# CCHCS Care Guide: Anticoagulation

## Summary

### Goals
- Choose appropriate anticoagulation for each patient based on clinical indication, adherence history, and absence of contraindications
- Monitor INR in every warfarin patient at least monthly
- Designate a sole provider responsible to adjust warfarin for each patient
- Achieve therapeutic INR within 30 days of warfarin initiation
- Identify a single target INR value as goal (e.g., target INR 2.5)

### Alerts
- Significant drug-drug interactions
- High risk of serious bleeding
- International Normalized Ratio (INR) outside desired range
- Extremity pain or swelling / Skin Necrosis
- Altered level of consciousness
- Acute Rash, Hepatitis, Diarrhea / Nausea, GI bleed
- Pregnancy / Breastfeeding

## Evaluation

### Identify Thrombotic Condition or Risk
- **Venous Thromboembolism (VTE)**
  - Provoked Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)
  - Cancer Associated DVT or PE
- **Unprovoked DVT or PE Recurrent VTE**
  - See algorithm on page 4
- **Cardiovascular Indications**
  - i.e., Arterial Thrombus, Valvular Heart Disease, Non-Valvular Atrial Fibrillation (A. fib), Acute Myocardial Infarction (AMI), Left Ventricular (LV) Dysfunction
  - See algorithm on page 5

### Determine Bleeding Risk
- See assessing the risk of bleeding on page 9

## Diagnostic Studies

- **Initial Labs:** CBC including platelets, PT/INR, PTT, chemistry panel, and UA
- Imaging as clinically appropriate
- Additional labs for inherited causes of hypercoagulability as clinically indicated:
  - **LABS TO ORDER**
    - WEAKLY THROMBOPHILIC
    - STRONGLY THROMBOPHILIC
    - COMMENTS
  - Factor V Leiden
    - YES
    - YES
    - Factor V Leiden is the most common clotting factor mutation in the US, most frequent in Caucasians.
  - Prothrombin mutation
    - YES
    - YES
    - Prothrombin mutation most common after Factor V Leiden.
  - Antiphospholipid Antibodies
    - YES
    - YES
    - Antiphospholipid antibodies may be present temporarily or permanently. May be measured during thrombotic event.
  - Antithrombin
    - NO
    - YES
    - Antithrombin function and quantity are measured to determine deficiency. The test should not be performed in presence of thrombosis or during treatment for thrombosis.
  - Protein C / Protein S
    - NO
    - YES
    - Protein C and Protein S should not be measured while patient is on warfarin or within 10 days of thrombotic event.

## Table of Contents

<table>
<thead>
<tr>
<th>Table/Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation</td>
<td>1</td>
</tr>
<tr>
<td>Treatment/Monitoring</td>
<td>2</td>
</tr>
<tr>
<td>Selection of APP</td>
<td>3-6</td>
</tr>
<tr>
<td>Direct Oral APP</td>
<td>7-8</td>
</tr>
<tr>
<td>Bleeding Risk</td>
<td>9</td>
</tr>
<tr>
<td>Procedures</td>
<td>10</td>
</tr>
<tr>
<td>Warfarin Dose Adj.</td>
<td>11</td>
</tr>
<tr>
<td>Medications/Interac.</td>
<td>12-15</td>
</tr>
<tr>
<td>Patient Educ.</td>
<td>16</td>
</tr>
<tr>
<td>Patient Educ.-Spanish</td>
<td>17</td>
</tr>
</tbody>
</table>

Information contained in the Care Guide is not a substitute for a health care professional's clinical judgment. Evaluation and treatment should be tailored to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient. Refer to “Disclaimer Regarding Care Guides” for further clarification. http://www.cphcs.ca.gov/careguides.aspx
### Selecting an Anticoagulant
1. Ensure there are no CONTRAINDICATIONS for anticoagulation:
   - Active/ severe bleeding
   - Platelets <50,000
   - Neurosurgery, ocular surgery, or intracranial bleed within the past 10 days
   - Pregnancy (absolute contraindication for warfarin)
   - Major trauma
   - Recent or planned emergent or high risk surgery
   - If contraindications present: Discuss with specialist– Consider non-anticoagulation options such as inferior vena cava (IVC) filter for DVT

2. Select anticoagulant and duration of therapy based on diagnosis and clinical factors:
   -Provoked DVT or PE or Cancer associated DVT/PE– See algorithm on page 3
   -Unprovoked DVT/PE or Recurrent VTE Treatment– See algorithm on page 4
   -Cardiovascular indications for anticoagulation: Arterial Thrombus, Valvular Heart Disease, Non-Valvular A. fib, Acute MI, LV dysfunction– See algorithm on page 5
   -DVT prophylaxis- for postoperative hip/knee refer to surgeons recommendations
   -Peri-operative Management of Anticoagulation– See page 10

3. Monitor as directed below:
   - Determine a Goal INR if taking warfarin (e.g., target INR 2.5)

### Monitoring
#### Vitamin K Antagonist (VKA) - Warfarin
- Baseline: CBC with platelets, creatinine, PT/INR, PTT, albumin and liver enzymes (ALT, AST).
- After 2 days of warfarin therapy, repeat INR on day 3. If > 2.0 after the first 2 doses, consider decreasing the dose by half. (Measure INR 16 hours after warfarin dose.)
- Adjust dose as indicated and order subsequent INR tests based on initial response.
- When desired level reached, test INR weekly for 1-2 weeks.
- At goal INR, test INR every 4 weeks.
  - If INR < ± 0.5 out-of-range: repeat INR within 7-14 days.
  - If INR more than 0.5 out of range, see dosing adjustment recommendations on page 11.
  - If INR unexpectedly out of range, consider ASAP repeat of test and review handling of specimens/lab procedures.

Consider causes of rapid INR rise such as: drug interactions, poor nutritional status, infection, systemic disease process.

NOTE: Select institutions may have a statewide, standardized, Pharmacist Managed Anticoagulation Clinic for INR monitoring. Providers are encouraged to check with their institution.

#### Indirect Thrombin Inhibitors - Enoxaparin - Low Molecular Weight Heparin (LMWH)
- Baseline: CBC with platelets, creatinine, PT/INR, PTT
- Ongoing monitoring:
  - Not routinely indicated.
  - Consider platelet monitoring in patients at risk for heparin induced thrombocytopenia (HIT)*.
  - Heparin anti-Xa level monitoring not routinely required (sometimes used in patients w/ obesity and/or renal insufficiency and in pregnant women receiving therapeutic doses of enoxaparin).

#### Direct Oral Anticoagulants (DOACs)
- Baseline: CBC with platelets, creatinine, PT/INR, PTT, albumin and liver enzymes (ALT, AST).
- Regular lab monitoring is not required.
- Close monitoring of renal function is recommended for patients at increased risk of renal insufficiency (i.e., dehydration) or underlying Chronic Kidney Disease (CKD).
- Renal function and a complete blood count should be monitored at least annually or more frequently as the clinical situation dictates1.

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*RF’s HIT: Heparin exposure > 4 days, unfractionated heparin instead of LMWH. Therapeutic dosing instead of prophylaxis, female sex, surgical patients, age >40.
Selection of appropriate anticoagulant for venous thromboembolism

- Environmental risk factors for VTE (non-surgical): trauma, immobilization, central venous catheters, pregnancy/post-partum, chemotherapy, recent travel, hormone therapy (i.e., oral, transcutaneous, vaginal contraceptives, depot progestin injections, hormone replacement therapy)

- Bleeding risks: (explained on page 9)

- Risk factors for extension of distal DVT that would favor anticoagulation over surveillance:
  - D-dimer is positive
  - Thrombosis is extensive (>5 cm in length, involves multiple veins, >7 mm in max diameter)
  - Thrombosis is close to the proximal veins
  - No reversible provoking factor for DVT
  - Active cancer
  - History of VTE
  - Inpatient Status

- Extended therapy: no scheduled stop date; the continued use of anticoagulation should be reassessed at periodic intervals (i.e., annually)

- Weak recommendation for DOAC over VKA (2B). If selecting a VKA, choose single Goal INR between 2-3 with target at 2.5.

