

# LECOM Point

WELCOME TO LECOM POINT...

A DRUG INFORMATION SOURCE DIRECT AND TO THE POINT

## Dabigatran and Bleeding

*Sara Dempsey, PharmD Candidate; Kathryn Samai, PharmD, BCPS*

After the approval of the new oral anticoagulant, dabigatran, practitioners raised concerns regarding the bleeding risk. The FDA noted a large number of post-marketing reports regarding bleeding among patients treated with dabigatran. Since dabigatran's FDA approval, clinicians are eager to know whether or not the post-marketing data is congruent with the rates of bleeding that were published in the preapproval trial (RE-LY trial). Because patients with renal dysfunction were excluded from the RE-LY trial, another concern is whether the use of dabigatran increases their risk of bleeding.

Dabigatran is an oral anticoagulant that acts by inhibiting thrombin. It is FDA approved for the prevention of stroke in nonvalvular atrial fibrillation.<sup>1</sup> In the United States, dabigatran's approved dosing is 150 mg twice daily in patients with creatinine clearance (CrCl) > 30 ml/min and 75 mg twice daily in patients with CrCl 15-30 ml/min.

In the RE-LY trial, dabigatran was shown to be non-inferior and then later updated showing superiority in reducing ischemic and hemorrhagic strokes relative to warfarin. The incidence of stroke was less with dabigatran (1.5% for 110 mg and 1.1% for 150 mg) than with warfarin (1.7%). Dabigatran also had less patients experience major bleeding than warfarin. Rates of major bleeding were 3.11 % for dabigatran 150 mg (p= 0.31) and 2.71% for dabigatran 110 mg (p= 0.003) compared to 3.36% for warfarin.<sup>4</sup>

Post-marketing studies have shown a substantial amount of bleeding episodes associated with dabigatran, as evidenced by the number of reports to the Institute for Safe Medication Practices (ISMP). In the first quarter of 2011, there were 505 cases of hemorrhage associated with use of dabigatran,<sup>3</sup> exceeding the hemorrhage rate of any other therapeutic agent, including warfarin. The FDA has investigated reported bleeding events associated with dabigatran, and in November 2012 released a position statement that dabigatran's bleeding rates appear to be no higher than that of warfarin. The position statement is based on post-marketing data reported to the FDA from October 19, 2010

through December 31, 2011. Both gastrointestinal bleeding and intracranial hemorrhage rates were analyzed. New warfarin users had a 1.6 to 2.2 times higher risk of gastrointestinal bleeding and 2.1 to 3.0 times higher risk of intracranial hemorrhage than new dabigatran users. These calculations were performed using insurance claims and the FDA's Sentinel Initiative. Rates were calculated by using the number of patients that had a diagnosis of intracranial or gastrointestinal hemorrhage and were new users of warfarin or dabigatran.<sup>2</sup>

In addition to concerns of post-marketing bleed rates, it is important to address the lack of safety outcomes data in patients with renal dysfunction. Originally, patients with severe renal impairment were excluded from the RE-LY trial.<sup>4</sup> The renal adjustment recommendation of a dose reduction to 75 mg twice daily for patients with CrCl between 15-30 ml/min is based on a single-dose, pharmacokinetic modeling and data demonstrating that dabigatran is approximately 80% renally excreted.<sup>1,2</sup>

There is no dosing adjustment recommended for patients with mild to moderate kidney function, but somewhat reassuringly, 19% of patients in the RE-LY trial had moderate renal insufficiency (CrCl= 30-49 ml/min). There is still a concern that elderly patients with moderate renal dysfunction may have an increased risk of bleeding with the 150 mg twice daily dosing.<sup>1</sup> A lower dose of 110 mg twice daily for patients older than 80 years has been approved in other countries.<sup>3</sup> Canada has also updated their recommendations to contraindicate use of dabigatran in patients with CrCl below 30 ml/min. One study evaluated case reports of patients that had impaired renal function (CrCl ranging from 15-43 ml/min) and had a bleeding event while receiving dabigatran. It found that these patients had plasma concentrations and coagulation parameters that were higher than what was reported in the RE-LY trial. In addition, two of the five patients sustained bleeding events that were fatal.<sup>1</sup>

*Continued on page 2*

Continued from page 1

Although dabigatran has been associated with increased risk of bleeding, it does not appear that this is occurring at rates greater than those seen with warfarin, according to the FDA. To date, practitioners should follow the approved package labeling and reported updates.<sup>2</sup>

- Continue use of dabigatran 150 mg twice daily in patients with CrCl >30 ml/min
- Continue use of dabigatran 75 mg twice a day in patients with CrCl 15-30 ml/min
- Avoid use of dabigatran in patients with CrCl <15 ml/min or requiring hemodialysis

More randomized, controlled studies need to be performed, especially studies that specifically look at subpopulations such as elderly patients and those with renal dysfunction. When choosing between starting a patient on warfarin or dabigatran, the decision should be patient specific and many factors need to be taken into account. Patients should be monitored closely for renal function and signs and symptoms of bleeding, especially those that are of advanced age or with renal insufficiency. Reevaluation of anticoagulation management is key as further reports of bleeding with dabigatran become available. A long-term safety trial is anticipated soon (RELY-ABLE).

