MTF Formulary Management for the Oral Anticoagulants

Defense Health Agency Pharmacy Operations Division

Bottom Line:

- **Generic warfarin remains the designated Basic Core Formulary (BCF) oral anticoagulant.**
- **When warfarin is appropriate, MTFs are encouraged to buy the contracted product (Exelan Pharmaceuticals).**
- **All the newer oral anticoagulants are on the Uniform Formulary; a newer oral anticoagulant was not selected for BCF status.**

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the May 2015 DoD P&T Committee meeting on July 20, 2015. Implementation will occur upon signing of the minutes.

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
BCF drugs – MTFs must have on formulary	**MTFs may have on formulary**	**MTFs must not have on formulary**
• warfarin (generic)	• apixaban (Eliquis) • dabigatran (Pradaxa) • edoxaban (Savaysa) • rivaroxaban (Xarelto)	None

Clinical Summary

Newer Oral Anticoagulants (NOACs) versus Warfarin

- Compared to warfarin, the NOACs 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, reliable reversal agent (vitamin K), and that its adverse effects are predictable and manageable.
- NOACs 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.
- No reversal agent is currently available with the NOACs, although several products are in the pipeline and expected to receive FDA approval in 2015.

Stroke Prevention in Non-Valvular Atrial Fibrillation (NVAF)

- All four of the NOACs are FDA-approved to prevent stroke and systemic embolism in patients with NVAF, based on four trials with warfarin as the comparator. Unlike warfarin, none of the NOACs 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 NOACs 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 NOAC to show superior ischemic stroke reduction versus warfarin, but has a higher incidence of GI bleeding than warfarin, causes dyspepsia, and is highly dependent on renal clearance (RE-LY trial).

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- 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 NOAC NVAF trials.
- Apixaban (Eliquis) had less major bleeding than warfarin, and was the only NOAC 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 NOACs are similar for mortality.
- All four of the NOACs 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 NOACs 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 NOACs 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 NOACs 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 + LMWH treatment provided a statistically significant reduction in the composite endpoint of VTE recurrence or VTE death, compared to the group treated with warfarin + 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)

- NOACs 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. Edoxaban has limited data and is not currently approved for this indication. Dabigatran was denied FDA approval for orthopedic surgery prophylaxis.
- 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 NOACs and LMWH. Apixaban had the lowest rate of clinically relevant bleeding of the NOACs (ADVANCE-1 trial).

Overall

- Due to a lack of head-to-head trials, there is insufficient evidence to determine if one NOAC has advantages over the others.
- Prescribers must consider patient-specific factors when selecting a NOAC, including thrombosis risk, bleeding risk, renal function, and compliance.
- Patients require education and clinical monitoring to ensure appropriate NOAC use and avoid adverse reactions.
- It is unknown whether NOACs 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
- Current/future drug classes under review by the DoD P&T Committee: http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee
- TRICARE Formulary Search Tool: http://www.express-scripts.com/tricareformulary
- Prior Authorization/Medical Necessity forms: see Formulary Search Tool above.
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

Price Comparison at MTF	
Drug	**MTF Cost/Month (May 2015)**
Basic Core Formulary	
Warfarin (generic)	**$ Most Cost-Effective**
Uniform Formulary	
Dabigatran (Pradaxa)	**$$ Less Cost-Effective**
Apixaban (Eliquis)	**$$$ Less Cost-Effective**
Edoxaban (Savaysa)	**$$$ Less Cost-Effective**
Rivaroxaban (Xarelto)	**$$$ Less Cost-Effective**
Non-Formulary	
None	

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

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