Grade of evidence shown in parenthesis:
1 = Strong recommendation  2 = Weak recommendation  A = High quality evidence  B = Moderate quality evidence  C = Low quality evidence

Adapted from University Health Systems, San Antonio Texas, Guidelines for anticoagulation Initiation and management, Oct 2016. American College of Chest Physicians 2016, Update on Antithrombotic therapy for VTE.
SELECTION OF APPROPRIATE ANTICOAGULANT FOR VENOUS THROMBOEMBOLISM

Unprovoked DVT or PE

Proximal DVT or PE

1st unprovoked

Low or Moderate Bleed Risk (see page 9)
- Duration: (2B)
  - Extended therapy*
- Oral Anticoagulant*

High Bleed Risk (see page 9)
- Duration: (1B)
  - 3 months
    - Oral Anticoagulant*, ASA if stopping anticoagulation and no contraindication to ASA

2nd unprovoked

Low or Moderate Bleed Risk (see page 9)

High Bleed Risk (see page 9)
- Duration: (1B)
  - Low Bleed Risk, (2B) Moderate Bleed Risk
  - Extended therapy*
- Oral Anticoagulant*

Isolated-distant DVT

Duration: (1B)
- At least 3 months
- Oral Anticoagulant*

*Weak recommendation for DOAC over VKA. If selecting a VKA, choose single Goal INR between 2-3 with target at 2.5.

Recurrent VTE Treatment On Extended Anticoagulation

Patient is already on DOACs/warfarin

1. Reevaluation of whether there truly was a recurrent VTE
2. Evaluation of compliance with anticoagulant therapy
3. Consideration of an underlying malignancy

Switch to LMWH temporarily for at least 1 month (2C)

Patient is already on LMWH

Increase the dose of LMWH by 25-33% (2C)

*Extended therapy: no scheduled stop date; the continued use of anticoagulation should be reassessed at periodic intervals (i.e., at least annually)

Grade of evidence shown in parenthesis:
1= Strong recommendation
2= Weak recommendation
A= High quality evidence
B= Moderate quality evidence
C= Low quality evidence

Adapted from University Health Systems, San Antonio, Texas, based on CHEST Guidelines and Expert Panel Report, Antithrombotic Therapy for VTE Disease, CHEST Feb 2016.
### Calculating the Risk of Ischemic Stroke in Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Acronym</th>
<th>Points</th>
<th>CHA2DS2-VASc Total Score</th>
<th>Adjusted Stroke Rate (At 1 year follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>Stroke or Transient Ischemic Attack</td>
<td>2</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>Vascular disease (Coronary Artery Disease, Peripheral Vascular Disease, Aortic plaque)</td>
<td>1</td>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1</td>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>Maximum score = 9</td>
<td></td>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

1 Adapated from University Health Systems, San Antonio, Texas, based on CHEST Guidelines and Expert Panel Report, Antithrombotic Therapy for VTE disease, CHEST Feb 2016.
2 Perioperative Management of Patients Receiving Anticoagulants, Gregory YH Lip, MD; James Douketis MD; UpToDate. April 07,2017.
3 Chronic Anticoagulation: After Acute Coronary Syndromes, Gregory YH Lip, MD; UpToDate. August 31, 2017.
### Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Choice of Anticoagulant</th>
<th>Qualifying Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease and CrCl &lt;30mL/min</td>
<td>VKA</td>
<td>DOACs and LMWH contraindicated with severe renal impairment. If mild/moderate renal impairment and DOAC is used, dose adjustment required.</td>
</tr>
<tr>
<td>Poor Adherence</td>
<td>VKA</td>
<td>INR monitoring can help to confirm adherence. However, some patients may be more compliant with a DOAC because no need for monthly INR.</td>
</tr>
<tr>
<td>Once daily oral therapy preferred</td>
<td>VKA; Rivaroxaban; Edoxaban</td>
<td>Only Dabigatran has reversing agent - Praxbind, not readily available.</td>
</tr>
<tr>
<td>Reversal agent needed</td>
<td>VKA</td>
<td>Dabigatran increases dyspepsia. Dabigatran, Rivaroxaban, and Edoxaban may be associated with more GI bleeding than VKA.</td>
</tr>
<tr>
<td>Dyspepsia or history of GI bleeding</td>
<td>VKA; Apixaban</td>
<td>The pharmacokinetics and pharmacodynamics of factor Xa inhibitors may be affected by weight but the clinical impact of these effects remains unknown. Pending further evidence in patients at extremes of weight (e.g., &lt;50 kg, &gt;120 kg or BMI ≥ 35 kg/m²) it is advisable to limit DOAC use to situations where vitamin K antagonists cannot be used.</td>
</tr>
<tr>
<td>Weight &lt; 50 kg</td>
<td>VKA</td>
<td>Coronary artery events appear to occur more often with Dabigatran than with VKA. This has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulant because of increased bleeding risk.</td>
</tr>
<tr>
<td>Weight &gt; 120 kg or BMI ≥ 35 kg/m²**</td>
<td>VKA</td>
<td>VKA, Dabigatran, and Edoxaban require initial parenteral therapy with IV heparin or LMWH when immediate anticoagulation is needed.</td>
</tr>
<tr>
<td>Thrombophilia** (Highly pro-thrombotic states such as antiphospholipid antibody syndrome or heparin-induced thrombocytopenia)</td>
<td>VKA</td>
<td>Caution or avoidance of DOACs, especially in highly pro-thrombotic states such as antiphospholipid antibody syndrome or heparin-induced thrombocytopenia, is suggested until further evidence becomes available. DOACs may be a viable option for VTE treatment in patients with weaker underlying thrombophiliases (e.g., heterozygous Factor V Leiden).</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Avoid Dabigatran</td>
<td>A systematic review and meta-analysis of 12 randomized controlled trials including over 100,000 patients with either Non-Valvular AF or VTE showed that DOACs are associated with less major bleeding, fatal bleeding, intracranial bleeding, clinically relevant non-major bleeding, and total bleeding compared to warfarin. This provides a compelling argument to favor these agents over conventional therapy for VTE treatment whenever possible.</td>
</tr>
<tr>
<td>Need for rapid anticoagulation with oral agent without using initial IV heparin</td>
<td>Rivaroxaban; Apixaban</td>
<td>DOACs contraindicated if INR elevated due to liver disease; VKA dosing difficult to control; INR may not reflect antithrombotic effect.</td>
</tr>
<tr>
<td>Liver disease and coagulopathy</td>
<td>LMWH</td>
<td>DOACs contraindicated. More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy. However, for those patients who cannot (or will not) use long term LMWH, either a DOAC or VKA could be prescribed as a second-line option**.</td>
</tr>
<tr>
<td>Cancer</td>
<td>LMWH</td>
<td>Potential for other agents to cross the placenta.</td>
</tr>
<tr>
<td>Pregnancy or pregnancy risk</td>
<td>LMWH</td>
<td>DOACs contraindicated**. It is unknown whether any of the DOACs are excreted in breast milk. Because of the potential for infant harm, a decision should be made to either avoid breastfeeding or use an alternative anticoagulant, such as warfarin, in these women.</td>
</tr>
</tbody>
</table>


DIRECT ORAL ANTICOAGULANTS

There are two classes of Direct Oral Anticoagulants (DOACs):
1. Direct Thrombin Inhibitor (Dabigatran)
2. Factor Xa inhibitors (Apixaban, Edoxaban, and Rivaroxaban)

- Due to the short half-life of DOACs, patients considered for taking these drugs should be highly adherent, as there is increased risk of thrombosis even if only one dose is missed.
- National Guidelines, including CHEST 2016, weakly recommend DOAC over VKA for VTE with moderate evidence due to patient convenience and decrease in risk of bleed, efficacy was similar in non-inferior studies.
- Literature review favors DOACs for Non-valvular A. fib due to decreased risk of bleed and greater convenience, however current national guidelines have not been updated.
- Drug-Drug Interactions (DDI) with P-glycoprotein and CYP3A4 inducers and inhibitors, which changes blood concentration of the drug.

