Direct Oral Anticoagulants (DOACs)
Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis) and Edoxaban (SAVAYSA)
Criteria for Use for Stroke Prevention in Nonvalvular Atrial Fibrillation (AF)

Updated December 2017
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 UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS 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. The VA National PBM-MAP-VPE DOAC Drug Class Review, individual Drug Monographs, and CFU for Venous Thromboembolism (VTE) Treatment and VTE prophylaxis are available at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/

Pivotal Studies Summary:

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>EDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal study</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
<td>ENGAGE-AF</td>
</tr>
<tr>
<td>DOAC vs. warfarin (INR 2-3)</td>
<td>Open-label</td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Double-blind</td>
</tr>
<tr>
<td>Mean CHADS2 score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean Time in Therapeutic Range (TTR)</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>65%</td>
</tr>
<tr>
<td>Efficacy: Reduction in all stroke, systemic embolism</td>
<td>Superior</td>
<td>Non-inferior</td>
<td>Superior</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Safety: Major bleeding</td>
<td>Similar</td>
<td>Similar</td>
<td>Superior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mortality</td>
<td>Favorable trend</td>
<td>Favorable trend</td>
<td>Superior</td>
<td>Favorable trend</td>
</tr>
</tbody>
</table>

No head to head clinical trials of DOACs are available; differences in trial design and patient populations limit the ability to make indirect comparisons between DOACs.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- Indication for anticoagulant treatment is other than nonvalvular AF or VTE treatment (see DOAC VTE Treatment Criteria for Use)
- Mechanical heart valve (See Issues for Consideration for bioprosthetic heart valves)
- Clinically significant valvular disease (e.g., moderate to severe mitral valve stenosis) (See Issues for Consideration)
- Following acute stroke or TIA
- Active endocarditis
- Active pathological bleeding
- Known significant liver disease (See Issues for Consideration)
- For dabigatran, concurrent use of a significant P-glycoprotein (P-gp) interacting drug (See Comparative Table for further discussion)
- For rivaroxaban and apixaban, concurrent use of a significant dual P-gp and CYP3A4 interacting drug (See Comparative Table for further discussion)
- For edoxaban, concurrent use of concomitant P-gp inducer (e.g., rifampin) (See Comparative Table for further discussion)
- For edoxaban, creatinine clearance (CrCl) greater than 95 ml/min (reduced efficacy)
- Previous hypersensitivity reaction to DOAC
- Pregnancy (i.e., 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 (See Issues for Consideration).
- Severe renal impairment* (See Comparative Table):
  - Dabigatran: CrCl <30 ml/min
  - Rivaroxaban: CrCl <30 ml/min
  - Apixaban: CrCl <25 ml/min or serum creatinine (SCr) >2.5 mg/dL
  - Edoxaban: CrCl <30 ml/min

INCLUSION CRITERIA (cont’d on page 2)

**ALL must be selected for patient to be eligible for DOAC:**

- Diagnosis of non-valvular AF or flutter (with AF or flutter documented by electrocardiogram)
- The decision has been made to use an oral anticoagulant (vs. aspirin or no treatment) in the presence of at least one additional risk factor for stroke (e.g., CHADS2 or CHA2DS2-VASc score ≥1) or prior TIA, stroke or systemic embolism.
- Renal function assessment (CrCl) (see Monitoring for additional information)
INCLUSION CRITERIA (cont’d from page 1)

Dabigatran is the preferred DOAC in the absence of a compelling rationale for an alternative agent (see algorithm for DOACs and Consideration for Using a DOAC)

For rivaroxaban (ONE or more of the following additional criteria must be selected for patient to be eligible):
- Renal impairment (CrCl 30-50 ml/min)
- Medical or other compelling reason to avoid twice daily medication
- Unable to swallow whole pills
- Need for use of a pill reminder box
- Patient is intolerant to or is not a candidate for dabigatran

For apixaban (ONE or more of the following must be selected for patient to be eligible):
- Renal impairment (Scr 1.5-2.5 mg/dL or CrCl 25-50 ml/min)
- Considered at increased risk of bleeding (including GI bleeding or age of 75 years or older)\\n- Patient is intolerant to or is not a candidate for dabigatran

