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Abstract

Serious clinical complications associated with venous thrombotic embolism (VTE) necessitate prophylaxis in patient groups who are at high risk of VTE, specifically those recovering from orthopedic surgery, with atrial fibrillation, with mechanical heart valves, at increased risk for stroke, or recovering post-MI. Currently, prophylaxis with warfarin, enoxaparin, or fondaparinux has been the standard of therapy, but these therapies each have their limitations.

Dabigatran etexilate is an orally available pro-drug of dabigatran, a competitive, reversible, direct inhibitor of thrombin (Factor IIa). The agent is converted by esterases, and, thus, not associated with the complications of the CYP enzyme system. Dabigatran follows a linear dose-response curve simplifying dosing compared to other agents. In the BISTRO II study, a dose as low as 50 mg dabigatran was found to be non-inferior to the current standard of therapy of 40 mg enoxaparin, and BISTRO I and II, RE-NOVATE, and RE-LY all found dabigatran was better or equivalent to warfarin therapy for post-hip and knee replacements.

Dabigatran could be especially beneficial in patients who have a contraindication to warfarin, need long-term anticoagulation and require less patient monitoring. With FDA approval and release of this drug, time will provide safety and efficacy data to solidify dabigatran's place in therapy along current anti-coagulation guidelines.

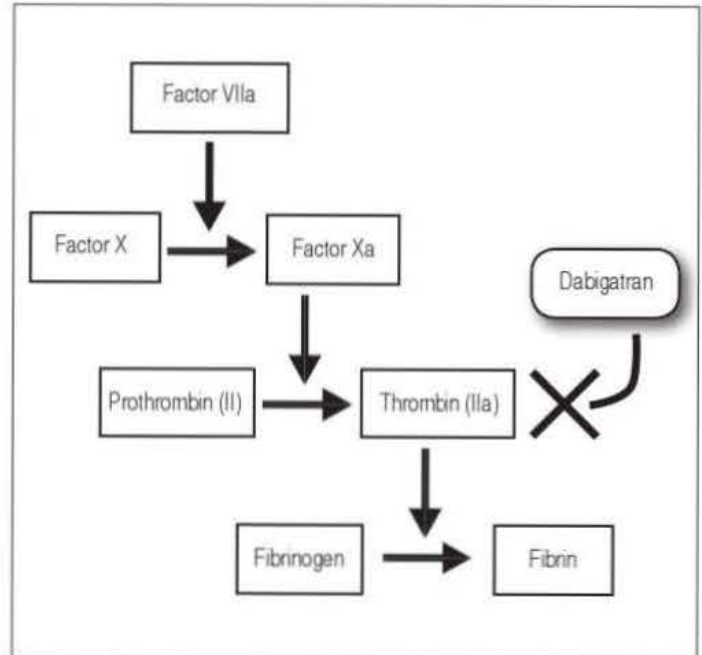


Figure 1: Target of dabigatran on clotting cascade

Background

Anticoagulants have commonly been used for the treatment of venous thromboembolism (VTE) and stroke prevention. VTE is a life-threatening complication consisting of either a deep vein thrombosis (DVT) or pulmonary embolism (PE). Immobility of post-surgical orthopedic patients, commonly hip and knee replacements, puts these patients at notable risk for fatal VTEs. Other specific patient groups at risk for thrombotic events include those with atrial fibrillation (a-fib) or mechanical valve replacements. Patients at risk for stroke, as well as at risk post-myocardial infarction patients, also benefit from anticoagulation therapy. Due to serious clinical complications associated with thrombotic events, such as stroke, death, loss of limb, blocked blood vessels or difficulty breathing, a prophylaxis regimen is vital for patients following surgery or those with increased risk for an event.^{1,2}

Post-surgery, low molecular weight heparin (LMWH), such as enoxaparin (Lovenox®) and factor Xa inhibitors like fondaparinux (Arixtra®), are typically used for prevention of thrombotic events. The American Chest Physicians Evidence-Based Clinical Practice Guidelines recommend prophylaxis start either before or as soon as possible after surgery and continue until the patient is fully ambulatory. However, this regimen is often difficult because it requires an injection, and there is a possibility of poor patient adherence. Heparin-induced thrombocytopenia (HIT) also presents as a risk for patients on LMWH therapy. An oral agent without the risk of HIT would be preferred. The current oral standard of therapy is warfarin, a vitamin K antagonist that is commonly used for a-fib patients as well as any patients indicated for long-term anticoagulation.