Potential Advantages and Disadvantages of DOACs Compared to VKAs*

<table>
<thead>
<tr>
<th>Advantages of DOACs</th>
<th>Disadvantages of DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No routine monitoring</td>
<td>No reliable, readily available measurement assay</td>
</tr>
<tr>
<td>Improved safety profile</td>
<td>Dose reduction or avoidance in renal impairment and avoidance in moderate or severe hepatic impairment</td>
</tr>
<tr>
<td>Rapid onset (may preclude the need for induction or bridging therapy)</td>
<td>No specific antidote (except for Dabigatran [Praxbind])</td>
</tr>
<tr>
<td>Short T1/2 (advantageous for invasive procedures or/active bleed)</td>
<td>Short half-life (mandates strict adherence)</td>
</tr>
<tr>
<td>Fixed dosing</td>
<td>Less flexibility in dosing</td>
</tr>
<tr>
<td>Greater convenience, patient satisfaction and quality of life</td>
<td>Fewer studies and approved indications (e.g., contraindicated in mechanical valve replacement)</td>
</tr>
<tr>
<td>Potentially more cost-effective from health system perspective</td>
<td>Potentially higher drug acquisition costs for patients</td>
</tr>
<tr>
<td>Fewer drug, disease and diet interactions</td>
<td>DOAC drug interactions do exist that may preclude use</td>
</tr>
</tbody>
</table>

Indications for DOAC Use: (Nonformulary Use Requirements)
VKA treatment remains an appropriate treatment of choice in our setting for the majority of patients, except in the following patients when a DOAC should be considered over VKA:

- Patients with non-cancer related VTE or non-valvular A. fib and:
  - History of intracranial hemorrhage
  - History of major non-GI bleed
    - For patients with history of GI bleed, VKA is preferred over DOACs due to increased risk of GI bleed with Dabigatran, Rivaroxaban, Edoxaban
  - Unstable INR despite patient adherence to VKA
  - Warfarin allergy or prohibited Drug-Drug interactions with VKA
  - Documented thrombotic event despite therapeutic INR
  - Unable to obtain monitoring INRs (difficult phlebotomy access)
  - New patients entering CCHCS system can be maintained on DOACs for up to 60 days until patient is evaluated for continued use versus switch to VKA
  - On a case-by-case basis for other indication
  - In CCHCS, must be given DOT for monitoring of adherence

Contraindications for DOAC Use:
- Patients with VTE in setting of active cancer
- Patients with prosthetic heart valve
- Patients with antiphospholipid antibody or other strongly thrombophilic condition
- Severe renal impairment CrCl < 30
- Known significant liver disease: LFT > 2-3X upper limit of normal Child-Pugh B/C
- Pregnancy or breastfeeding
- Non-adherent patient: due to short half-life of these drugs, there is increased risk of thrombosis even if only one dose is missed
- Not Recommended in patients with BMI >35, weight > 120 kg or weight < 50 kg due to potential of pharmacokinetics and pharmacodynamics being affected by weight
- History of GI bleed Pradaxa (Dabigatran)

### DIRECT ORAL ANTICOAGULANTS

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dabigatran (Pradaxa) (nonformulary, preferred)</th>
<th>Apixaban (Eliquis) (nonformulary)</th>
<th>Rivaroxaban (Xarelto) (nonformulary)</th>
<th>Edoxaban (Savaysa) (nonformulary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin Inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Half Life</th>
<th>12-17 hours</th>
<th>12 hours</th>
<th>5-9 hours</th>
<th>10-14 hours</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Dosing</th>
<th>150 mg BID AFTER ≥ 5 days of parental anticoagulation (usually LMWH)</th>
<th>10 mg BID for 7 days, then 5 mg BID Reduce to 2.5 mg BID after at least 6 months for prevention of VTE recurrence</th>
<th>15 mg BID with food x 3 weeks then 20 mg once daily with food</th>
<th>60 mg once daily AFTER ≥ 5 days of parental anticoagulation (usually LMWH)</th>
</tr>
</thead>
</table>

| Storage | • Must be used w/in 4 months after opening  
• Protect from moisture  
• Store at 25 °C (77 °F); allowed range 15-30 °C (59-86 °F)  
• Store in original package until time of use  
• Do Not crush or chew  
• Not recommended for splitting | • Store between 20-25 °C (68 to 77 °F); allowed range 15-30 °C (59-86 °F)  
• Store at 25 °C (77 °F); allowed range 15-30 °C (59-86 °F)  
• Store between 20-25 °C (68 to 77 °F); allowed range 15-30 °C (59-86 °F) | | |

| Special Considerations | Avoid concurrent use with any P-gp inducer  
Avoid concurrent use with any P-gp inhibitor IF CrCl < 50 mL/min  
Avoid in patients with history of GI bleed, severe hepatic/renal disease | Avoid use with dual strong CYP3A4 and P-gp inducers  
If patient is taking strong CYP3A4 and P-gp inhibitor:  
• If dose > 2.5 mg BID decrease dose by 50%  
• If already taking 2.5 mg BID avoid use | Avoid use with dual strong CYP3A4 and P-gp inhibitors or inducers  
CrCl >95 mL/min, increased rate of thrombosis seen  
Use dose of 30 mg once daily if any of the following:  
• CrCl 15-50 mL/min  
• Weight < 60 kg  
• Use with P-gp inhibitor | |

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>BID See page 13 for details</th>
<th>BID See page 13 for details</th>
<th>Once daily with food See page 14 for details</th>
<th>Once daily See page 14 for dose adjustments</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Renal Elimination</th>
<th>Avoid in patient with CrCl &lt; 30 mL/min</th>
<th>No dose adjustment for renal impairment</th>
<th>Avoid in patient with CrCl &lt; 30 mL/min</th>
<th>Avoid in patient with CrCl &lt; 15 mL/min</th>
</tr>
</thead>
</table>

| Convert TO Warfarin | Based on CrCl start warfarin 3 days (> 50 mL/min), 2 days (31-50 mL/min) or 1 day (15-30 mL min) before discontinuation of Dabigatran | D/C Apixaban and start warfarin plus parenteral anticoagulant at time of next Apixaban dose.  
D/C parenteral anticoagulant when INR is therapeutic | D/C Rivaroxaban and start warfarin plus parenteral anticoagulant at time of next Rivaroxaban dose.  
D/C parenteral anticoagulant when INR is therapeutic | D/C Edoxaban and start warfarin plus parenteral anticoagulant at time of next Edoxaban dose.  
D/C parenteral anticoagulant when INR ≥ 2.0 |
|---------------------|------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|