For edoxaban (ONE or more of the following additional criteria must be selected for patient to be eligible):
- Renal impairment (CrCl 30-50 ml/min)
- Medical or other compelling reason to avoid twice daily medication
- Need for use of a pill reminder box
- Considered at increased risk of bleeding (excluding GI bleeding)
- Patient is intolerant to or is not a candidate for dabigatran

DOsing
- Usual doses for nonvalvular AF:
  - Apixaban: 5 mg twice daily
  - Dabigatran: 150 mg twice daily
  - Edoxaban: 60 mg once daily
  - Rivaroxaban: 20 mg once daily

- See prescribing information for reduced dosing in special populations
- Due to lack of clinical trial data, PBM recommends avoiding the use of each DOAC in the following degrees of renal impairment:
  - Apixaban: CrCl <25 ml/min or Scr >2.5 mg/dL
  - Dabigatran: CrCl <30 ml/min or 30-50 ml/min and on interacting drug (dronedarone or ketoconazole)
  - Edoxaban: CrCl <30 ml/min
  - Rivaroxaban: CrCl <30 ml/min

monitoring
- Patients should be monitored for adherence, signs and symptoms of bleeding, stroke, and other adverse effects.
- Prior to starting therapy, it should be assured that the patient does not have anemia or thrombocytopenia and has adequate renal function. In patients with chronic kidney disease or other conditions where CrCl may fluctuate or in patients >75 yrs of age, monitoring of serum creatinine and estimating CrCl should be performed more frequently at the discretion of the provider; therapy should be adjusted as needed.
- No routine laboratory monitoring of anticoagulant activity is recommended.

issues for consideration
- Discontinuation of therapy: Patients are at increased risk of thrombotic events (e.g., stroke) when the DOAC is discontinued in the absence of alternative anticoagulation based on data from ARISTOTLE (apixaban) and ROCKET AF (rivaroxaban). If the DOAC must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
- Prosthetic heart valves and valvular heart disease:
  - DOACs should not be used in patients with mechanical prosthetic heart valves or moderate-to-severe mitral stenosis.
  - Data are limited on the use of DOACs in patients with NAFV and a prior bioprosthetic heart valve (that in and of itself does not require anticoagulation). 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.
  - Though not specifically studied, subgroup analyses and meta-analyses of the pivotal DOAC trials evaluating patients with other forms of valvular heart disease (e.g., mitral regurgitation, aortic regurgitation, mild mitral stenosis, aortic stenosis, tricuspid regurgitation) have been conducted. Overall, the presence of these other forms of valvular heart disease did not appear to impact the relative effectiveness and safety of DOACs compared to warfarin.
- Contraindications due to increased bleeding risk: Risk and benefit assessment for individual patients should be conducted. Some of the following examples may be considered relative contraindications to anticoagulation in general depending on the patient scenario: anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100,000/μL), cancer considered to be at risk for bleeding based on the type of cancer and/or type of cancer treatment being administered, history of intracranial, intracranial, spinal, retropertioneal, atrumatic intra-articular bleeding, or gastrointestinal bleeding, uncontrolled hypertension (persistently elevated systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg), recent and concomitant treatment with fibrinolytic agent (refer to prescribing information [P]), or chronic treatment with a nonsteroidal anti-inflammatory drug (NSAID).
- Use in significant liver disease: see PI for details. Language in the product label and from the exclusion criteria of the pivotal trials differ between agents. Overall, avoid DOAC use in patients with moderate-to-severe impairment - e.g., acute clinical hepatitis, cirrhosis, liver enzyme elevations (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] >2-3x upper limit of normal, or hepatic disease associated with coagulopathy.
- Dabigatran 75 mg twice daily dose: Dabigatran is eliminated primarily through the kidneys. Based on pharmacokinetic modeling, a reduced dose of dabigatran (75 mg twice daily) was FDA approved for use in patients with CrCl 15-30 ml/min; however, there are no clinical trial data evaluating the safety and effectiveness of the reduced dose, as patients with CrCl <30 ml/min were excluded from the pivotal RE-LY study. PBM recommends avoiding the use of dabigatran 75 mg twice daily with availability of alternatives (e.g., warfarin).
- Pharmacodynamic interactions: Concomitant use of DOACs and medications that affect hemostasis are expected to increase the risk of bleeding (e.g., aspirin, anti-platelet agents, other anticoagulants, fibrinolitics, NSAIDs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors). Low dose aspirin (≤165 mg/day) combined with DOACs (or warfarin) increases the risk of bleeding. In acute coronary syndrome (ACS) populations, the addition of apixaban (full dose), rivaroxaban (low dose), or dabigatran (varying dose) to aspirin plus a P2Y12-receptor antagonist (e.g., clopidogrel) was found to significantly increase bleeding risk. The need for concurrent use of anti-platelet medications or other medications that may increase the risk of bleeding should be re-evaluated when a DOAC is prescribed.
**Reversal of anticoagulant effects:** Idarucizumab is a reversal agent specific for dabigatran only. There is no reversal agent for rivaroxaban, apixaban, or edoxaban, although the DOACs have a relatively short duration of action compared to warfarin. Information on the optimal management of bleeding with DOACs is limited. Management should be individualized according to the specific situation but may reasonably include discontinuation of treatment and implementation of supportive measures (compression, surgical hemostasis, transfusion). Dialysis may be effective for dabigatran but is not expected to be effective for removal of apixaban, rivaroxaban, or edoxaban (given the high protein binding of the drugs). Activated charcoal may reduce absorption of the DOACs and may be considered in cases of suspected overdose or bleeding if administered within 2 hours of the last DOAC dose.