Many issues make the clinical use of warfarin difficult, including high patient variability, many food and drug interactions involving the CYP450 enzyme system, and diets varying in levels of vitamin K. This therapy requires substantial monitoring of PT/INR levels to ensure patients fall within a narrow therapeutic range. This therapy can be difficult, leading to a high proportion of patients outside of their therapeutic range at any given time. With low PT/INR, patients are at risk for VTE, and with high levels, patients are at risk for stroke or hemorrhage. Due to the difficulty of treatment, warfarin-induced necrosis, contraindications to warfarin and those who have trouble understanding changes in dosages, warfarin is not a good therapy option for all candidates.^{1,6}

Drug information

Dabigatran etexilate is an orally available pro-drug of dabigatran, a competitive, reversible, direct inhibitor of thrombin (Factor IIa) (Figure 1). The drug has fast onset, peaking two hours after administration, and a half-life of 12-17 hours. Dabigatran is converted by esterases and not by the CYP enzyme system, and 80 percent is excreted by the kidneys unchanged. Other available agents in the direct thrombin inhibitor class include bivalirudin, lepirudin and argatroban, which are all injectable.⁷

Pharmacokinetics/Pharmacodynamics

Creatinine clearance (CrCl) has shown to affect the clearance of dabigatran but may not be clinically significant, since plasma concentrations in renally impaired patients are similar with levels in healthy patients. Patients with a CrCl of less than 30 ml/min were not included in the

studies, so safety has not been confirmed in this patient population. In three studies, men and women were shown to have different plasma concentrations of dabigatran, with women having slightly higher concentrations. This could potentially be explained by increased overall body fat distribution, decreased muscle mass and smaller volume of distribution.^{8,10} Reduced renal clearance could affect bleeding risk in high doses of dabigatran shown by BISTRO I, which found no major bleeding until reaching 300 mg of dabigatran twice daily.¹¹ Therefore, higher doses of dabigatran should be avoided or monitored closely in patients with renal impairment.

In a small study, patients with moderate hepatic impairment exhibited similar plasma concentrations of dabigatran when compared to healthy males.¹⁰ The study found slightly less activation of the pro-drug, but the study was not large enough to make a conclusion of clinical significance. Absorption of dabigatran requires an acidic environment and could be affected by variation in gastric pH. The dosage form of dabigatran etexilate studied is formulated with tartaric acid to standardize the microenvironment which helps increase dissolution and absorption.¹¹ Bioavailability is lowered to some extent by co-administration of proton pump inhibitors. A PK study in the elderly (n=35) found use of pantoprazole with dabigatran to decrease dabigatran absorption by 20-25 percent.⁸ The authors claim there is no clinical significance, but it has not yet been proven in a larger study. Bioavailability has been studied in both fasting and fatty meals but has not been shown to be affected by either.

Efficacy

All of the studies assigned VTE rates as primary or secondary outcomes. BISTRO I and RE-NOVATE evaluated efficacy of dabigatran in total hip replacement patients, and BISTRO II expanded upon BISTRO I by including total knee replacements. RE-LY evaluated dabigatran in patients with a-fib.⁴ The trials concluded dabigatran is either better or equivalent to warfarin therapy for these conditions. Lower rates of DVT were found with higher doses of dabigatran. The BISTRO II study concluded the lowest rate of VTE was found with 225 mg twice a day.¹⁴ In the same study, a dose as low as 50 mg dabigatran was found to be non-inferior to the current standard of therapy of 40 mg enoxaparin.

