THE OREGON STATE DRUG REVIEW©

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

October 2014 Volume 4, Issue 7

What's New with Oral Anticoagulants?

By Kathy Sentena, Pharm.D., from Oregon State University College of Pharmacy

The landscape of oral anticoagulation has been in constant flux since the approval of the direct thrombin inhibitor, dabigatran, in 2010.[1] Factor Xa inhibitors, apixaban and rivaroxaban, were approved shortly thereafter. Apixaban and dabigatran have new indications and updated guidelines on the management of atrial fibrillation (AF) have been released. The focus of this newsletter will be on the evidence supporting the new indications, comparison of available anticoagulant therapies and review of new guideline recommendations.

Apixaban - Approval for Prophylaxis

In March of this year apixaban received approval to be used in patients undergoing hip or knee surgery requiring anticoagulation prophylaxis.[2] This approval was based on three studies, ADVANCE 1-3 (table 1).[3-5] These were fair to good quality, double-blind, double-dummy, randomized trials involving 11,659 patients. The primary endpoint used for all the ADVANCE studies was the composite of asymptomatic and symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) or death from any cause.

Apixaban use in patients undergoing total knee replacement (TKR) produced conflicting results. In the ADVANCE-1 trial, apixaban 2.5 mg twice daily was found to be inferior to the enoxaparin 30 mg every 12 hour regimen.[3] However, in the ADVANCE-2 study, apixaban 2.5 mg twice daily was found to be superior to enoxaparin 40 mg daily with a number needed to treat (NNT) of 11.[4] In ADVANCE-3, apixaban 2.5 mg twice daily was found to be superior to enoxaparin 40 mg daily in patients requiring anticoagulation for total hip replacement (THR) (NNT 40).[5] Major bleeds and clinically relevant non-major bleeds were similar between groups in the ADVANCE-2 and 3 trials and significantly less in the apixaban group in the ADVANCE-1 trial.[3-5]

Table 1. Efficacy Comparison of Newer Oral Anticoagulants in Orthopedic Prophylaxis

Study/ Indication	Therapy	Results for the Primary Endpoint: Composite of asymptomatic and symptomatic DVT, non-fatal PE or all-cause mortality*
ADVANCE-1[3] TKR	apixaban 2.5 mg bid vs. enox 30 mg bid	**Apixaban inferior to enoxaparin** (RR 1.02; 95% CI, 0.78 to 1.32, p=0.06)
ADVANCE-2[4] TKR	apixaban 2.5 mg bid vs. enox 40 mg daily	**Apixaban superior to enoxaparin** (RR 0.62, 95% CI 0.51 to 0.74, p<0.001)
ADVANCE-3[5] THR	apixaban 2.5 mg bid vs. enox 40 mg qd	**Apixaban superior to enoxaparin** (RR 0.36, 95% CI, 0.22 to 0.54, p<0.001)
RE-MODEL[6] TKR	dabigatran 220 mg qd vs. enox 40 mg qd	**Dabigatran noninferior to enoxaparin** (RR 0.97, 95% CI 0.82 to 1.1)
RE-MOBILIZE[7] TKR	dabigatran 220mg qd vs. enox 30 mg bid	**Dabigatran inferior to enoxaparin** (RR 1.2, 95% CI 1.0 to 1.5)
RE-NOVATE[8] THR	dabigatran 220 mg qd vs. enox 40 mg qd	**Dabigatran noninferior to enoxaparin** (RR 0.90, 95% CI 0.63 to 1.3)
RE-NOVATE II[9] THR	dabigatran 220mg qd vs. enox 40 mg qd	**Dabigatran noninferior to enoxaparin** (ARR -1.1%, 95% CI -3.8 to 1.6%, p<0.0001)
RECORD 1[10] THR	rivaroxaban 10 mg qd vs. enox 40 mg qd	**Rivaroxaban superior to enoxaparin** (RR 0.30, 95% CI 0.12 to 0.51, p)
RECORD 2[11] THR	rivaroxaban 10 mg qd vs. enox 40 mg qd	**Rivaroxaban superior to enoxaparin** (RR 0.21, 95% CI 0.13 to 0.35)
RECORD 3[12] TKR	rivaroxaban 10 mg qd vs. enox 40 mg qd	Rivaroxaban superior to enoxaparin (RR 0.51, 95% CI 0.39 to 0.65)
RECORD 4[13] TKR	rivaroxaban 10 mg qd vs. enox 30 mg bid	**Rivaroxaban superior to enoxaparin** (RR 0.67, 95% CI 0.51 to 0.93)