**Switching from or to warfarin:** When switching from warfarin to a DOAC, prescribing information recommends starting the DOAC when INR is < 3 for rivaroxaban, ≤ 2.5 for edoxaban, and ≤ 2 for dabigatran and apixaban. DOACs reach therapeutic effects within a few hours. When converting from DOAC to warfarin, consider that DOACs affect INR. If continuous anticoagulation is needed, discontinue DOAC and start a parenteral anticoagulant with warfarin at the time the next scheduled DOAC dose would have been due. For edoxaban, an alternative to parenteral therapy is to continue half-dose edoxaban along with warfarin until the INR on warfarin is therapeutic and stable. INR must be checked just prior to edoxaban dose to minimize interference. See PI for details. (See “Discontinuation of therapy” or Boxed Warning in prescribing information on the increased risk of thrombotic events)

**Switching from or to anticoagulants other than warfarin:** Discontinue the anticoagulant being used and start the other at the next scheduled dose.

**Interruptions in therapy for surgery and interventions:** If possible, DOACs should be discontinued at least 24 hours prior to surgery or invasive procedures with an increased bleeding risk. Discontinuations of longer durations are recommended for surgery and procedures with a higher bleeding risk where complete hemostasis is required and for patients with renal impairment. Recommendations regarding alterations in anticoagulant therapy for dental procedures can be found at the American Dental Association at: [http://www.ada.org/2526.aspx](http://www.ada.org/2526.aspx). The risk of thromboembolism off anticoagulation and the risk of peri-procedural bleeding need to be considered (See PIs and Comparative Table for additional, more specific information).

**Pregnancy:** PBM recommends generally avoiding the DOACs during pregnancy because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.

**Coronary Artery Disease:** Dabigatran was associated with a small elevated risk of myocardial infarction (MI)/acute coronary syndrome (ACS) in clinical trials. Overall, there appears to be about a 30% relative increase in MI/ACS that translates to about a 0.2-0.3% annual absolute increase in events. No excess of MI/ACS was observed with dabigatran in a large, real-world, database U.S. study. No excess of MI/ACS with rivaroxaban, apixaban, or edoxaban has been observed.

**Altered gastrointestinal absorption:** There are little clinical data evaluating the DOACs in patients with prior bariatric surgery, gastric bypass, or other procedures or conditions where gastrointestinal absorption could be significantly altered.

**Obesity:** Very 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 pivotal phase 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 on the use of DOACs in obese patients (2016) suggests not using DOACs in patients with a body mass index (BMI) of >40 kg/m² or weight of >120 kg. 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.

**Adherence to drug regimen:** Patients should be able to adhere to a twice daily drug regimen with dabigatran and apixaban and to a once daily regimen with rivaroxaban and edoxaban. Adherence rates were very high with the DOACs in the pivotal nonvalvular AF trials, and it is unclear how outcomes may be affected with lower adherence rates, given their relatively short half-lives.

**Dual care patients:** All patients receiving the drug from VA should be managed according to the same standards (e.g., eligibility, monitoring, follow-up), consistent with the VHA National Dual Care Directive 2009-038.