[<Click for references>](#)

---

## Rivaroxaban: Expanded Indication

Edward McLean, PharmD Candidate

In November 2012, the FDA expanded the approved use of the factor Xa inhibitor, rivaroxaban to include treatment of deep vein thrombosis (DVT), treatment of pulmonary embolisms (PE), and risk reduction of recurrent DVT and PE after acute treatment.<sup>1</sup> Prior to this action, rivaroxaban gained FDA approval in 2011 for two indications: DVT / PE prophylaxis in post-surgical patients undergoing knee / hip procedures and the treatment of patients with atrial fibrillation. Rivaroxaban can be given orally, provides standardized dosing, and requires less invasive monitoring compared to alternative agents. The expanded use approval was based on results of three separate clinical trials that evaluated the safety and efficacy of rivaroxaban in an international patient population of 9,478 patients.

The Oral Rivaroxaban for Symptomatic Venous Thromboembolism (EINSTEIN-DVT) study was an open-label, randomized, event-driven, non-inferiority trial published in the New England Journal of Medicine in 2010.<sup>2</sup> Initially, the investigators compared safety and efficacy of once daily dosed rivaroxaban with subcutaneous enoxaparin and subsequent Vitamin K Antagonists (VKA) for the treatment of acute, symptomatic DVT for 3, 6, and 12 months in a patient population of 3,449. The primary efficacy endpoint was recurrent DVT events and the primary safety endpoint was major or clinically relevant non-major bleeding events. The results demonstrated non-inferiority of rivaroxaban to standard treatment causing recurrent events in 2.1% of the patient population vs. 3.0% in the control group, (hazard ratio, 0.68; 95% CI, 0.44 to 1.04; P<0.001). The primary safety outcome occurred in 8.1% of the patient population in both groups.

The EINSTEIN-DVT Continued Treatment Trial evaluated the use of rivaroxaban for an additional 6 to 12 months in a patient population which had completed a treatment course for an acute DVT / PE.<sup>2</sup> The study was a double-blind, randomized, event-driven superiority clinical trial evaluating the safety and efficacy of rivaroxaban vs. placebo in a study population of 1,196 patients. The primary efficacy and safety

endpoints were the same as the initial EINSTEIN-DVT Trial. The study concluded that rivaroxaban demonstrated superior efficacy, with thromboembolic event rate of 1.3% vs. 7.1%, (hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001). However, bleeding events occurred in 0.7% of the rivaroxaban treatment group vs. 0.0% for the placebo group.

The Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism (EINSTEIN-PE) study was a randomized, open-label, event driven, non-inferiority trial published in The New England Journal of Medicine in 2012.<sup>3</sup> Similar to the EINSTEIN-DVT trial, the investigators compared once daily dosed rivaroxaban with the standard treatment of enoxaparin and subsequent VKA for the treatment of acute symptomatic pulmonary embolism for 3, 6, and 12 months. Patient population for the study was 4,832, and the primary endpoints were recurrent events (efficacy) and major or clinically relevant non-major bleeding events (safety). The results demonstrated non-inferiority of rivaroxaban to standard treatment, with recurrent events occurring in 2.1% vs. 1.8%, (HR = 1.12; 95% CI, 0.75 to 1.68; P = 0.003). Additionally, there was no difference in primary safety endpoints which occurred in 10.3 % of the rivaroxaban treatment group vs. 11.4% in the standard of care group (P = 0.23). Major bleeding occurred in 1.1% of the rivaroxaban group vs. 2.2% in the standard of care group (HR = 0.49; 95% CI, 0.31 to 0.79; P = 0.003).

Rivaroxaban offers an alternative option for clinicians to utilize in the treatment and prophylaxis of thromboembolic events. It should be noted that non-blinded, non-inferiority, comparative efficacy studies are not designed to demonstrate superiority. Use should be dictated by patient specific variables and clinicians should be mindful of the lack of adequate reversal agents for this particular medication.