* The clinical relevance of asymptomatic DVTs is unknown and in some studies this finding was the dominating factor in determining results.
TKR – total knee replacement, THR – total hip replacement, Enox – enoxaparin, QD – daily, BID – twice daily, RR – relative risk, ARR – absolute risk reduction, DVT – deep vein thrombosis, PE – pulmonary embolism

Multiple anticoagulants are available for patients requiring prophylaxis when undergoing TKR or THR. Consideration of the evidence is an important component in the anticoagulant selection process (Table 1). There are no studies directly comparing the newer oral anticoagulants for orthopedic prophylaxis. A recent systematic review done by the Veterans Administration on the comparative effectiveness of the new oral anticoagulants and standard prophylaxis in patients undergoing TKR and THR, found rivaroxaban to be the most effective in reducing the risk of venous thromboembolism (VTE) compared to apixaban and dabigatran, based on indirect comparisons.[14] This same review found factor Xa inhibitors to reduce the rate of symptomatic DVT to a greater extent than low molecular weight heparins (LMWH) based on high strength of evidence (4 fewer events per 1000 patients treated; OR 0.46, 95% CI 0.30 to 0.79). A limitation to this finding was that studies using the 40mg once daily dose of enoxaparin, which is not approved in the United States, were included. The efficacy of dabigatran was not found to be statistically different from LMWH.[14] Major bleeding was found to be higher with factor Xa inhibitors compared to enoxaparin (OR 1.27, 95% CI 0.98 to 1.65).[14] The Drug Effectiveness Review Project (DERP) found apixaban, dabigatran and rivaroxaban to have similar efficacy, based on indirect comparisons, in preventing symptomatic VTE in patients undergoing orthopedic surgery, with similar risks of major bleeding.[15] The report also found that there was no significant difference between the newer agents compared to enoxaparin for the outcomes of mortality and symptomatic PE, based on moderate to high strength of evidence.[15] The American College of Chest Physicians (ACCP) Practice Guideline weakly recommends LMWH over fondaparinux, apixaban, dabigatran, rivaroxaban and unfractionated heparin for patients requiring anticoagulation for orthopedic surgery.[16]

Apixaban - Approval for DVT and PE Treatment

Last month apixaban was approved for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy.[2] The double-blind AMPLIFY and AMPLIFY-EXT randomized controlled trials were used as evidence for approval.[17,18] AMPLIFY was a good quality trial in which patients were randomized to apixaban 5 mg twice daily (after 7 days of 10 mg twice daily) or conventional treatment with enoxaparin and warfarin (international normalized ratio [INR] 2.0 to 3.0) for 6 months.[17] In the fair quality AMPLIFY-EXT study 2482 patients were randomized to apixaban 2.5 mg twice daily, apixaban 5 mg twice daily or placebo.[18] Patients were included in the AMPLIFY-EXT trial if they had a prior VTE and completed 6 to 12 months of anticoagulation and for whom there was clinical equipoise regarding continuing or discontinuing treatment. The primary outcome studied was symptomatic recurrent VTE or death from VTE in both studies. In AMPLIFY apixaban was shown to be non-inferior to conventional treatment with enoxaparin and warfarin for the primary endpoint (RR 0.84, 95% CI, 0.60 to 1.18, p<0.001).[17] Patients in the warfarin group were reported to have INRs in the therapeutic range 61% of the time. Apixaban was shown to be superior to placebo in the AMPLIFY-EXT trial with similar rates of major bleeding.[18]

