THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

November 2013 Volume 3, Issue 5

Update on the New Oral Anticoagulants with a Focus on Apixaban

By Kathy Sentena, Pharm.D., Oregon State University College of Pharmacy – Drug Use Research and Management Group

Since the approval of dabigatran (Pradaxa®) in 2011, two additional new oral anticoagulants (NOA), rivaroxaban (Xarelto®) and apixaban (Eliquis®), are offered as alternatives to warfarin.[1,2,3,4] All the NOAs are approved by the US Food and Drug Administration (FDA) for use in non-valvular atrial fibrillation (NVAF).[1,2,3] Rivaroxaban is the only NOA which has obtained approval for the additional indications of deep vein thrombosis (DVT) and pulmonary embolism (PE) prophylaxis and treatment. While no direct comparisons between the NOAs have been studied, emerging data, guideline updates and systematic reviews can help to navigate the best options for patients requiring anticoagulation. This review will present the evidence for apixaban and provide guidance on the use of oral anticoagulants.

Apixaban

Apixaban joins rivaroxaban as a factor Xa inhibitor approved to reduce the risk of stroke and systemic embolism in patients with NVAF.[4] Apixaban has also been studied in additional indications, as shown in Table 1.

Table 1 - Summary of Apixaban Studies [5-13]

Primary Endpoint	Results
Atrial Fibrillation	
ARISTOTLE: Apixaban 5 mg twice daily (A5) vs. warfarin (W) (INR 2-3)	
Apixaban superior to warfarin for the incidence of stroke and systemic embolism.	**A5** :1.27% / **W**:1.60% HR: 0.79 (95% CI, 0.66 to 0.95, p= 0.01 for superiority
AVERROES: Apixaban 5 mg twice daily (A5) vs. aspirin 81-324 mg (ASA) daily	
Apixaban superior to aspirin for the incidence of stroke and systemic embolism.	**A5**: 1.6% / **ASA**: 3.7% HR: 0.45 (95% CI, 0.32 to 0.62, p<0.001)
Total Knee Replacement Prophylaxis	
ADVANCE-1 & 2: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin (E)	
Apixaban inferior to enoxaparin 30mg twice daily (E30) and superior to enoxaparin 40mg daily (E40) for composite endpoints (DVT, non-fatal PE or death from any cause).	**Advance-1** **A2.5**: 9.0% / **E30**: 8.8% RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) **Advance-2** **A2.5**: 15.1% / **E40**: 24.4% RR: 0.62 (95% CI 0.51 to 0.74, p<0.0001 for superiority)
Total Hip Replacement Prophylaxis	
ADVANCE-3: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin 40 mg daily (E)	
Apixaban superior to enoxaparin for composite endpoints (DVT, non-fatal PE or death from any cause).	**A2.5**: 1.4% / **E**: 3.9% RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority)
Acute Coronary Syndrome	
APPRAISE-2: Apixaban 5 mg twice daily (A5) vs. placebo (P)	
Similar rates of ischemic events in both groups.	**A5**: 7.5% / **P**: 7.9% HR: 0.95 (95% CI 0.80 to 1.11, p=0.51)
Prophylaxis in Medically Ill Patients	
ADOPT: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin 40mg daily (E)	
Similar rates of death due to a clotting event.	**A2.5**: 2.71% / **E**: 3.06% RR: 0.87 (95% CI 0.62 to 1.23, p=0.44)
Treatment of Venous thromboembolism	
AMPLIFY: Apixaban 10mg x 7 days then 5 mg twice daily (A) vs. conventional tx (CT)	
Apixaban non-inferior to conventional tx (enoxaparin + warfarin) for recurrent VTE or death.	**A**: 2.3% / **CT**: 2.7% RR: 0.84 (95% CI 0.60 to 1.18, p<0.001)
AMPLIFY-EXT: Apixaban 2.5mg (A2.5) or 5mg (A5) twice daily vs. placebo (P)	
Apixaban doses superior to placebo for recurrent VTE or death from VTE.	**A2.5**: 0.2% / **A5**: 0.1% / **P**: 0.5% **A2.5 vs. P**: RR 0.49 (95% CI 0.09 to 2.64) **A5 vs. P**: RR: 0.25 (95% CI 0.03 to 2.24)
Pulmonary embolism-PE, venous thromboembolism-VTE, deep vein thrombosis- DVT, HR-hazard ratio, RR-relative risk	

For the prevention of stroke in patients with NVAF, apixaban was shown to be superior to warfarin (1.3% for apixaban vs.1.6% for warfarin, HR 0.69 [95% CI, 0.66 to 0.95, p=0.01]) for the primary endpoint, which was primarily driven by the reductions in hemorrhagic strokes.[5] All-cause mortality rates were also significantly lower for apixaban. The rate of major bleeding was higher with warfarin (3.1%) compared to apixaban (2.1%).[5] Apixaban was also found to be superior to aspirin (ASA). The applicability of these findings are limited due to 64% of patients having taken 81mg of ASA in the study. ASA 325mg daily has the most robust evidence for stroke prevention.[14]

