This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Drug:** apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), rivaroxaban (Xarelto), warfarin (Coumadin)

**Class:** Oral Anticoagulant

**Formulary Medication:** warfarin (Coumadin)

**Code 1 Medications:** apixaban (Eliquis), rivaroxaban (Xarelto)

**LOB:** Non-Medicare

**Effective Date:** August 19, 2015

**Revision Date:** August 19, 2015

**Policy/Criteria:**

**Code 1 Criteria:**

1. **Apixaban (Eliquis), Rivaroxaban (Xarelto)**
   a. Confirmed diagnosis of deep venous thrombosis (DVT) and/or pulmonary embolism (PE)
   OR
   DVT thromboprophylaxis following hip or knee replacement surgery

**Prior Authorization Criteria:**

1. **Apixaban (Eliquis)**
   a. Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)
   - Failure or significant adverse effects to the alternative: warfarin

2. **Dabigatran (Pradaxa)**
   a. Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)
   - Failure or significant adverse effects to all of the alternatives: Eliquis and Xarelto

   b. Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)
   - Failure or significant adverse effects to all of the alternatives: Eliquis and Xarelto

3. **Rivaroxaban (Xarelto)**
   a. Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)
   - Failure or significant adverse effects to the alternative: warfarin
4. **Edoxaban (Savaysa)**

   a. Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)
      
      - Failure or significant adverse effects to the alternative: warfarin
   
   b. Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)
      
      - Failure or significant adverse effects to the alternative: warfarin

**Clinical Justification:**

Comparison of Indications

<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>Stroke prevention in non-valvular atrial fibrillation (AF)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Venous thromboembolism (VTE) prophylaxis following hip or knee replacement</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>VTE treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Reduction in the risk of recurrence of DVT/PE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Thromboembolism prevention in heart valve replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Post myocardial infarction</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<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>Usual Dosage AF: 150mg bid VTE tx: 150mg bid</td>
<td>AF: 20mg daily VTE tx: 15mg bid x 21 days, then 20mg daily VTE ppx: 10mg daily</td>
<td>AF: 5 mg bid VTE tx: 10mg bid x 7 days, then 5mg bid VTE ppx: 2.5mg daily</td>
<td>AF: 60mg daily VTE tx: 60mg daily</td>
<td>AF: once daily titrate to INR 2-3</td>
<td></td>
</tr>
<tr>
<td>Routine Lab Anticoagulant Monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversal Agent</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Dietary Consideration</td>
<td>No</td>
<td>Yes, take with evening meal for doses &gt; 10mg</td>
<td>No</td>
<td>No</td>
<td>Yes; consistency with vitamin K food</td>
</tr>
<tr>
<td>Time to maximum concentration</td>
<td>1-2 hours (no bridging required)</td>
<td>2-4 hours (no bridging required)</td>
<td>3-4 hours (no bridging required)</td>
<td>1-2 hours (no bridging required)</td>
<td>Peak effect delayed 72-96 hours Required bridging (e.g. LMWH)</td>
</tr>
<tr>
<td>Half-Life</td>
<td>12-17 hours</td>
<td>5-9 hours</td>
<td>12 hours</td>
<td>10-14 hours</td>
<td>~40 hours</td>
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</tbody>
</table>
Renal Dosing Adjustment

<table>
<thead>
<tr>
<th>Renal Function Parameter</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF:</strong> CrCl 15-30 ml/min: 75mg bid</td>
<td>RELY: CrCl &lt;30ml/min: excluded</td>
</tr>
<tr>
<td>VTE tx: CrCl≤30 mL/min: avoid use</td>
<td>ROCKET AF: CrCl&lt;30ml/min excluded</td>
</tr>
</tbody>
</table>

Atrial Fibrillation

**2012 American College of Chest Physicians (ACCP) CHEST Guidelines:**
A weak preference (Grade 2B) for dabigatran over warfarin is recommended for patients with non-valvular atrial fibrillation at intermediate to high risk of stroke. Only dabigatran is FDA-approved for atrial fibrillation at the time guideline was published. In other clinical conditions including rheumatic mitral valve disease, mitral valve stenosis, stable coronary artery disease status post intracoronary stent placement or acute coronary syndrome, stroke prevention with dabigatran in atrial fibrillation is not preferred over warfarin.

**2012 American Heart Association (AHA) and American Stroke Association (ASA) Science Advisory on Oral Antithrombotic Agents in Nonvalvular Atrial Fibrillation:**
Dabigatran and apixaban are recommended as an efficacious alternative to warfarin in patients with nonvalvular atrial fibrillation with risk factor for stroke (Class I; Level of Evidence B). On the other hand, rivaroxaban is a reasonable alternative to warfarin (Grade IIb; Level of Evidence C).

**2014 American College of Cardiology and American Heart Association Task Force on Practice Guidelines for the Management of Patients with Atrial Fibrillation:**
Oral anticoagulant options include warfarin (Level of Evidence A), dabigatran (Level of Evidence B), rivaroxaban (Level of Evidence B), or apixaban (Level of Evidence B) for patients with nonvalvular atrial fibrillation with prior stroke or CHADS-VAS score of 2 or greater. For patients with moderate to severe CKD, safety and efficacy for reduced doses of dabigatran, rivaroxaban or apixaban have not been established.

1. According to the three pivotal large clinical trials, RELY, ROCKET AF and ARISTOTLE, dabigatran, rivaroxaban and apixaban, respectively, demonstrated noninferior efficacy in the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Furthermore, dabigatran and apixaban were shown to be superior to warfarin for their primary composite endpoint of stroke or systemic embolism. Favorable mortality benefits were noted with all three newer agents than warfarin.
2. There is no head-to-head comparison study among the newer oral anticoagulant agents.
3. Dabigatran is associated with increased gastrointestinal bleeding, particularly in patients of age 75 years and older.
4. Despite concerns of post-marketing reports of bleeding, dabigatran did not appear to associate with higher bleeding rates than warfarin according to the FDA statement issued in November 2012.

Venous Thromboembolism (VTE) Treatment

**2012 ACCP CHEST Guidelines:**
Warfarin is preferred over rivaroxaban or dabigatran in the treatment of acute and long term treatment of VTE in patients with no cancer (Grade 2C), contributed by the lack of long term safety data for the newer agents. Guidelines were published before the AMPLIFY study with apixaban.

1. Rivaroxaban, apixaban and dabigatran have established noninferior efficacy and comparable major bleeding rates in comparison to warfarin in the prevention of recurrent VTE in patients with acute VTE.

VTE Prophylaxis in Total Knee Replacement and Total Hip Replacement

**2012 ACCP CHEST Guidelines:**
LMWH is preferred over rivaroxaban or dabigatran in the prevention of VTE in patients undergoing total knee replacement or total hip replacement (Grade 2B), given the lack of long term safety data with the newer agents.

**2011 American Academy of Orthopedia Surgeons Guidelines:**
Do not have preference for one agent over another for VTE prophylaxis for total knee replacement or total hip replacement

1. Rivaroxaban, apixaban and dabigatran have demonstrated noninferior efficacy as enoxaparin 40mg once daily for VTE prophylaxis in patients undergoing total hip replacement with comparable major bleeding rates.

References:


