In a normally functioning body system, “hemostasis is regulated to promote blood flow.” [1] When this process is interrupted (e.g. trauma), the hemostatic system will rapidly try to clot the blood to prevent loss. Once bleeding has been stopped, damaged vessels are remodeled to repair regular blood flow. This system is comprised of three major components: platelets and blood cells; plasma proteins; and the wall structure of the vessel – all which function together to maintain hemostasis. [1]

Disease states including atrial fibrillation, deep vein thrombosis (DVT), and pulmonary embolism (PE), or genetic abnormalities, such as Factor V Leiden or Protein C and S deficiencies often require anticoagulation therapy. [2] Additionally, patients with biological or mechanical valves may also need anticoagulation therapy. This article focuses on the available oral therapies used in antithrombotic management, with emphasis on the newer agents and their comparison to conventional treatment with warfarin in patients with atrial fibrillation.

Apixaban and dabigatran require twice daily dosing while rivaroxaban and warfarin are once a day. [4-6] Each of the three newer agents requires renal monitoring with adjustments based on the creatinine clearance. Hepatic monitoring is also required for all three newer agents with apixaban and rivaroxaban requiring adjustments at different stages of impairment. There is no required monitoring or adjustments for hepatic or renal function with warfarin, though close INR monitoring is recommended. [3-7] Additional monitoring recommendations can be found in Table 1 on page 2.

All of the newer agents have been compared to warfarin in phase III clinical trials (“RE-LY for dabigatran, ROCKET AF for rivaroxaban, and ARISTOTLE for apixaban”) for stroke and systemic embolism in patients with atrial fibrillation. [8] The RE-LY trial used two doses (110 mg and 150 mg) of dabigatran versus warfarin, while the ROCKET AF and the ARISTOTLE trial used one dose of rivaroxaban (20 mg) and apixaban (5 mg), respectively, versus warfarin. While the medications have not been studied head-to-head, Coccheri and Orlando compared the three trials by looking at areas of absolute difference in safety and efficacy events, their corresponding numbers needed to treat, and secondary versus primary prevention. [8] The authors concluded that apixaban, dabigatran, and rivaroxaban were non-inferior to warfarin, with two (dabigatran 150 mg and apixaban), showing superiority in the composite end point of all strokes (ischemic or hemorrhagic) and side effects. All three newer agents were associated with less intracranial bleeding but were similar in major bleeding events when compared to warfarin. Apixaban and dabigatran 150 mg showed greater efficacy when compared to warfarin in secondary prevention, while rivaroxaban showed the lowest efficacy. However, Coccheri and Orlando discuss that the ROCKET study may not be fit to distinguish differences between primary and secondary prevention due to the high risk.

continued on page 3
P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on May 16, 2013.

Highlights of this meeting include:

Personnel changes have occurred at GHS as Sara Howe was promoted to the Account Manager position. Amy Stockton was welcomed to the Clinical Pharmacy Manager position and will resume Sara’s previous duties including review of prior authorization requests.

The following prior authorization criteria were approved:

A 90 day trial and failure of metformin is required prior to use of Invokana.

Tecfidera will be a non-preferred multiple sclerosis agent, requiring a trial and failure of Avonex and Copaxone prior to approval.

All anticonvulsants will be limited to labeled indication. Clonazepam will be allowed for post-traumatic stress disorder and valproate for all forms of bipolar disorder.

Adderall XR will be allowed for children down to the age of three.

All proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to June 30, 2013.

The next P&T Committee meeting will be held August 22, 2013 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Table 1: Additional Monitoring Recommendations

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Apixaban (Eliquis®) December 2012 | 1. S/Sx of bleeding  
2. Renal and hepatic fxn  
3. Although not necessary, Anti-FXa show a linear relationship; could be used to guide clinical decisions  
4. Reduced dosing when used concomitantly with strong 3A4 and p-glycoprotein inhibitors |
| Dabigatran etexilate (Pradaxa®) October 2010 | 1. S/Sx of bleeding  
2. Renal fxn prior to and during therapy as indicated  
3. CBC with differential  
4. Extent of anticoagulation does not need to be monitored; if necessary, aPTT (>2.5 x control may indicate over anticoagulation) or TT (most sensitive) could be used to guide clinical decisions  
5. Reduced dosing when used concomitantly with strong 3A4 and p-glycoprotein inhibitors |
| Rivaroxaban (Xarelto®) July 2011 | 1. S/Sx of bleeding  
2. CBC with differential  
3. Renal and hepatic fxn  
4. Extent of anticoagulation does not need to be monitored; if necessary, use PT or antifactor Xa (preferred); not intended to be used for dose adjustments |
| Warfarin (Coumadin®) June 1954 | 1. PT/INR based on patient response; once stable, every 1-4 weeks; goal range varies based on indication for use  
2. Dietary changes  
3. Hematocrit  
4. Optional genotyping (CYP2C9 and VKORC1) prior to initiation  
5. Stool guaiac testing |
patients enrolled. Overall, “adoption of the new oral anticoagulants should be gradual and controlled.” [8] It is also important to note that the phase III trials only studied patients with atrial fibrillation. No other FDA approved indications were evaluated. Other areas of consideration, such as how stable the patient is, patient preference, cost, genetic factors, and adherence, should play a role in the clinical decision making process. Finally, monitoring, though reduced with the newer agents, should be done on all patients, including “non-clotting laboratory or diagnostic tests” as appropriate. [8]

The Wyoming Medicaid Drug Utilization Review claims data from the second quarter of 2010 to the first quarter of 2013 for the use of oral anticoagulants reveals that warfarin is still the most heavily prescribed choice in this population. The 2010-2012 fourth quarter and the 2013 first quarter claims with warfarin far surpass claims for both rivaroxaban and dabigatran. Claims also show a substantial increase in rivaroxaban use in recent months, likely due to the new indication for the treatment DVT/PE, added in November of 2012. [9] No claims for apixaban in any quarter were reported.

Factors such as physician preference, more long-term data to support warfarin use, additional FDA approved indications for warfarin use, the increase in and success of anticoagulation management services, and the cost of warfarin versus the new agents are all probable explanations for its sustained use.

References
In This Issue

A Closer Look at Anticoagulants
P&T Committee Meeting Update

Please contact WY-DUR at 307-766-6750 to have your name added or removed from our mailing list, or if you need to update your address. The WY-DUR newsletter is also available on-line at www.uwyo.edu/DUR/newsletters.