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### CHADS2 assessment (JAMA. 2001;285(22):2864-70.)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

### CHA2DS2-VASc assessment (Stroke. 2010;41(12):2731-8.)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 yrs</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, peripheral arterial disease, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Sc (Sex category) female gender</td>
<td>1</td>
</tr>
</tbody>
</table>
Patient with NVAF and decision to use anticoagulant has been made

Direct Oral Anticoagulant (DOAC) or warfarin (WARF)?
- WARF and DOACs are acceptable 1st line agents
- DOACs not recommended and WARF should be used in patients with the following:
  - CrCl <30 ml/min or end stage renal disease (ESRD) on dialysis
  - Prosthetic heart valve
  - Additional indication for anticoagulation other than venous thromboembolism (VTE) history
  - On concomitant therapy with interacting drugs
- WARF may be effectively initiated or continued in the setting of good INR control and acceptability to patient and provider
- DOACs may be useful in the setting of poor INR control on WARF despite adherence, difficulty obtaining regular INR checks, and drug interactions that can’t be managed by adjusting WARF dose

Decision to use DOAC has been made
(Consider all clinical factors prior to final drug selection)

Is patient at increased risk of bleed* (especially 75 yrs or older) including GIB or have history of GIB?

YES

Does the patient have renal impairment? (CrCl † ≤50 ml/min)

NO

YES

DABI preferred in the absence of compelling rationale for another DOAC

Consider APIX
- DABI, RIVA, and EDOX were associated with higher risk of GIB than WARF in all patients; no excess of GIB found with APIX
- DABI was associated with an increased risk of extracranial and GI bleeding and trend of more major bleeding vs. WARF in patients ≥75 yrs
- RIVA was associated with a trend of increased risk of clinically relevant bleeding vs. WARF in patients ≥75 yrs
- APIX was associated with less bleeding vs. WARF in all patients and in subgroup of patients ≥75 yrs
- EDOX was associated with less non-GI bleeding vs. WARF in all patients and subgroup of patients ≥75 yrs (but higher risk of GI bleeding with EDOX)

Consider RIVA or APIX or EDOX
- Portion of renal elimination of DOACs: DABI > EDOX > RIVA > APIX
- RIVA: reduced dose recommended and studied clinically in patients with CrCl 30-50 ml/min
- APIX: reduced dose recommended (if other risk factors are present) and studied clinically in patients with CrCl ≥25 ml/min
- DABI: eliminated primarily by kidneys; DABI OK if no drug interactions are present and patient is not at high bleed risk* (full dose recommended unless drug interactions are present or CrCl <30 ml/min; reduced dose not studied in clinical trials and not recommended)
- EDOX: reduced dose recommended and studied clinically in patients with CrCl 30-50 ml/min

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.
- See comparative table for more information
- Patients with CAD: DABI is associated with a small but significant increased risk of MI when data are considered in total. It is not known whether patients with CAD are at higher risk of events with DABI. Triple therapy (ASA, P2Y12 antagonist and anticoagulant) is associated with increased bleeding vs. dual antiplatelet therapy
- RIVA and EDOX are the only once daily DOACs and may be considered in patients with medical or other reason to avoid twice daily dosing

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

* 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).
## Direct Oral Anticoagulants: Criteria for Use and Algorithm


Updated versions can be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/](https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/)

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### COMPARATIVE TABLE: CONSIDERATIONS IN CHOICE OF ORAL ANTICOAGULANT FOR NVAF