At this time there is still no antidote to reverse the effects of apixaban in case of a bleeding emergency. The dose of apixaban should be reduced in those 80 years of age and older, weighing ≤60 kg and those with reduced renal function (serum creatinine ≥1.5 mg/dL).[2] Apixaban is recommended as a second-line agent, after enoxaparin, for orthopedic prophylaxis and second-line, after warfarin, for the treatment of DVT and PE for Oregon Medicaid fee-for-service (FFS) patients.[19]

Dabigatran - Approval for Treatment and Reduction in Recurrent DVT and PE

Dabigatran 150 mg twice daily has received FDA approval for use in the treatment of DVT and PE in patients receiving 5 to 10 days of parenteral anticoagulation.[1] The RECOVER and RECOVER II studies were the main studies used to support this indication.[20,21] RE-COVER and RE-COVER II were both non-inferiority studies comparing dabigatran 150 mg twice daily to warfarin (target INR 2-3), after initial parenteral anticoagulation for 5-10 days, for the acute treatment of DVT or PE in over 5000 patients.[20,21]

In both studies dabigatran demonstrated noninferiority to warfarin.[20,21] A pooled analysis of RE-COVER and RE-COVER II patients, found recurrent VTE rates to be similar with a HR of 1.09 (95%CI, 0.76 to 1.57).[1] Patients randomized to warfarin were in the therapeutic range 57-60% of the time.[20,21] Major bleeding rates were similar for dabigatran and warfarin. Baseline patient characteristics did not influence efficacy results to a significant extent, however, warfarin appeared to be more effective in patients under 60 years of age. For the outcome of clinically relevant bleeding, dabigatran demonstrated a significantly higher risk reduction in younger patients up to the age of 85 years.[1]

The fair quality RE-MEDY trial and good quality RE-SONATE trial were used for dabigatran's approval for reduction in risk of recurrent VTE in patients previously treated.[22,23] RE-MEDY compared dabigatran 150 mg daily to warfarin in 2,856 patients for a median duration of 128 days. Dabigatran was found to be non-inferior to warfarin (HR 1.44, 95% CI 0.78 to 2.64, p=0.01 for noninferiority).[22] TTR for warfarin treated patients was 65%. Major bleeding was less with dabigatran but not significantly so. The composite endpoint of major or clinically relevant bleeding was significantly less with dabigatran. In the RE-SONATE trial dabigatran was found to be superior to placebo with higher rates of bleeding in the dabigatran group.[23]

Efficacy results for oral anticoagulants for the treatment of DVT and PE are presented in table 2. Limitations to the data complicate the comparisons of oral anticoagulants for the treatment of DVT and PE. Large inferiority margins (RE-MEDY), open-label study design (EINSTEIN-DVT) and lack of direct comparisons between the newer agents make it difficult to draw firm efficacy conclusions.[22,24] Systematic reviews and guideline recommendations can be useful tools in analyzing comparative efficacy. The DERP report found moderate strength of evidence that mortality and recurrent VTE rates were similar between dabigatran and rivaroxaban compared to warfarin.[15] The ACCP Practice Guidelines recommend warfarin over LMWH, dabigatran and rivaroxaban for long-term treatment of DVT and PE.[16]

As with all the newer oral agents, there is no antidote for dabigatran in the event of a bleeding emergency. Dabigatran has been associated with dyspepsia resulting in tolerability issues. In Oregon Medicaid FFS patients, warfarin is the preferred treatment for DVT and PE with apixaban, dabigatran and rivaroxaban available as second-line options if clinical criteria are met.[19]

