s) to the following criteria must be fulfilled for patient to be eligible:

- **Cancer associated VTE**: A DOAC may be used in lieu of LMWH based on shared decision making between provider and patient given the evolving data evaluating efficacy and safety in this population**

- **Female patients of child-bearing potential**: Counseling provided on contraception and risks vs. benefits of treatment

- **Weight greater than 120 kg or body mass index greater than 40 kg/m^2**: DOAC may be used with shared decision making regarding: a) the limited data available with DOACs in those of extreme weight; and b) the recommendation of some groups against use in this situation.

**Evidence is still evolving. DOACs appear to be at least as effective as LMWH but may be associated with more bleeding. A DOAC (edoxaban, apixaban, or rivaroxaban) may be a reasonable as an alternative to LMWH. Consider individual patient risks, preferences, and lifestyle. Use caution in prescribing DOACs to patients with gastrointestinal or genitourinary cancers due to concerns of increased bleeding.**
Supplemental Information

- **Prosthetic heart valves and valvular heart disease:**
  - DOACs should not be used in patients with mechanical prosthetic heart valves or in patients with atrial fibrillation and moderate-to-severe mitral stenosis.
  - DOACs are generally avoided in the first 3 months after surgically placed bioprosthetic heart valve, though the decision to use a DOAC vs. warfarin should be made on an individual basis. Specific DOAC package labeling varies, though language generally states DOACs are not recommended.
  - There is no consensus for or against the use of DOACs post trans-catheter aortic valve intervention/replacement (TAVI/TAVR).

- **Cancer-associated VTE:** Patients with cancer are at higher risk for thromboembolism (and death following VTE) and may be at higher risk of bleeding as part of their underlying cancer or chemotherapy. Low molecular weight heparin (LMWH) is superior to vitamin K antagonists (VKA) for the reduction in recurrent VTE risk in patients with cancer. Emerging data are becoming available from trials comparing DOAC to LMWH. In total thus far, it appears that DOACs are at least as effective as LMWH in the reduction of VTE but may be associated with increased bleeding. There is concern of excess bleeding with DOACs in patients with genitourinary and gastrointestinal cancers. A DOAC (edoxaban, rivaroxaban, or apixaban) may be a reasonable alternative to LMWH in patients with cancer associated VTE considering individual patient risks, preferences, and lifestyle. Dabigatran should be avoided at this time due to lack of data. Recommendations may continue to change.

- **Obesity:** Limited data are available on the use of DOACs in extremes of body weights. Some pharmacokinetic and pharmacodynamic data have found modest effects of body weight extremes on DOAC exposure, but the clinical relevance is unknown. Subgroup analysis of obese patients from the landmark 3 DOAC trials suggests that DOACs generally appear to be safe and effective; however, data are limited. The International Society on Thrombosis and Haemostasis (ISTH) guidance (2016) on the use of DOACs in obese patients suggests not using DOACs in patients with a body mass index (BMI) of >40 kg/m² or weight of >120 kg. Observational studies of obese patients (>120 kg) in the atrial fibrillation and VTE populations published after the 2016 ISTH guidance have not identified significant differences in effectiveness and bleeding between DOAC and warfarin treated patients. VA PBM recommends that when a DOAC is being considered in such patients, a shared decision making approach should be utilized with information provided on the limited data regarding the efficacy and safety of these agents in extremes of body weight and recommendations of some groups against use in this situation.

- **Extended treatment of VTE:** Certain patients who experience a first VTE episode are at increased risk of recurrent VTE following the initial treatment course (3 to 12 months) and may benefit from extended anticoagulation. The decision to extend anticoagulation treatment must balance the patient’s recurrent VTE and bleeding risk and consider their preferences.
  - In total, DOACs (dabigatran, rivaroxaban, and apixaban) have been shown to reduce the risk of recurrent, symptomatic VTE with similar-to-higher bleeding compared to placebo for extended treatment durations in patients at risk for VTE recurrence (e.g., unprovoked VTE).
  - Dosing: Note that reduced doses of apixaban and rivaroxaban were studied only in patients with clinical equipoise for continuing anticoagulation. Patients with clear indications for continued anticoagulation treatment were not studied on the reduced dose.
    - Dabigatran: 150 mg twice daily
    - Rivaroxaban: 10 mg once daily after at least 6 months of treatment
    - Apixaban: 2.5 mg twice daily after at least 6 months of treatment
Anticoagulation Algorithm – Considerations for Selection of DOACs for VTE Treatment in VA Patients