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>EDOXABAN</th>
<th>WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>150 mg BID</td>
<td>20 mg once daily</td>
<td>5 mg BID</td>
<td>60 mg once daily</td>
<td>Variable dose; once daily</td>
</tr>
<tr>
<td><strong>Special considerations</strong></td>
<td>Caps cannot be crushed or opened</td>
<td>Cannot be administered via feeding tube placed distal to stomach</td>
<td>Can be crushed</td>
<td>No data on crushing tablets or feeding tube admin</td>
<td>Can be crushed</td>
</tr>
<tr>
<td><strong>Dietary considerations</strong></td>
<td>Take with full glass of water</td>
<td>Must take with meal for adequate absorption</td>
<td>None</td>
<td>None</td>
<td>Steady intake of Vitamin K containing foods</td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>Primarily renal elimination</td>
<td>~1/3 renal elimination</td>
<td>~1/4 renal elimination</td>
<td>~1/2 renal elimination</td>
<td>Minimal renal elimination</td>
</tr>
<tr>
<td><strong>Prosthetic Heart Valve</strong></td>
<td>Data showing increased adverse outcomes in mechanical prosthetic valves; contraindicated; not recommended for other valvular disease</td>
<td>Not studied and not recommended</td>
<td>Not studied and not recommended</td>
<td>Mechanical heart valves excluded and not recommended</td>
<td>OK</td>
</tr>
<tr>
<td><strong>Geriatric Patients</strong></td>
<td>Increased bleeding vs. warfarin in pts ≥75 yrs</td>
<td>Trend of increased bleeding in pts ≥75 yrs</td>
<td>No increase bleeds vs. warfarin</td>
<td>No increased bleeds vs. warfarin in pts ≥75 yrs</td>
<td>Less bleeding vs. DABI and RIVA. Consider lower initiation dose and greater sensitivity to dose/INR response in elderly</td>
</tr>
<tr>
<td><strong>PUD/GI issues</strong></td>
<td>Increased risk of GIB vs. warfarin</td>
<td>Increased risk of GIB vs. warfarin</td>
<td>No increased GIB found vs. warfarin</td>
<td>Increased risk of GIB vs. warfarin</td>
<td>Less GIB vs. DABI, RIVA, and EDOX</td>
</tr>
</tbody>
</table>

**Note:** The VA PBM recommendations for renal dosing are based on evidence from the pivotal clinical trials and may differ from information provided in the package label.

- **PBM recommendations:** Avoid if CrCl <30 ml/min (not studied in clinical trials)
  - Reduced dose of 15 mg once daily if CrCl 15-50 ml/min
  - End stage renal disease and on stable dialysis: 5 mg BID if age <80 yrs and wt >60 kg; 2.5 mg BID if age ≥80 yrs or wt ≤60 kg
  - Reduced dose of 2.5 mg BID if patients have 2 or more:
    - SCr ≥1.5 mg/dL
    - ≥80 yrs
    - wt ≤60 kg
  - Reduced dose of 2.5 mg BID if CrCl <30 ml/min (not studied in clinical trials)

- **Package Labeling:**
  - Reduced dose of 75 mg BID if CrCl 15-30 ml/min
  - Reduced dose of 75 mg BID if CrCl 30-50 ml/min AND on concomitant dronedarone or systemic ketoconazole.
  - Reduced dose of 15 mg once daily if CrCl 15-50 ml/min
  - Avoid if CrCl <15 ml/min or dialysis

- **Warfarin**
  - Package Labeling: Reduced dose of 30 mg once daily if CrCl 30-50 ml/min (studied and FDA approved)

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### Additional indications for anticoagulation

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approved for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DABIGATRAN</td>
<td>VTE treatment; VTE prophylaxis in hip replacement surgery</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>VTE treatment; VTE prophylaxis in orthopedic surgery</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>VTE treatment; VTE prophylaxis in orthopedic surgery</td>
</tr>
<tr>
<td>EDOXABAN</td>
<td>VTE treatment</td>
</tr>
<tr>
<td>WARFARIN</td>
<td>Several indications for use</td>
</tr>
</tbody>
</table>

### CAD considerations

- Numerical increase in MI vs. warfarin; 30% relative increased risk; 0.2-0.3% per yr absolute increase in MI/ACS events. No increase found in real-world, elderly U.S. population.

### ASA/thienopyridine concomitant use

- Increased bleeding
  - Little data on ASA+thienopyridine in AF;
  - Increased bleed with unknown benefit in Phase 2 study of ACS pts

- Increased bleeding
  - No data on ASA+thienopyridine in AF;
  - Increased bleed with benefit in ACS pts (low dose rivaroxaban)

- Increased bleeding
  - No data on ASA+thienopyridine in AF;
  - Increased bleed without benefit in ACS pts

### Drug interactions

- Prodrug is substrate of P-gp
  - AVOID use with P-gp inducers (e.g., rifampin, St. John’s Wort)- reduced dabigatran effect

- Caution with P-gp inhibitors (e.g., dronedarone, ketoconazole); AVOID in concurrent renal impairment