<table>
<thead>
<tr>
<th>Convert FROM Warfarin</th>
<th>D/C warfarin, start Dabigatran when INR &lt; 2.0</th>
<th>D/C warfarin, start Apixaban when INR &lt; 2.0</th>
<th>D/C warfarin, start Rivaroxaban when INR &lt; 3.0</th>
<th>D/C warfarin, start Edoxaban when INR &lt; 2.5</th>
</tr>
</thead>
</table>

| Convert FROM one DOAC TO another DOAC | Discontinue Dabigatran and initiate the preferred agent at the time that the next Dabigatran dose would have been administered | Discontinue Apixaban and initiate the preferred agent at the time that the next Apixaban dose would have been administered | Discontinue Rivaroxaban and initiate the preferred agent at the time that the next Rivaroxaban dose would have been administered | Discontinue Edoxaban and initiate the preferred agent at the time that the next Edoxaban dose would have been administered |

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SUMMARY

DECISION SUPPORT

PATIENT EDUCATION/SELF MANAGEMENT

FACTORS WHICH MAY INCREASE RISK OF BLEEDING WHILE ON ANTICOAGULANTS

- Age > 65 years
- Anemia
- Diabetes
- Cancer
- Frequent falls
- Malignancy
- Hypertension
- Acute or chronic alcohol use
- Liver failure
- Renal failure
- Comorbidity and reduced functional capacity
- Presence of bleeding lesion or injury (GI, PUD, etc.)
- Bleeding disorder (coagulation, Thrombocytopenia)
- Poor anticoagulant control
- Recent surgery
- Previous bleed
- Previous stroke
- Concomitant use of: aspirin, NSAID, clopidogrel, antibiotics, amiodarone, statins, or fluoroquinolones

RISK OF BLEEDING BASED ON RISK FACTORS

<table>
<thead>
<tr>
<th># of Risk Factors</th>
<th>Risk Category</th>
<th>Bleed Risk 0-3 months</th>
<th>Bleed Risk After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 risk factors</td>
<td>Low</td>
<td>1.60%</td>
<td>0.8%/year</td>
</tr>
<tr>
<td>1 risk factor</td>
<td>Moderate</td>
<td>3.20%</td>
<td>1.6%/year</td>
</tr>
<tr>
<td>≥ 2 risk factors</td>
<td>High</td>
<td>12.80%</td>
<td>≥ 6.5%/year</td>
</tr>
</tbody>
</table>

SITE OF ACTION FOR ORAL ANTICOAGULANTS

*Warfarin Mechanism of Action: Warfarin competitively inhibits the subunit 1 of the multi-unit VKOR complex, depleting functional vitamin K reserves and hence reduces synthesis of active clotting factors.

3Leung, Lawrence LK, Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects, uptodate.com, April 2017.
**PERI-OPERATIVE MANAGEMENT OF ANTICOAGULATION**

**RISK ASSESSMENT**
Determine risk of bleed vs. thrombosis in peri-operative period and adjust anticoagulant therapy accordingly.
For those surgeries not listed here, follow recommendations from surgery consultants.

**LOW BLEEDING RISK PROCEDURES THAT CAN BE PERFORMED**
WITHOUT DISCONTINUING OR CHANGING WARFARIN/ VITAMIN K ANALOG (VKA)

<table>
<thead>
<tr>
<th>DENTAL</th>
<th>Endodontics</th>
<th>Prosthetics</th>
<th>Restorations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teeth cleaning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated extractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontal therapy</td>
<td></td>
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</tbody>
</table>

For most dental procedures no change in anticoagulant dosing is needed. It may be reasonable to allow the patient to "drift" to the low end of his/her therapeutic INR prior to a dental procedure with a higher risk of bleeding.

<table>
<thead>
<tr>
<th>DERMATOLOGIC</th>
<th>Skin Biopsy</th>
<th>Simple excisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohs surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple excisions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continue anticoagulant around the time of the procedure and optimize local hemostasis.

<table>
<thead>
<tr>
<th>OPHTHALMIC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabeculectomy</td>
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</tr>
</tbody>
</table>

Continue Anticoagulation around the time of surgery.

<table>
<thead>
<tr>
<th>GASTROINTESTINAL</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic esophagogastroduodenoscopy (EGD)</td>
<td>Endoscopy without biopsy</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy without biopsy</td>
<td>Diagnostic ERCP</td>
<td></td>
</tr>
</tbody>
</table>

Continue Anticoagulation around the time of surgery.

**General Guidance for Peri-operative Anticoagulation**
- For Procedures with Intermediate and High risk of Bleed (not listed here), follow recommendations from the surgeon regarding Peri-Operative management of anticoagulation.
- Generally, DOACs are stopped 2-3 days before surgery depending on CrCl (earlier if CrCl <30-50 ml/min).
  - Restart DOAC 24 hours after procedure in patients who are at low risk of bleed.
  - In patients with high risk of bleed, resume DOACs 2-3 days after the procedure, after hemostasis has occurred.
- Bridging decision based on Thromboembolic Risk of Underlying Condition – See table below.

**ACCP’S* PERIOPERATIVE THROMBOEMBOLISM RISK STRATIFICATION**

| LOW THROMBOSIS RISK | < 4% / yr risk of Arterial Thromboembolism (ATE) or > 2% / mo risk of VTE |
|                    | Bi-leaflet aortic valve without AF and no other risk factors for stroke |
|                    | AF and CHAD2** score of 0-2 (and no prior stroke or TIA) |
|                    | Single VTE within past 3-12 mo and no other risk factors |

Consider no bridging anticoagulation during anticoagulation interruption.

<table>
<thead>
<tr>
<th>MODERATE THROMBOSIS RISK</th>
<th>4% -10% / yr risk of ATE or 4%-10% / mo risk of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bileaflet aortic valve and one of the following: AF, prior stroke/TIA, HTN, DM, CHF, age &gt; 75 yr</td>
</tr>
<tr>
<td></td>
<td>AF and CHAD2** score of 3 or 4</td>
</tr>
<tr>
<td></td>
<td>VTE within past 3-12 mo</td>
</tr>
<tr>
<td></td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td>Non-severe thrombophilic conditions</td>
</tr>
<tr>
<td></td>
<td>Active cancer</td>
</tr>
</tbody>
</table>

Bridging or no bridging decision needs to be individualized based on the surgical risk of bleeding and patient risk factors.

<table>
<thead>
<tr>
<th>HIGH THROMBOSIS RISK</th>
<th>10% / yr risk of ATE or &gt; 10% / mo risk of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any mechanical mitral valve</td>
</tr>
<tr>
<td></td>
<td>Older aortic valve</td>
</tr>
<tr>
<td></td>
<td>Mechanical heart valve and recent (&lt; 6 mo) stroke or TIA</td>
</tr>
<tr>
<td></td>
<td>AF and CHAD2** score of 5 or 6, recent (&lt; 3 mo) stroke or TIA, or Rheumatic valvular heart disease</td>
</tr>
<tr>
<td></td>
<td>Recent (&lt; 3 mo) VTE</td>
</tr>
<tr>
<td></td>
<td>Severe thrombophilia</td>
</tr>
</tbody>
</table>

Consider bridging anticoagulation with LMWH; stop VKA 5 days prior to surgery.

Stop DOACs 2-3 days prior to procedure and restart within 24 hours.