[Click here references](#)

## Reader Question: Rivaroxaban and INR

### Reader Question:

Does rivaroxaban (Xarelto) have an effect on INR?

**Response:** *Katie Kelly, PharmD; Abbey Powers, PharmD*

Currently, there is limited evidence on proper monitoring techniques for rivaroxaban in regards to INR. We have contacted the manufacturer (Janssen) and have received information regarding *ex vivo/in vitro* studies conducted. Some of these studies have been published, while others have not.

*Asmis et al. (2012)*<sup>1</sup> – conducted a study to evaluate the feasibility of rivaroxaban quantification with a commercial anti-Fx assay and to assess its accuracy and precision across 9 laboratories. In addition, the influence of rivaroxaban 10 mg on routine coagulation tests in the different laboratories was assessed using plasma samples from 20 healthy volunteers taken 2-3 hours following rivaroxaban ingestion. Thrombin time, Fibrinogen, FXIII, and D-Dimer results were not affected by rivaroxaban, and PT, INR, and aPTT were significantly altered by rivaroxaban ( $p \leq 0.05$ ).

*Samama et al. (2010)*<sup>2</sup> – conducted an *in vitro* study to evaluate the effects of rivaroxaban on various coagulation assays to determine whether a commercially available assay could accurately and appropriately assess rivaroxaban pharmacodynamics. The results of this study showed that

several coagulation tests, including PT, with rivaroxaban specific calibration, prothrombinase-induced clotting time (PiCT), and heparin clotting time, may be appropriate to assess the pharmacodynamics of rivaroxaban. PT is currently reported as a percentage of normal or as an INR value; neither is appropriate for rivaroxaban assessment. Currently, INR is calibrated and validated for vitamin K antagonists only. There is currently one *in vitro* feasibility study that supports the use of INR calibration with an international sensitivity index (ISI) derived specifically for rivaroxaban.<sup>3</sup>

*Tripodi et al. (2011)*<sup>3</sup> – conducted an *in vitro* study to assess the feasibility of using the INR calibrated for rivaroxaban to normalize PT results for rivaroxaban treated patients. The study listed above described that PT was prolonged in a concentration dependent manner; however there is inter-variability among specific reagents used. This study aimed to develop an ISI through testing for PT with thromboplastins. This ISI was then utilized to obtain an INR calibrated for rivaroxaban. Results of this *in vitro* study support possible INR calibration for rivaroxaban, but also states that further *in vivo* testing needs to be done.

### Conclusions/Recommendations:

There is limited data supporting the direct association between rivaroxaban and INR. However, FDA approved labeling for rivaroxaban states that it affects INR, and it is recommended that this be taken into consideration when switching patients between warfarin to rivaroxaban. Also, the manufacturer recommends that INR not be used to monitor rivaroxaban.

[<Click for references>](#)

## December Drug Shortages: *Check with your pharmacy for availability*

- Acyclovir Injection
- Amiodarone Injection
- Aztreonam Injection
- Bemetanide Injection
- Bupivacaine Injection
- Ciprofloxacin Injection
- Furosemide Injection
- Methylprednisolone Acetate Injection
- Metronidazole Injection
- Oxytocin Injection
- Protamine Sulfate
- Succinylcholine Injection

The **LECOM** School of Pharmacy operates out of two locations. Consistent with LECOM's core value of creating student-centered education, two distinct learning pathways are offered for the Doctorate of Pharmacy (PharmD) degree providing students the option of choosing a pathway most suited to their learning needs. In Erie, PA, an accelerated three-year pathway is offered enabling students to complete the PharmD degree in three calendar years; in Bradenton, FL, a traditional four-year pathway is offered. Both curricula offer the same spectrum of didactic courses, credit hours, and experiential education and experiences. The full array of supporting services and state-of-the-art physical facilities exists at both campuses.

Managing Editor: Marcus W. Campbell, PharmD

Drug Info Team: Ryan Wargo, PharmD  
Danielle Debias, PharmD  
Justin Scholl, PharmD  
Alejandro Vazquez, PharmD

Michael Mueller, Ph.D.  
Marcus W. Campbell, PharmD  
Abbey Powers, PharmD  
Kathryn Samai, PharmD, BCPS

Stephanie Peshek, PharmD  
Julie Wilkinson, PharmD, BCPS  
Katherine Tromp, PharmD

LECOM Bradenton  
5000 Lakewood Ranch Blvd.  
Bradenton, FL 34211-4909

941-756-0690 Phone  
941-782-5721 Fax



LECOM Erie  
1858 West Grandview Blvd/  
Erie, PA 16509-1025

814-866-6641 Phone  
814-866-8123 Fax