- CYP3A4, P-gp substrate
  - AVOID use with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort) – reduced rivaroxaban effect

- AVOID use with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir and ritonavir combinations)- increased rivaroxaban effect

### Cardioversion

- Post-hoc, retrospective analysis, small retrospective cohort study: low thromboembolic and bleed event rates in both DABI and WARF groups; case reports of thromboembolic events

- Prospective, open-label RCT, small retrospective cohort study; low rates of embolic and bleeding events with RIVA and WARF; post-hoc combo analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in small number of pts

- Post-hoc analysis showed no thromboembolic events and low rates of bleeding outcomes in both APIX and WARF groups

### Ablation

- Low quality data; most but not all studies suggest similar thromboembolic/bleeding risk

- Limited data; published combined analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in small no. of pts

- No data

### Switching from WARF

- Start DOAC when INR <2

- Start DOAC when INR <3

- Start DOAC when INR <2

- Start DOAC when INR ≤2.5

### Switching to WARF

- DABI affects INR

- RIVA affects INR

- APIX affects INR

- EDOX affects INR

### Surgery and Invasive Procedures

- The risk of

  - (From PI) Discontinue 1-2 days (if CrCl ≥50 ml/min) or 3-5 days (CrCl <50 ml/min) before invasive

- (From PI) Discontinue at least 24 hrs before surgery or procedures with increased bleeding

- (From PI) Discontinue at least 24 hrs prior to surgery/procedures where risk of bleeding is

- (From PI) Discontinue at least 24 hrs prior to surgery/procedures due to increased bleeding

### Standard of care

- Altered in plasma protein binding; CYP2C9, 1A2, 3A4 induction or inhibition; antibiotics, antifungals, herbas
<table>
<thead>
<tr>
<th>Anticoagulant Lab testing</th>
<th>Anticoagulant Reversal</th>
<th>Anticoagulant Reversal</th>
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</tr>
</thead>
<tbody>
<tr>
<td>None routinely recommended; if urgently needed, aPTT, TT (qualitative estimate; presence or absence)</td>
<td>Idarucizumab <em>specific</em> reversal agent for dabigatran only; discontinue drug, provide supportive care.</td>
<td>No reversal agent; discontinue drug, provide supportive care.</td>
<td>No reversal agent; discontinue drug, provide supportive care.</td>
</tr>
<tr>
<td>None routinely recommended; if urgently needed, PT, anti-Factor Xa (qualitative estimate; presence or absence)</td>
<td>No reversal agent; discontinue drug, provide supportive care.</td>
<td>None routinely recommended; if urgently needed, anti-Factor Xa (qualitative estimate; presence or absence)</td>
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</tr>
<tr>
<td>None routinely recommended</td>
<td>Idarucizumab</td>
<td>No reversal agent; discontinue drug, provide supportive care.</td>
<td>No reversal agent; discontinue drug, provide supportive care.</td>
</tr>
<tr>
<td>None routinely recommended</td>
<td>Inr</td>
<td>Vitamin K, 4-factor prothrombin complex concentrate (PCC) for life threatening bleeding</td>
<td></td>
</tr>
</tbody>
</table>

thromboembolic events vs. peri-op bleeding should be considered with use of anticoagulant therapy; expert consultation may be warranted.

- Consider longer times for higher risk procedures where complete hemostasis is required.
- Risk.
- Low and could be easily managed. Discontinue at least 48 hrs prior to surgery/procedures with moderate to high bleeding risk.
- Risk.
- Events off of anticoagulation, warfarin may be held and bridge therapy with parenteral anticoagulant considered.

Anticoagulant Lab testing
- None routinely recommended; if urgently needed, aPTT, TT (qualitative estimate; presence or absence)
- None routinely recommended; if urgently needed, PT, anti-Factor Xa (qualitative estimate; presence or absence)
- None routinely recommended; if urgently needed, anti-Factor Xa (qualitative estimate; presence or absence)
- None routinely recommended

Anticoagulant Reversal
- Idarucizumab *specific* reversal agent for dabigatran only; discontinue drug, provide supportive care. Hemodialysis may be effective.
- No reversal agent; discontinue drug, provide supportive care.
- No reversal agent; discontinue drug, provide supportive care.
- No reversal agent; discontinue drug, provide supportive care.