Off-label Uses

Evidence to support the use of apixaban use in total knee replacement (TKR) prophylaxis is mixed, with data showing inferiority and superiority to enoxaparin (Table 1).[7,8] One study of apixaban use in total hip replacement (THR) prophylaxis shows superiority to enoxaparin[9] Apixaban use in the treatment of venous thromboembolism (VTE) proved to be non-inferior to traditional therapies (enoxaparin and warfarin) with less bleeding.[12] The reduction in ischemic events did not outweigh the increased risk of bleeding with apixaban in patients with acute coronary syndrome (ACS), causing the trial to be stopped early. In patients who are medically ill, apixaban and enoxaparin death rates were similar but treatments were given for different durations.[11]

Role of New Oral Anticoagulants

Studies of NOAs in NVAF have shown apixaban and dabigatran 150mg twice daily to be slightly more effective for the prevention of strokes compared to warfarin.[5,15] The number-needed-to -treat (NNT) to avoid 1 stroke during 1 year of treatment is 167 patients for dabigatran and 303 for apixaban. In the ROCKET-AF trial, rivaroxaban was shown to be non-inferior to warfarin.[16] Dabigatran was the only NOA to decrease both hemorrhagic and ischemic strokes compared to warfarin.[15] Apixaban was the only NOA found to be associated with lower all-cause mortality than warfarin (HR 0.89, (95% CI, 0.80 to 0.998, p=0.047).[5] A systematic review done by the Drug Effectiveness Review Project (DERP) found NOAs to be of similar efficacy for NVAF, based on indirect comparisons.[17] Subgroup analysis found NOAs not to be superior to warfarin, when international normalized ratios (INR) were therapeutic at least 66% of the time.[17] The FDA analysis of the RE-LY data also found warfarin and dabigatran efficacy to be similar in patients with well controlled INRs.[18] The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends NOAs as an option for patients with NVAF if they have a $CHAD_2$ score ≥1and whom are not suitable candidates for warfarin.[19] Guidelines for AF are conflicted, with some preferring NOAs over warfarin, while others recommend NOAs only in patients who aren't suitable for warfarin therapy.[20-22]

In AF studies, the risk of intracranial bleeds are lower with NOAs compared to warfarin, irrespective of INR.[5,15,16] In indirect comparisons, apixaban was associated with less major bleeding than the other NOAs.[17] These findings were repeated when apixaban was directly compared to warfarin.[5] Studies have found less risk of gastrointestinal bleeding (GIB) with warfarin compared to dabigatran and rivaroxaban.[15,16] A systematic review and meta-analysis found an overall increased risk of GIB with the NOAs.[23] Myocardial infarction risk was also less with warfarin compared to dabigatran.[15]

The NOAs have been studied in multiple conditions requiring anticoagulation including **orthopedic prophylaxis.** The DERP Report found NOAs to have comparable efficacy in reducing the risk of VTEs with no differences in rates of bleeding.[17] Event and bleeding rates in a pooled analysis done by CADTH showed dabigatran and enoxaparin efficacy and bleeding rates to be similar.[24] Rivaroxaban was found to be superior to enoxaparin (40mg daily dose) with comparable rates of bleeding.[24] ACCP guidelines support the use of low molecular weight heparins (LMWH) over NOAs for this indication.[25]

For the treatment of **acute VTE** NOAs were compared to standard care (enoxaparin and vitamin K antagonists) and were found to be non-inferior.[12,26,27] Rivaroxaban and dabigatran were found to have similar rates of bleeding. Apixaban was shown to have statistically significantly less of the composite outcome of major bleeds and nonmajor bleeds (relative risk, 0.44 (95% CI, 0.36 to 0.55; p<0.001).[12]

New trials are examining the use of NOAs in the **extended treatment of VTE**.[13,27,28] These studies look at patients who could generally stop therapy but may be at higher risk of VTE recurrence or whom physicians are uncertain about the continuing need for anticoagulation. A study with dabigatran found it to be non-inferior to warfarin but only by a small margin.[28] All the other studies have been placebo comparisons. Apixaban was shown to have no increase risk of bleeding compared to placebo, while the other NOAs were shown to have a higher risk of bleeding.[13,27,28] Appropriate patient selection is important, as patients in these studies were younger and healthier with less risk of recurrent VTE than those seen in other studies.

