MTF Formulary Management for the Oral Anticoagulants  
Defense Health Agency Pharmacy Operations Division

**Bottom Line**
- Generic warfarin remains on the Basic Core Formulary (BCF).
- Apixaban (Eliquis) was added to the BCF; it has the same number of FDA indications as rivaroxaban, and has the highest percentage of new patient starts in DoD. Due to contracting conditions, only one direct-acting oral anticoagulant could be added to the BCF.
- Rivaroxaban (Xarelto) and dabigatran (Pradaxa) remain on the Uniform Formulary (UF). Patients currently stabilized on rivaroxaban and dabigatran can remain on therapy; no switching is required.
- Edoxaban (Savaysa) was designated nonformulary; medical necessity is needed for patients to continue therapy. There are approximately 60 patients receiving edoxaban at the MTFs.
- When warfarin is clinically appropriate, MTFs are encouraged to buy the contracted product (Exelan Pharmaceuticals).

**Uniform Formulary Decision:** The Director, DHA, approved the recommendations from the November 2016 DoD P&T Committee meeting on February 2, 2017. Implementation will occur on May 10, 2017.

<table>
<thead>
<tr>
<th>Uniform Formulary (UF) Agents</th>
<th>Nonformulary (NF) Agents</th>
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<tbody>
<tr>
<td><strong>BCF drugs — MTFs must have on formulary</strong></td>
<td><strong>MTFs may have on formulary</strong></td>
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<tr>
<td>• warfarin (generic)</td>
<td>• dabigatran (Pradaxa)</td>
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<tr>
<td>• apixaban (Eliquis)</td>
<td>• rivaroxaban (Xarelto)</td>
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**Clinical Summary**

**Direct-Acting Oral Anticoagulants (DOACs) versus Warfarin**
- The preferred terminology for the non-vitamin K antagonists is now “direct-acting oral anticoagulant,” according to the International Society for Thrombosis and Haemostasis Scientific and Standardization Committee.
- Compared to warfarin, the DOACs have advantages of predictable anticoagulant effect, fixed dosing, and fewer drug interactions.
- Advantages of warfarin include its long history of use, wide number of FDA indications, availability of a reliable and inexpensive oral reversal agent (vitamin K), and that its adverse effects are predictable and manageable.
- DOACs offer a convenience to patients because laboratory monitoring for efficacy and safety, and dietary restrictions, are not required. More data is needed in patients with renal and hepatic impairment.
- Idarucizumab (Praxbind) is an injectable reversal agent specifically approved for excessive bleeding due to the direct thrombin inhibitor dabigatran. A reversal agent for the factor Xa inhibitors, andexanet alfa, is currently under investigation.
- Since the May 2015 DoD P&T Committee review, there are no major clinical updates for the oral anticoagulants, with the exception that dabigatran is now approved for prevention of venous thromboembolism (VTE) following total hip replacement surgery in a new 110 mg capsule formulation.
- Knowledge of the differences in dosing regimens, particularly in patients with compromised renal function, and clinical trial data is essential in determining the most appropriate candidates for an individual DOAC over warfarin.
Stroke Prevention in Non-Valvular Atrial Fibrillation (NVAF)

- All four of the DOACs are FDA-approved to prevent stroke and systemic embolism in patients with NVAF, based on four individual trials with warfarin as the comparator. Unlike warfarin, none of the DOACs are approved for use in patients with mechanical cardiac valves.

- In NVAF, superiority to not optimally controlled warfarin [the time in therapeutic range (TTR) was less than 65%] at preventing stroke was shown with edoxaban, dabigatran, and apixaban, while non-inferiority was shown with rivaroxaban.

- Intracranial bleeding was lower with all four DOACs than warfarin.

- Edoxaban 60 mg (Savaysa) has the advantage of QD dosing in NVAF and, with the exception of gastrointestinal (GI) bleeding, has a lower incidence of bleeding than warfarin. Disadvantages include its contraindication in patients with normal renal function, which resulted in a higher incidence of ischemic events in the ENGAGE trial. Estimates are that only 20% of the NVAF patient population has normal renal function (CrCl >95 mL/min).

- Dabigatran 150 mg (Pradaxa) was the only DOAC to show superior ischemic stroke reduction versus warfarin, but it has a higher incidence of GI bleeding than warfarin, causes dyspepsia, and is highly dependent on renal clearance (RE-LY trial).

- Rivaroxaban (Xarelto) has the advantage of QD dosing in atrial fibrillation, but had increased GI bleeding and major bleeding compared to warfarin (ROCKET AF trial). The patient population studied with rivaroxaban had more comorbidities than the other three DOAC NVAF trials.