**See CHADs scoring system on page 5.
**Warfarin Dose Adjustment**

*Use only for patients already taking warfarin. Do not use for initiation or during first one to two weeks of warfarin therapy. There is no uniformly accepted protocol for warfarin dose adjustment.*

### Goal INR 2.5 (Range 2.0–3.0) vs. Goal INR 3.0 (Range 2.5–3.5)

<table>
<thead>
<tr>
<th>If INR Result Is:</th>
<th>Action</th>
<th>If INR Result Is:</th>
<th>Action</th>
</tr>
</thead>
</table>
| ≤1.5*             | • Increase weekly dose by 15%  
                  • Repeat INR in 7 - 14 days | ≤1.5*             | • Increase weekly dose by 20%  
                  • Repeat INR in 7 - 14 days |
| 1.51–1.99*        | • Continue same dose warfarin  
                  • Repeat INR within 7 - 14 days  
                  • If still 1.5-1.99, increase weekly dose by 10%  
                  and repeat INR in 7 - 14 days | 1.51–1.99*        | • Increase weekly dose by 15%  
                  • Repeat INR in 7 - 14 days |
| 2.00–3.00         | • Continue same dose warfarin  
                  • Repeat INR in no later than 4 weeks | 2.00–2.49*        | • Continue same dose warfarin  
                  • Repeat INR within 7 - 14 days  
                  • If INR still 2.0 - 2.49, increase weekly dose by 10%  
                  and repeat INR in 7 - 14 days |
|                   |        | 2.50–3.50         | • Continue same dose warfarin  
                  • Repeat INR in no later than 4 weeks |

### Greater than goal INR, but < 4.5 (between 3.0-4.5 and no bleeding)

(Consider medical hold for any patient with INR above 4.0)

- Option 1: Decrease or hold dosage, increase frequency of monitoring, and resume at lower dosage once INR is within therapeutic range
- Option 2: May continue current dosage if INR is minimally elevated (0.5 or less above therapeutic range in a previously stable patient)

### 4.5–10 and no bleeding

(Consider medical hold for any patient with INR above 4.0)

- Consider possible cause (new medication, acute illness, etc.)
- Hold next 1-2 warfarin doses
- Increase frequency of INR monitoring (every 24 hours as long as INR ≥ 5)
- Resume warfarin when INR is within therapeutic range; restart at a dosage that reflects a 10% decrease in the total weekly warfarin dose
- Repeat INR in 7–14 days
- Vitamin K is not recommended

### > 10 and no bleeding

- Consider possible cause (new medication, acute illness, etc.)
- Hold warfarin
- Administer vitamin K 2.5 - 5 mg orally** once
- Increase frequency of INR monitoring (every 24 hours as long as INR ≥ 5)
- If INR remains > 10, repeat vitamin K** 2.5 - 5 mg orally** once
- Resume warfarin when INR reaches < 3.0; restart at a dosage that reflects a 15% decrease in the total weekly warfarin dose

### Serious bleeding regardless of INR

- Hold warfarin and transfer to higher level of care
- If elevated INR, hold warfarin, give vitamin K 2.5-5 mg orally**, and transfer to a higher level of care

*Clinical and professional judgment may allow variation in the application of the algorithm.

**Oral vitamin K administration is preferred in non-emergency situations. Avoid subcutaneous or intramuscular administration of vitamin K.

*Adapted from: Holbrook, A et al. Evidence-Based Management of Anticoagulant Therapy. Chest 2012; 141(2) (Suppl):e152s-e184s, e326s-e350s. Hull, Russell D, MBBS, MSc and Valentine, Karen A, MD, PhD, “Correcting excess anticoagulation after warfarin” - UpToDate. 11/10/2014. Hull, Russell D, MBBS, MSc and Valentine, Karen A, MD, PhD, “Outpatient management of anticoagulation with warfarin” - UpToDate. 10/16/2013. Hull, Russell D, MBBS, MSc and Valentine, Karen A, MD, PhD, “Therapeutic use of warfarin and other vitamin K antagonists” - UpToDate. 10/16/2013.
## CCHCS Care Guide: Anticoagulation

### Summary

**Medication**

<table>
<thead>
<tr>
<th><strong>Warfarin</strong></th>
<th><strong>Lovenox</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumadin®</td>
<td>LMWH</td>
</tr>
<tr>
<td>Jantoven,</td>
<td></td>
</tr>
</tbody>
</table>

**Formulary**

- **Nonformulary**

**Strengths:**

1 mg-pink
2 mg-lavender
2.5 mg-green
3 mg-tan
4 mg-blue
5 mg-peach
6 mg-teal
7.5 mg-yellow
10 mg-white

**Strengths:**

- **Formulary**

1 mg/kg subQ once daily

**Nonformulary**

1 mg/0.5 ml
10 mg/ml

**Dosing**

<table>
<thead>
<tr>
<th><strong>Vitamin K Antagonist (VKA) (Oral) / VKA Reversing Agent (Vitamin K)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td>Initial daily dose is usually 5 mg orally every evening.</td>
</tr>
</tbody>
</table>

**Avoid loading doses**

- Consider lower starting dose: 2.5 mg every evening if:
  - Age > 75 yrs
  - Multiple comorbidities
  - Hypoalbuminemia
  - Elevated pretreatment INR
  - Elevated LFTs
  - Changing thyroid status

Consider higher starting dose: 7.5 mg every evening for patients > 80 kg

Patients restarting warfarin can usually start at their previous dose. If stopped due to bleeding, assess risk of thrombosis vs. risk of rebleeding

Recheck INR on day 3 after first two doses, if INR > 2.0, consider reducing dose by 1/2 (evaluate for cause of rapid rise in INR)

(See page 11)

**Steady-state INR will take up to 3 weeks**

**Assess variables affecting the INR before changing dose (e.g., patient adherence, medication interactions, dietary changes)**

- 10% warfarin dose adjustment changes INR approximately 0.7-0.8

- **Vitamin K**

**Strengths:**

Mephyton 5 mg (scored)

**AquaMephyton Injectable**

1 mg/0.5 ml
10 mg/ml

**Nonformulary**

$ - $$$$-$

**Indirect Thrombin Inhibitor (Parenteral) LMWH**

<table>
<thead>
<tr>
<th><strong>Enoxaparin</strong></th>
<th><strong>LMWH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovenox®</td>
<td></td>
</tr>
</tbody>
</table>

**Contraindications:**

- Absolute:
  - Pregnancy (teratogenic)
  - Active hemorrhage

**Risk of bleeding is highest in 1st month of therapy.**

**GU bleeding in a patient on warfarin must be evaluated.**

**A baseline INR value is helpful to rule out underlying coagulopathy.**

**Aortic dissection**

Unsupervised patients with conditions associated with increased potential for non-compliance.

Note: do not cut pills.

**Adverse Effects / Interactions**

**Warfarin**

**Bleeding**

Patients treated with usual doses of warfarin have a 2%-4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage.

Skin necrosis: rare but serious complication typically occurs on the 3rd to 8th day of therapy; four times as common in women as in men.

Purple toe syndrome (or other manifestations of peripheral emboli) may rarely complicate warfarin therapy, usually 3-10 weeks after initiation of therapy.

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Note: do not cut pills.

**Indirect Thrombin Inhibitor (Parenteral) LMWH**

**Enoxaparin**

**Do not administer IM; administer by subQ injection**

**IVT treatment (acute):**

- **Inpatient treatment** (with or without pulmonary embolism): 1 mg/kg subQ every 12 hours or 1.5 mg/kg subQ once daily

- **Outpatient treatment** (without pulmonary embolism): 1 mg/kg subQ every 12 hours**

**Note:** Start warfarin on 1st treatment day and continue enoxaparin until repeat administration

Most people do not experience any side effects taking small doses of vitamin K.

Serious allergic reactions to vitamin K are rare (patient should report any rash, itching, dizziness or breathing problem).