Considerations

Study limitations and unanswered questions complicate selection of optimal anticoagulation treatment. RE-LY (dabigatran in AF) and EINSTEIN-DVT (rivaroxaban in VTE tx) were open-label studies, which may introduce bias inherent to this study design.[14,27] Rivaroxaban has only been studied in AF patients with a $CHAD_2$ score of ≥2, leaving efficacy in patients with lower $CHAD_2$ scores unknown .[16] Orthopedic prophylaxis studies in patients undergoing TKR have shown NOAs to have inferior efficacy when compared to the US approved enoxaparin doses of 30mg twice daily.[3,29] The inability to monitor the degree of anticoagulation and reverse treatment if necessary is also a concern with NOAs. All NOAs have black box warnings of increased risk of thrombosis upon drug discontinuation. Dabigatran was found to be inferior to warfarin in patients with mechanical heart valves and is therefore not recommended.[23]

Experts believe that without head-to-head studies there is insufficient evidence to recommend one NOA over another. Evidence suggests that NOAs are an appropriate option for oral anticoagulation in some patients. However, careful consideration of the data and patient specific characteristics needs to be taken into account when choosing an anticoagulant regimen. Limited widespread use, lack of long-term evidence, the inability to reverse anticoagulation and relatively small treatment differences, when compared to traditional agents, should not be overlooked.

Peer Reviewed By: Jack McAnulty, MD, Cardiologist, Legacy Health and Colleen Colley, Pharm.D., Anticoagulation Program Manager, Portland VA Medical Center.

References

1. Boehringer Ingelheim Pharmaceuticals, Inc. Pradaxa Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022512s016lbl.pdf. Accessed November 12, 2012.
2. Janssen Pharmaceuticals, Inc. Xarelto Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022406s001s002s003lbl.pdf. Accessed September 25, 2012
3. Bristol-Meyers Squibb. Eliquis Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf. Accessed September 25, 2012.
4. Bristol-Meyers Squibb. Coumadin Label. US Food and Drug Administration. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed September 25, 2013.
5. Granger C, Alexander J, McMurray J, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011; 365:981-92.
6. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in Patients with Atrial Fibrillation. N Engl J Med. 2011;364:806-817.
7. Lassen M, Raskob G, Gallus A, et al. Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement. NEJM 2009; 361 (6):594-604.
8. Lassen M, Raskob G, Gallus A, et al. Apixaban versus Enoxaparin for Thromboprophylaxis after Knee Replacement (ADVANCE-2): a Randomized Double-Blind Trial. The Lancet 2010; 375:807-815.
9. Lassen M, Gallus A, Raskob G, et al. Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. NEJM 2010; 363 (26):2487-2498.
10. Alexander J, Lopes R, James S, et al. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome. NEJM 2011; 365 (8):699-708.
11. Goldhaber S, Leizorovicz A, Kakkar A, et al. Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients. NEJM 2011; 365 (23):2167-2177.
12. Agnelli G, Buller H, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 2013;369:799-808.
13. Agnelli G, Buller H, Cohen A, et al. Apixaban for Extended Treatment of Venous Thromboembolism. NEJM 2012. Epub ahead of print. Available at:www.nejm.org.liboff.ohsu.edu/doi/pdf/10.1056/NEJMoa1207541. Accessed February 1, 2013.
14. American Heart Association. Stroke Prevention in Atrial Fibrillation. Final results. Circulation 1991;84:527-539. Available online at: http://circ.ahajournals.org/content/84/2/527.long. Accessed November 4, 2014.
15. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). N Engl J Med. 2009;361:1139-51.
16. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban Versus Warfarin In Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883-891.
17. Carson S, Selph S, Thakurta S. Summary Review: Newer Oral Anticoagulant Drugs. Final original report. Drug Effectiveness Review Project 2013. Available at http://derp.ohsu.edu/about/final-document-display.cfm.
18. Dabigatran, FDA Center for Drug Evaluation and Research. Summary Review Document. October 19, 2010. Accessed 6/13/11. ww.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf
19. Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Mar. 16. Available at: http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_RecsReport-e.pdf. Assessed October 7, 2013.
20. Camm A, Lip G, De Caterina R, et al. 2012 Focused Update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation. Eur Heart J 2012;33:2719-2747.
21. Anderson J, Halperin J, Alber N, et al. Management of Patients with Atrial Fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:1935-44.
22. Eikelboom J, Connolly S, Brueckmann M, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. NEJM 2013;369(13):1206-14.
23. Holster Lisanne, Valkhoff V, Kuipers, et al. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. J Gastro 2013;145:105-112.
24. Ndegwa S, Moulton K, Argaez C. Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety. Canadian Agency for Drugs and Technologies in Health. 2009. Available at: http://www.cadth.ca/media/pdf/M0006_Rivaroxaban_and_Dabigatran_L3_e.pdf.
25. Guyatt G, Akl E, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: Executive Summary. CHEST 2012; 141(2)(Suppl):7S-47S.
26. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
27. The EINSTEIN Investigators. Oral Rivaroxaban for the Symptomatic Venous Thromboembolism. NEJM 2010; 363 (26):2499-2510.
28. Schulman S, Kearon C, Kakkar A, et al. Extended use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. NEJM 2013;368:709-18.
29. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC et al. Oral thrombin inhibitor dabigatran etexilate vs. North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty. 2009;24(1):1-9.