- Apixaban (Eliquis) had less major bleeding than warfarin, and was the only DOAC to show a reduction in mortality, but the upper limit of the confidence interval approached one (ARISTOTLE trial). The point estimates for all of the DOACs are similar for mortality.

- All four of the DOACs require dosage reductions in patients with renal dysfunction and NVAF; however, there is very limited clinical trial information available for these alternate dosing regimens. Rivaroxaban and apixaban are less dependent on renal elimination than dabigatran or edoxaban.

- It remains to be determined whether the DOACs will increase the numbers of patients currently undertreated for stroke prevention in NVAF.

Treatment of Venous Thromboembolism (VTE), Deep Vein Thrombosis (DVT), and Pulmonary Embolism (PE)

- All four DOACs are FDA-approved for treatment of acute VTE.
  - No overlap with low-molecular weight heparin (LMWH) is required with apixaban or rivaroxaban.
  - Apixaban and rivaroxaban are FDA-approved for extended treatment of VTE out to one year.

- All four DOACs were non-inferior to LMWH-warfarin for the composite endpoint of recurrent VTE, nonfatal PE, or death.

- For the endpoint of major bleeding, apixaban and rivaroxaban had significantly less bleeding than LMWH-warfarin.

- For the endpoint of major bleeding and clinically relevant non-major bleeding (defined as overt bleeding not meeting criteria for major bleeding, but needing medical intervention), edoxaban and apixaban had significantly less bleeding than LMWH-warfarin.

- Edoxaban has a potential role in the subset of patients with PE and right ventricular dysfunction (Hokusai VTE trial). In this study, edoxaban plus LMWH treatment provided a statistically significant reduction in the composite endpoint of VTE recurrence or VTE death, compared to the group treated with warfarin plus LMWH. This was a pre-specified endpoint.

- There is only limited data in patients with cancer, or those with hypercoagulable disorders.
Prevention of VTE following hip or knee replacement surgery (Orthopedic Surgery Prophylaxis)

- DOACs offer a convenience to patients over LMWH or warfarin, in that LMWH injections are not required and no laboratory monitoring for efficacy or safety is required.

- Rivaroxaban and apixaban are FDA-approved for prophylaxis of VTE following orthopedic surgery for both total hip replacement (THR) and for total knee replacement. Dabigatran is now approved following THR only. Edoxaban has limited data and is not currently approved for this indication.

- Compared to enoxaparin for VTE prophylaxis:
  - Rivaroxaban is more effective, with no increase in bleeding events.
  - Apixaban has mixed results for efficacy.

- Similar major bleeding rates were shown with the DOACs and LMWH. Apixaban had the lowest rate of clinically relevant bleeding of the DOACs (ADVANCE-1 trial).

Overall

- Due to a lack of head-to-head trials, there is insufficient evidence to determine if one DOAC has advantages over the others.

- Prescribers must consider patient-specific factors when selecting a DOAC, including thrombosis risk, bleeding risk, renal function, and compliance.

- Patients require education and clinical monitoring to ensure appropriate DOAC use and avoid adverse reactions.

- It is unknown whether DOACs will improve persistence with anticoagulation therapy.

- Warfarin remains a viable option due to its large number of FDA-approved indications, long history of use, and availability of an antidote.

References

- DoD P&T Committee minutes: [http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes](http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes)


- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.


- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

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**Price Comparison at MTF**

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<tr>
<th>Drug</th>
<th>MTF Cost/Month (November 2016)</th>
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<tr>
<td><strong>Basic Core Formulary</strong></td>
<td></td>
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<tr>
<td>Warfarin (generic)</td>
<td>$ Most Cost-Effective</td>
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<tr>
<td>Apixaban (Eliquis)</td>
<td>$$ Less Cost-Effective</td>
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<tr>
<td><strong>Uniform Formulary</strong></td>
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<tr>
<td>Dabigatran (Pradaxa)</td>
<td>$$$ Less Cost-Effective</td>
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<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>$$$ Less Cost-Effective</td>
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<tr>
<td><strong>Nonformulary</strong></td>
<td></td>
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<tr>
<td>Edoxaban (Savaysa)</td>
<td>$$$$ Least Cost-Effective</td>
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Legend:
- $ = “Most Cost-Effective” represents Rxs with the lowest cost and best clinical efficacy
- $\$ = “Less Cost-Effective” represents higher cost Rxs with similar clinical efficacy
- $$$ = “Less Cost-Effective” represents next higher cost Rxs with similar clinical efficacy
- $$$$$ = “Least Cost-Effective” represents Rxs with the highest cost with similar clinical efficacy