**Bleeding**

Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin exposure due to an HIT antibody which activates platelets and can cause life-threatening arterial and venous thrombosis. HIT should be suspected in patients who:

- Develop necrosis at the injection site
- Have a systemic reaction (fever, chills, dyspnea, etc.) to a bolus administration of heparin
- Develop a greater than 50% decrease in platelet count from baseline labs while on heparin
- Experience a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if the heparin has been discontinued

HIT can occur in patients getting ≥ 1 dose of unfractionated heparin (including heparin IV flushes) within the past 100 days

**Contraindications:**

- Absolute:
  - Active major bleeding, including intracerebral hemorrhage within past 2 weeks, subarachnoid hemorrhage until definitively treated
  - Thrombocytopenia, with positive antiplatelet test in presence of enoxaparin
  - Hypersensitivity to heparin or pork products

Other contraindications:

- Recent thrombolytic therapy
- History Heparin-induced thrombocytopenia (HIT)

Reversal of enoxaparin:

No agent is effective for complete reversal in the event of supertherapeutic anticoagulation (e.g., FFP, vitamin K, protamine) if life threatening bleeding, consider protamine: (Do not exceed 50 mg in 10 minutes)

- First dose: 1 mg for each 1 mg enoxaparin; give by slow IV over 10 minutes
- Second dose: 0.5 mg protamine for each 1 mg enoxaparin; give by slow IV infusion over 10 minutes

*See prescribing information for complete description of adverse effects and drug interactions.*
DIRECT THROMBIN INHIBITORS AND DIRECT FACTOR Xa INHIBITORS ARE ORAL ANTICOAGULANTS

All DOACs remain nonformulary, if chosen for treatment: Dabigatran is the preferred nonformulary agent

- The evidence for particular class of anticoagulants for VTE (non-cancer patients) and for non-valvular atrial fibrillation comes from most recent guidelines from Society of Chest Physicians (VTE) and review of literature (A. fib) and is based on weak recommendation and moderate quality evidence.
- In most cases the efficacy of DOAC vs VKA was the same, but the intracranial bleeding risk higher with VKA.

Patients who come to CCHCS on one of these direct acting agents should be evaluated to see if they qualify for continued DOAC use or should be converted to VKA.

If a patient comes to CCHCS on a Non-preferred nonformulary DOAC they should be transitioned to the preferred agent unless

- History of Intracranial hemorrhage
- History of Major non-Gl bleed (For patients with history of Gl bleed, VKA is preferred over DOACs due to increased risk of Gl bleed with Dabigatran, Rivaroxaban, Edoxaban)
- Unstable INR despite patient adherence to VKA
- Warfarin allergy or prohibited Drug-Drug interactions with VKA

Nonformulary use considerations of DOACs in patients with VTE or Non-valvular A. fib

VKA treatment remains an appropriate treatment of choice in our setting for the majority of patients, except in the following patients when a DOAC should be considered over VKA:

- Documented thrombotic event despite therapeutic INR
- Unable to obtain monitoring INRs (difficult phlebotomy access)
- New patients entering CCHCS system can be maintained on DOACs for up to 60 days until patient is evaluated for continued use vs. switch to VKA
- On a case-by-case basis for other indication
- In CCHCS, must be given DOT for monitoring of adherence

### Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Adverse Effects / Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT THROMBIN INHIBITOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DABIGATRAN PRADAXA®</strong></td>
<td>150 mg twice daily</td>
<td><strong>Bleeding</strong></td>
<td>Do not chew, break, or open capsules. Capsules must be dispensed in original container and not repackaged due to sensitivity to moisture.</td>
</tr>
<tr>
<td>Nonformulary Preferred</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Strengths:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>75 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer DOT Only</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| $$$$$

- Renal Impairment:
  - Non-valvular A-fib
    - CrCl >30 mL/min: No dose adjustment needed
    - CrCl 15-30 mL/min: 75 mg twice daily
    - CrCl <15 mL/min: No data
  - CrCl 30-50 mL/min and concurrent use of dronedarone or systemic ketoconazole: 75 mg twice daily
  - CrCl <30 mL/min and concurrent use of P-glycoprotein inhibitor: Avoid co-administration
- VTE
  - CrCl >30 mL/min: No dose adjustment needed
  - CrCl <30 mL/min: No data
  - CrCl <50 mL/min and concurrent use of P-glycoprotein inhibitor: Avoid co-administration
- Monitoring: Renal function prior to initiation of therapy, periodically throughout treatment and more frequently in clinical situations where renal function may decline.
- When converting from dabigatran to another DOAC – see page 10 |

**DIRECT FACTOR XA INHIBITORS** |

| Apixaban Eliquis® |
| 5 mg twice daily for stroke prevention in Non-valvular A. fib |
| Treatment and secondary prevention of VTE: 10 mg twice daily for 10 days, then 5 mg twice daily |
| 2.5 mg twice daily for VTE prophylaxis in surgical pts (35 days hip replacement, 12 days knee replacement) |
| Consider 2.5 mg twice daily if patient has at least 2 of the following: |
|  - age ≥ 80 years |
|  - body weight of ≤ 132 lb (60 kg) |
|  - serum creatinine level of ≥ 1.5 mg/dL |
| Dose reduction (2.5 mg twice daily) recommended if patient is on a strong dual inhibitor of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin [Biaxin]). Avoid use of these medications if baseline dose is 2.5 mg twice daily |
| Monitoring: none recommended |
| When converting from apixaban to another DOAC – see page 10 |
| **Adverse Effects / Interactions** |
| **Bleeding** |
| **Dyspepsia** |
| Increased risk of epidual spinal hematoma with neuroaxial anesthesia or spinal puncture |
| **Drug-drug Interactions:** |
| Increased bleeding risk with certain medications (e.g., clopidogrel, NSAIDs) |
| Avoid concurrent use with P-glycoprotein inducers (e.g., rifampin). Evaluate P-glycoprotein inhibitors individually. |

| Indications: reduce risk of stroke in patients with Non-valvular A. fib, management of VTE |
| Half-Life: 12-17 hours |
| Antidote: Praxbind |

Contraindications:
- Active pathological bleeding
- Prosthetic heart valves (mechanical/ bioprosthetic)
- Pregnancy or breastfeeding
- CrCl < 15 mL/min |

| **APRILIBAN ELIQUIS®** |
| 5 mg twice daily for stroke prevention in Non-valvular A. fib |
| Treatment and secondary prevention of VTE: 10 mg twice daily for 10 days, then 5 mg twice daily |
| 2.5 mg twice daily for VTE prophylaxis in surgical pts (35 days hip replacement, 12 days knee replacement) |
| Consider 2.5 mg twice daily if patient has at least 2 of the following: |
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| Monitoring: none recommended |
| When converting from apixaban to another DOAC – see page 10 |
| **Bleeding** |
| Increased risk of epidual spinal hematoma with neuroaxial anesthesia or spinal puncture |
| **Drug-drug Interactions:** |
| Increased bleeding risk with certain medications (e.g., clopidogrel [Plavix], NSAIDs) |
| Avoid concurrent use with strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, phenytoin, carbamazepine) |

| Indications: reduce risk of stroke in patients with Non-valvular A. fib, management of VTE |
| Half-Life: 12 hours |
| Antidote: none available |

Contraindications:
- Active pathological bleeding
- Prosthetic heart valves |

No data on usage with renal or hepatic impairment |

*See manufacturer prescribing information for complete description of adverse effects and drug interactions.
## SUMMARY