Table 2. Clinical Trials of Newer Oral Agents for Treatment of VTE

Study	Therapy	Results for the Primary Endpoint: Recurrent VTE or death related to VTE
AMPLIFY[17]	apixaban 5 mg bid vs. CT	**Apixaban noninferior to conventional therapy** (RR 0.84; 95% CI, 0.60 to 1.18, p<0.001)
AMPLIFY-EXT[18]	apixaban 2.5 mg bid vs. placebo	**Apixaban superior to placebo** (RR 0.33, 95% CI 0.22 to 0.48, p<0.001)
	apixaban 5 mg bid vs. placebo	**Apixaban superior to placebo** (RR 0.36, 95% CI 0.25 to 0.53, p<0.001)
RE-COVER[20]	dabigatran 150 mg bid vs. CT	**Dabigatran noninferior to conventional therapy** (HR 1.10, 95% CI, 0.65 to 1.84, p<0.001)
RE-COVER II[21]	dabigatran 150 mg bid vs. CT	**Dabigatran non-inferior to conventional therapy** (RR 1.08, 95% CI 0.64 to 1.80, p<0.001)
REMEDY[22]	Dabigatran 150 mg qd vs. warfarin	**Dabigatran noninferior to warfarin** (HR 1.44, 95% CI 0.78 to 2.64, p=0.01)
RESONATE[22]	Dabigatran 150 mg qd vs. placebo	**Dabigatran superior to placebo** (HR 0.08, 95% CI 0.02 to 0.25, p<0.001)
EINSTEIN-DVT[23]	Rivaroxaban 20mg qd vs. CT	**Rivaroxaban noninferior to conventional therapy** (HR 0.68, 95% CI 0.44 to 1.04, p<0.001)
***EINSTEIN PE**[24]	Rivaroxaban 20 mg daily vs. CT	**Rivaroxaban noninferior to conventional therapy** (HR 1.2, 95% CI 0.75 to 1.68)
***EINSTEIN-EXT**[25]	rivaroxaban 20 mg qd vs. placebo	**Rivaroxaban superior to placebo** (HR 0.18, 95% CI 0.09 to 0.39, p<0.001)

* Recurrent VTE only
Conventional therapy (CT) – enoxaparin + warfarin, QD – daily, BID – twice daily, RR – relative risk, HR- hazard ratio

AHA/ACC/HRS Guidelines Updated

The America Heart Association, American College of Cardiology and the Heart Rhythm Society collaborated on an updated guideline for the management of AF (Table 3).[26] This guideline utilizes the CHA_2DS_2-VASc scoring system, which helps to better identify those patients at low risk of stroke and appropriate candidates for anticoagulation. Warfarin is recommended with higher certainty than the newer oral anticoagulants (table 3). If an anticoagulant is indicated, therapy should be based on a discussion of risk versus benefit and patient's preference (Class I, LOE C).[26] Due to limited long term data, concerns over a lack of an antidote for the new oral agents and tolerability issues, warfarin is the preferred treatment for AF in Oregon Medicaid FFS patients.[19]

Table 3: AHA/ACC/HRS Drug Therapy Recommendations for AF[26]

Recommendation*	Indication	Therapy	LOE**
Class I	Prior stroke, TIA or CHA_2DS_2-VASc ≥2	Warfarin Dabigatran Rivaroxaban Apixaban	A B B B
Class IIa	CHA_2DS_2-VASc ≥2 and end-stage chronic kidney disease or hemodialysis	Warfarin	B
Class IIb	Nonvalvular AF and CHA_2DS_2-VASc of 1	No treatment, anticoagulants or ASA	C
Class IIb	CHA_2DS_2-VASc ≥2 with coronary revascularization	Clopidogrel + anticoagulants but not ASA	B
Class III: No benefit	AF and end-stage chronic kidney disease or on hemodialysis	Dabigatran Rivaroxaban	B B
Class III: Harm	Mechanical Heart Valves	Dabigatran	B