**Patient with Acute VTE**

**DOAC or warfarin (WARF)?**
- DOACs have been shown to be noninferior to warfarin for reducing recurrent VTE with overall similar-to-lower bleeding (except certain agents are associated with more GI bleeding).
- DOACs are not recommended and WARF should be used in patients with the following:
  - Mechanical heart valve
  - Antiphospholipid syndrome (APS), particularly triple positive; data lacking on single or double positive states
  - On concomitant therapy with drugs known to significantly interfere with DOACs
  - CrCl <30 ml/min or end stage renal disease (ESRD) on dialysis (for apixaban, 25 ml/min or Scr >2.5 g/dL)
- Data are limited on the use of DOACs in the following settings. Use shared decision making with provider and patient for treatment determinations:
  - Bioprosthetic heart valves
  - Obesity (weight greater than 120 kg or body mass index greater than 40 kg/m²)
- Certain DOACs have been shown to be at least as effective as LMWH in patients with cancer associated VTE (edoxaban, rivaroxaban, apixaban) but may cause more bleeding. Data are still evolving. WARF is inferior to LMWH in the setting of cancer associated VTE.
- WARF may be effectively initiated or continued in the setting of good INR control and acceptability to patient and provider

**Is patient at increased risk of bleed**?
- **YES**
  - **Consider APIX**
    - Bleeding rates similar-to-lower with DOACs vs. WARF overall
    - APIX was associated with less major bleeding vs. WARF
    - APIX, EDOX, and DABI were associated with less major plus nonmajor clinically relevant bleeding (as a combined endpoint)
    - Excess GI bleeding events with DABI, RIVA, and EDOX vs. WARF; fewer GI bleeding events with APIX vs. WARF

  **NO**

**Does the patient have renal impairment?** (CrCl ≤50 ml/min)
- **YES**
  - **Consider RIVA or APIX or EDOX**
    - Portion of renal elimination of DOACs: DABI > EDOX > RIVA > APIX
    - DABI primarily undergoes renal elimination; DABI OK if no clinically significant drug interactions are present and patient is not at high bleed risk* (DABI should be avoided if on a P-gp inhibitor and CrCl ≤50 ml/min)

  **NO**

**Consider DABI or other DOAC**
- DABI or EDOX require initial treatment with an injectable anticoagulant
- RIVA or APIX do not require initial treatment with injectable anticoagulant

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* Examples of factors that increase bleeding risk include advanced age, renal impairment, history of bleeding, concomitant use of meds that affect bleeding, hypertension, prior stroke, and anemia. Several bleeding risk score systems that were developed for warfarin (e.g., HAS_BLED, Outpatient Bleeding Risk Index, HEMORR2HAGES) are available, though their predictability has been shown to be limited.

† CrCl was estimated using the Cockcroft-Gault equation in the pivotal clinical trials of DOACs (and using actual body weight in the dabigatran, rivaroxaban, and edoxaban trials).

**Notes:**
- The algorithm is not all inclusive, and complex patients may not fit the algorithm. Clinical judgment should be used.
- No head to head clinical trials between DOACs have been conducted; considerations for one agent over another are based on data from pivotal trials with a DOAC vs. warfarin or on indirect comparisons of DOACs.
- RIVA and APIX are initiated without the need for initial therapy with an injectable anticoagulant.
- EDOX, RIVA, APIX have been studied in cancer-associated VTE and may be considered alternatives to LMWH. DABI should be avoided in the absence of data in this setting.

APIX=apixaban; CAD=coronary artery disease; CrCl=creatinine clearance; DABI=dabigatran; DVT=deep vein thrombosis; EDOX=edoxaban; GIB=gastrointestinal bleed; INR=international normalized ratio; PE=pulmonary embolism; RIVA=rivaroxaban; WARF=warfarin; VTE=venous thromboembolism