### Decision Support

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Adverse Effects / Interactions*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT FACTOR XA INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RIVAROXABAN XARELTO®</strong> Nonformulary</td>
<td>Post surgical DVT prophylaxis: 10 mg once daily</td>
<td>Indications: FDA approved for the prevention of DVT and PE in patients undergoing knee or hip replacement surgery, treatment of DVT and PE and stroke prevention in non-valvular A. fib</td>
<td></td>
</tr>
<tr>
<td>Strengths: 10 mg 15 mg 20 mg</td>
<td>Duration: 12 days (knee replacement), 35 days (hip replacement)</td>
<td>Half-Life: 5-9 hours</td>
<td></td>
</tr>
<tr>
<td>Administer DOT Only</td>
<td>DVT prophylaxis following recurrent DVT or PE (after acute treatment): 20 mg once daily with food</td>
<td>Monitoring: Renal function prior to initiation of therapy, periodically throughout treatment and more frequently in clinical situations where renal function may decline.</td>
<td></td>
</tr>
<tr>
<td>$$$$$</td>
<td>Treatment of acute DVT (NOT recommended in place of unfractionated heparin): 15 mg twice daily with food for 21 days then 20 mg once daily with food for a total of 6 months</td>
<td>Antidote: none available</td>
<td></td>
</tr>
</tbody>
</table>
| | Prevent stroke in patients with Non-valvular A. fib: 20 mg once daily | Contraindications:  
- Active pathological bleeding  
- Pregnancy or breastfeeding  
- Prosthetic heart valves  
- CrCl < 15 mL/min  
- Moderate-severe hepatic impairment | |
| | Renal Impairment:  
DVT prophylaxis: CrCl < 30 mL/min: avoid use  
Prevent stroke in patients with Non-valvular A. fib:  
CrCl 15-50 mL/min: 15 mg once daily | | |
| | Convert from rivaroxaban to warfarin: D/C rivaroxaban and begin warfarin plus parenteral anticoagulant at time of next rivaroxaban dose. D/C parenteral anticoagulant when INR is therapeutic. | | |
| | Convert from warfarin to rivaroxaban: D/C warfarin and start rivaroxaban when INR < 3.0 | | |
| | When converting from rivaroxaban to another DOAC – See page 10 | | |
| **EDOXABAN SAVAYSA®** Nonformulary Tablet | Treatment of Non-valvular A. fib (dosing based on CrCl)  
CrCl > 95 mL/min: Use not recommended  
CrCl > 50-95 mL/min: 60 mg orally once daily  
CrCl 15-50 mL/min: 30 mg orally once daily  
CrCl < 15 mL/min: Use not recommended | Indications: reduction in risk of stroke and systemic embolism in Non-valvular A. fib; treatment of DVT and PE | |
| Strengths: 10 mg 15 mg 20 mg 30 mg 60 mg | Treatment of DVT and PE: 60 mg orally once daily following 5-10 days of initial therapy with parenteral anticoagulant  
Dose reduction to 30 mg once daily recommended if:  
- CrCl 15-50 mL/min; or  
- Body weight ≤ 60 kg; or  
- Concomitant use of P-gp inhibitors (e.g., verapamil, quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole)  
CrCl < 15 mL/min: Use not recommended | Half-life: 10-14 hours | |
| Administer DOT Only | Moderate or severe hepatic impairment: use not recommended | Monitoring: Renal function prior to initiation of therapy, periodically throughout treatment and more frequently in clinical situations where renal function may decline. | |
| $$$$$ | Convert from edoxaban to warfarin: D/C edoxaban and administer parenteral anticoagulant and warfarin at same time of next scheduled edoxaban dose. D/C parenteral anticoagulant when INR ≥ 2.0 | Antidote: none available | |
| | Convert from warfarin to edoxaban: D/C warfarin and start edoxaban when INR ≤ 2.5 | Contraindications:  
- Active pathological bleeding  
- Mechanical heart valves  
- Moderate to severe mitral stenosis | |
| | When converting from edoxaban to another DOAC – See page 10 | | |

*See prescribing information for complete description of adverse effects and drug interactions.
FACTORS AFFECTING INR WHEN TAKING ANTICOAGULANTS

<table>
<thead>
<tr>
<th>Endogenous Factors that may DECREASE INR</th>
<th>Endogenous Factors that may INCREASE INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood dyscrasias</td>
<td>Hepatic disorders (infectious hepatitis, jaundice)</td>
</tr>
<tr>
<td>Cancer</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>Poor nutritional state</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Steatorrhea</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Elevated temperature</td>
<td>Hereditary factors: CYP2CP and/or VKORC1 genotype</td>
</tr>
</tbody>
</table>

FACTORS AFFECTING INR WHEN TAKING VKA (WARFARIN)

<table>
<thead>
<tr>
<th>Effect on INR</th>
<th>Anti-infectives</th>
<th>Anticonvulsants</th>
<th>Analgesic / Antipyretics</th>
<th>Cardiovascular Agents</th>
<th>Gastro-intestinal Agents</th>
<th>Thyroid Agents</th>
<th>Psychiatric Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased INR</td>
<td>Ciprofloxacin, Clarithromycin Erythromycin Fluconazole Isoniazid Itraconazole Levofloxacin Metronidazole Sulfamethoxazole Trimethoprim Tetracyclines</td>
<td>Tegretol Phenobarbital Phenytoin (Initial increase, but decreased INR w/ long term use)</td>
<td>Acetaminophen (&gt;2 g/day) Aspirin (&gt;6 g/day)</td>
<td>Amiodarone Gemfibrozil Simvastatin</td>
<td>Pritosec (Minimal Interaction)</td>
<td>Levothyroxine Alprazolam (Xanax) Depakote Quetiapine (Seroquel) SSRI and Tricyclic Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Decreased INR</td>
<td>Rifampin</td>
<td>Phenytoin, Tegretol, Phenobarbital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>St. John’s Wort Oxcarbazepine Carbamazepine Trazodone</td>
</tr>
</tbody>
</table>

DRUG-DRUG INTERACTIONS IN DOACS

<table>
<thead>
<tr>
<th>Drug-Drug Interactions in DOACs</th>
<th>DABIGATRAN</th>
<th>APIXABAN</th>
<th>RIVAROXABAN</th>
<th>EDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrg is substrate of P-gp</td>
<td>CYP3A4, P-gp substrate</td>
<td>AVOID use with strong P-gp and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) - reduced apixaban effect</td>
<td>AVOID use with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) - reduced rivaroxaban effect</td>
<td>Substrate of P-gp</td>
</tr>
<tr>
<td>AVOID use with P-gp inducers (e.g., rifampin) - reduced dabigatran effect</td>
<td>REDUCE dose for use with strong P-gp and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) - increased Apixaban effect</td>
<td>AVOID use with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) - increased rivaroxaban effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVOID in concurrent renal impairment</td>
<td>CAUTION with P-gp inhibitors (e.g., ketoconazole)</td>
<td>VARIAXABAN</td>
<td>VARIOXABAN</td>
<td>EDOXABAN</td>
</tr>
</tbody>
</table>

UpToDate – “Correcting excess anticoagulation after warfarin” - Karen A Valentine, MD, PhD, Russell D Hull, MBBS, MSc UpToDate. 11/10/2014

USING THE DRUG- DRUG INTERACTION TOOL ON LIFELINE

When selecting an anticoagulant for your patient, use the Drug-Drug Interaction tool available through Lifeline.

To access this tool:
1. Go to Lifeline (http://lifeline/Pages/Home.aspx)
2. Under Divisions/Programs on the left, and subheading Health Care Operations, select Quality Management
4. Under Care Team Tools, select All Care Team Tools
5. Under Pharmacy/Medication Management, select Drug-Drug Interaction Checker

BLOOD THINNER: WHAT YOU SHOULD KNOW

Q: What is a blood thinner and why do I need it?
Blood thinner is a type of medicine that helps your blood not clot as fast. Sometimes it is prescribed to prevent serious blood clots from forming in your body, which can cause a stroke or other life-threatening events.