* The class of recommendation estimates the size of the treatment effect (Class I being stronger and Class III being of no benefit or harmful).
** The level of evidence refers to the estimate of certainty of the treatment effect.
ASA – aspirin, AF – atrial fibrillation, CHA_2DS_2-VASc – scoring system that predicts stroke risk, LOE- level of evidence, TIA- transient ischemic attack, VTE- venous thromboembolism

Conclusions

Multiple anticoagulants options are available for those patients in need of anticoagulation. There are limited direct comparisons to guide decision-making strategies. Anticoagulant selection should be based on the consideration of the evidence, as well as patient characteristics. Guidance on optimal anticoagulant management will continue to evolve as more evidence and experience in the general population is gained.

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. 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 December 7, 2012.
3.Lassen M, Raskob G, Gallus A, et al. Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement. NEJM 2009; 361 (6):594-604.
4. 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.
5.Lassen M, Gallus A, Raskob G, et al. Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. NEJM 2010; 363 (26):2487-2498.
6. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5:2178-85.
7. 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.
8. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for the prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. Lancet. 2007;370:949-956. (RE-NOVATE)
9. Eriksson B, Dahl O, Huo M, et al. Oral Dabigatran versus Enoxaparin for Thromboprophylaxis After Primary Total Hip Arthroplasty (RE-NOVATE II) A Randomised, Double-blind, Non-inferiority Trial. Thrombo Haemost 2011;105(4):721-729.
10. Eriksson B, Borris L, Friedman R, et al. Rivaroxaban Versus Enoxaparin for Thromboprophylaxis After Hip Arthroplasty. N Engl J Med 2008;358:2765-75.
11. Kakkar A, Brenner B, Dahl O, et al. Extended Duration Rivaroxaban Versus Short-term Enoxaparin For The Prevention of Venous Thromboembolism After Total Hip Arthroplasty: A Double-blind, Randomised, Controlled Trial. Lancet 2008;372:31-39.
12. Lassen M, Ageno W, Borris L, et al. Rivaroxaban Versus Enoxaparin For Thromboprophylaxis After Total Knee Arthroplasty. N Engl J Med 2008;358:2776-86.
13. Turpie A, Lassen M, Davidson B, et al. Rivaroxaban Versus Enoxaparin For Thromboprophylaxis After Total Knee Arthroplasty (RECORD4): A Randomised Trial. Lancet 2009;373:1673-80.
14. Adams S, McDuffie J, Lachiewicz P, et al. Comparative Effectiveness of New Oral Anticoagulants and Standard Thromboprophylaxis in Patients Having Total Hip or Knee Replacement. Ann Intern Med 2013;159:275-284.
15. Carson S, Selph S, Thakurta S. New Oral Anticoagulant Drugs. Drug Effectiveness Review Project 2013.
16. 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.
17. Agnelli G, Buller H, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. New Engl J of Med 2013;369:799-808.
18. 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.
19. Oregon Medicaid Pharmaceutical Services Prior Authorization Criteria. Oregon Health Authority. August 2014. Available at: http://www.oregon.gov/oha/healthplan/tools/Oregon%20Medicaid%20PA%20Criteria,%20August%202014.pdf. Accessed August 6, 2014.
20. 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.
21. Schulman S, Kakkar A, Goldhaber S, et al. Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis. Circulation 2014;129:764-772.
22. Schulman S, Kearon C, Kakkar A, et al. Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism. N Engl J of Med 2013;368:709-718.
23. The EINSTEIN Investigators. Oral Rivaroxaban for the Symptomatic Venous Thromboembolism. NEJM 2010; 363 (26):2499-2510.
24. The EINSTEIN-PE Investigators. Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. NEJM 2012; 366 (14):1287-1297.
25. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Eng J Med 2009;361:1139-51.
26. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, J of the Amer Coll of Cardiol (2014), doi: 10.1016/j.jacc.2014.03.022.