Q: How long do I have to be on blood thinners?
It depends on why you take the blood thinner and what other health problems you have. Some people take a blood thinner for only a few months, but many people take it for the rest of their life.

Q: How should I take the blood thinner?
Always follow your doctor’s or nurse’s instructions and take the pills exactly as prescribed.
- Go to the pill line every day to get your pill. A blood thinner is rarely given as a “carry med.”
- Take your blood thinner at about the same time every day.
- Never take extra pills or skip a day. If you forget your pills one day, write it down and tell a doctor or nurse.
- Never stop taking your blood thinner unless your doctor tells you to stop. If you have any trouble with taking blood thinners or getting refills, send an Urgent CDC 7362 request to the triage nurse.

Q: What tests will I need if I take a blood thinner?
It depends on the type of blood thinner. A simple blood test called “INR” needs to be done regularly when taking warfarin. Your doctor will adjust your dose to get to a certain “INR.” When you first start warfarin, you may need your blood checked often. Once your dose is adjusted, you only need blood tests about once a month.

Q: What do I need to know about using other medication when I am taking warfarin?
- When warfarin is taken with other medicines, it can change the way other medicines work, and other medicines can change the way certain blood thinners work and your blood can get thinner than needed.
- Tell your doctor or nurse if you are taking other medications, including over-the-counter medicines. Some common medications also raise the risk of bleeding like aspirin, ibuprofen, naproxen, or Motrin®-like medications (Naprosyn®, Advil®, Aleve®). Some “cough and cold medicines,” herbal medications, and Pepto-Bismol may have aspirin.

Q: What are the side effects of blood thinners?
Side effects with blood thinners are uncommon but can include bleeding or bruising. A little bleeding that stops after a few minutes is okay, such as bleeding gums when brushing your teeth or a small nosebleed.

Tell your doctor or nurse right away if you have more serious bleeding, such as:
- Red, dark, coffee or cola–colored urine
- Stools that are black, bloody, or look like tar
- Bad nosebleeds, bleeding gums, or coughing up blood
- Throwing up coffee-colored or bright red vomit
- New bruises that come for no reason
- A cut that will not stop bleeding within 10 minutes
- Stomach, back or side pain that won’t go away
- New or bad headache, problems with vision or speech, numbness or weakness, or confusion
- Too much menstrual bleeding

Q: What else should I know?
- Because of the risk of bleeding, don’t do sports or other activities that could cause you to get hurt.
- Do not drink alcohol (Pruno), which can cause serious side effects with warfarin.
- Let your provider know if you are fasting or doing a hunger strike, this can effect your medication level.
- Do not change your diet too much if you are taking warfarin. Green vegetables like spinach, lettuce, broccoli, cabbage and frozen peas have a lot of vitamin K and change the way warfarin works. Try to keep the amount of vitamin K foods you eat the same every day.
- Know your dose and the color of your pills. The color of warfarin/Coumadin®/Jantoven® pills tells you how strong the pill is. CDCR uses:

1mg pink
2mg light purple
2.5mg green
3mg tan
4mg blue
5mg orange
6mg blue-green
7.5mg yellow
10mg white
P: ¿Qué es un diluyente sanguíneo y por qué lo necesito?
Un diluyente sanguíneo es un medicamento que ayuda a que su sangre no coagule tan rápido. A veces es prescrito para prevenir la formación de serios coágulos sanguíneos en su organismo los cuales pueden causar un derrame cerebral u otros incidentes que podrían poner en peligro su vida.

P: ¿Durante cuánto tiempo debo tomar un diluyente sanguíneo?
Depende de la causa por la cual esté tomando el diluyente sanguíneo así como de que otros problemas de salud tenga usted. Algunas personas toman un diluyente sanguíneo durante unos pocos meses, pero muchas otras personas lo toman por el resto de sus vidas.

P: ¿Cómo debo tomar un diluyente sanguíneo?
Siga siempre las instrucciones de su médico o su enfermera y tome las pastillas exactamente como fueron recetadas.

P: ¿Qué necesito saber sobre el uso de otros medicamentos cuando estoy tomando la warfarina?
Depende del tipo de diluyente sanguíneo. Si esta tomando la warfarina deberá hacerse regularmente un examen de sangre llamado “INR.” Su médico ajustará su dosis dependiendo del “INR.” Al comenzar a tomar la warfarina, es posible que necesite un análisis de sangre con frecuencia. Una vez ajustada la dosis, solo necesitará un análisis de sangre una vez al mes.

P: ¿Qué examenes médicos necesitaré hacerme si tomo un diluyente sanguíneo?
Los efectos secundarios producidos por el diluyente sanguíneo son poco comunes, pero pueden incluir hemorragias o hematomas. Sangrar un poco durante algunos minutos se considera dentro de los parámetros normales, por ejemplo, sangrar por las encías después de cepillarse los dientes o pequeñas hemorragias nasales. Informe inmediatamente a su médico o enfermera si Ud. está tomando otros medicamentos, incluyendo aquellos sin receta médica.

P: ¿Qué necesito saber sobre el uso de otros medicamentos cuando estoy tomando la warfarina?
Cuando se toma la warfarina junto con otros medicamentos, esto podría cambiar la manera en que funcionan los otros medicamentos, y otros medicamentos pueden afectar la acción de ciertos diluyentes sanguíneos y su sangre podría diluirse más de lo necesario.

P: ¿Qué exámenes médicos necesitaré hacerme si tomo un diluyente sanguíneo?
Vaya a la línea de medicamentos todos los días para obtener su pastilla de diluyente sanguíneo. Raramente es recetado como un medicamento que Ud. mantiene en su poder.

P: ¿Qué otras cosas debo saber?
Dado el riesgo de sangrados, no practique deportes o actividades que podrían causarle alguna lesión.

- Informe a su proveedor médico si esta ayunando o en huelga de hambre, esto puede afectar el nivel del medicamento.
- No haga mayores modificaciones en su dieta mientras esté tomando la warfarina. Los vegetales verdes como la espinaca, lechuga, brócoli, repollo y los guisantes congelados contienen altas cantidades de vitamina K que podrían modificar el funcionamiento de la warfarina. Procure que la cantidad de alimentos que consuma con vitamina K sea la misma todos los días.

No beba sustancias alcohólicas (Pruno) que pudiesen causarle efectos adversos con la warfarina.

Dado el riesgo de sangrados, no practique deportes o actividades que podrían causarle alguna lesión.

- No haga mayores modificaciones en su dieta mientras esté tomando la warfarina.
- Procure que la cantidad de alimentos que consuma con vitamina K sea la misma todos los días.

Es muy importante saber su dosis y el color de sus pastillas. El color de las pastillas de warfarina/coumadin®/jantoven® le indica qué tan fuerte es su dosis. CDCR utiliza pastillas de:

<table>
<thead>
<tr>
<th>Dosis</th>
<th>Color</th>
<th>Nombre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg</td>
<td>rosa</td>
<td>Motrin</td>
</tr>
<tr>
<td>2mg</td>
<td>púrpura claro</td>
<td>Aspirin</td>
</tr>
<tr>
<td>2.5mg</td>
<td>verde</td>
<td>Aleve</td>
</tr>
<tr>
<td>3mg</td>
<td>marrón claro</td>
<td>Naprosyn</td>
</tr>
</tbody>
</table>