In the RE-LY study, which studied dabigatran in a-fib patients, 110 mg of dabigatran was shown to be non-inferior to warfarin, while 150 mg actually performed better than warfarin. Warfarin had fewer incidences of myocardial infarction compared to dabigatran, but the 150 mg dabigatran dose prevented more strokes. RE-NOVATE found no absolute difference or rates between the two groups of dabigatran and enoxaparin with major VTE or thrombosis-related death.¹⁵ RE-MOBILIZE, which evaluated dabigatran in knee arthroplasty surgery patients, found enoxaparin to be more efficacious than dabigatran, concluding dabigatran had a higher risk of VTE and VTE-related mortality.¹⁶ The authors suggested this result was because of the more intense, prolonged dosing of enoxaparin and the different European procedure that was used during trial. The other studies outweigh the negative results of RE-MOBILIZE and the indifferent results of RE-NOVATE by involving more than 20,000 patients compared to 1,896 and 3,493 patients in the other trials, respectively. More trials should be done on a larger scale to solidify or disregard the two former studies' evidence.

Several of the studies allowed the use of aspirin (doses <160 mg), COX-2 inhibitors and compression stockings during the trials without considering the effects on the results. During a review, Eriksson ad-

dressed the aspirin issue stating no platelet aggregation was seen when administering dabigatran along with aspirin. Preliminary data shows potential increased bleeding when aspirin is used with higher doses of dabigatran.¹⁵

Although dabigatran studies have several valid points, flaws in trial design become the limiting factors to validity of findings. BISTRO II and RE-NOVATE have inadequate or lack of proper venographies, and both studies had high dropout rates. These same two studies also failed to take into account the use of aspirin, COX-2 inhibitors or compression stockings. Lack of blinding and misuse of power also limit various trials. Many articles do not show calculations for power or use the statistic properly.^{14,15}

Safety

Dabigatran has been found to be safe according BISTRO I, BISTRO II and the RE-LY studies. All three studies found dabigatran follows a linear dose-response curve, making dosing easier than other agents. In BISTRO I and BISTRO II, there were no major or clinically significant major bleeding issues for 150 or 300 mg doses.¹¹ RE-LY found similar results, although further data showed, at 150 mg, there were comparable bleeds to warfarin. It may be of clinical benefit to dose patients at 110 mg for fewer major bleeds and hospitalizations.⁴ RE-NOVATE confirmed safety by finding no substantial differences for major bleeding events between dabigatran doses 220 mg or 150 mg compared to enoxaparin 40 mg (p=0.44 for 220 mg and p=0.6 for 150 mg).¹⁵ However, results from PETRO, a study comparing dabigatran to warfarin with and without aspirin in patients with atrial fibrillation, suggest dabigatran may be unsafe with aspirin at high doses. A 300 mg dose along with aspirin was found to cause major hemorrhage and was discontinued.¹⁷ Significant differences between the dabigatran groups and enoxaparin were found when comparing bleeding event frequencies. In the RE-COVER trial, which evaluated dabigatran versus warfarin in patients with acute venous thromboembolism, 9 percent of patients taking dabigatran discontinued use due to adverse drug effects, compared with 6.8 percent of patients taking warfarin. This difference was not explained by the authors.¹³ The overall result was more total bleeds in the warfarin group. The trial found dyspepsia as the most common adverse effect of dabigatran. One potential safety issue is the long half-life making reversibility difficult in a hemorrhage situation, especially since there is no antidote. A study by Stangier deemed a drug interaction with atorvastatin was clinically insignificant in a study, with its concentrations being increased by 18 percent, and caused an 18 percent decrease in dabigatran concentration when taken concomitantly.⁹ Finally, patients on verapamil, amiodarone or quinidine have P-glycoprotein interactions, causing a significant rise in dabigatran serum concentrations. Concluding information regarding the safety of dabigatran is difficult to assess with direct comparison to other agents, as trials have been designed following various standardized guidelines. Further trials with more patients and a comparison to current U.S. guidelines would help in making a strong argument for Food and Drug Administration (FDA) approval.

Where is it useful?

Due to its oral availability and low number of known interactions, dabigatran could be used clinically for post-orthopedic surgery in both hip and knee patients and in a-fib patients. Although not currently researched, long-term anticoagulation with dabigatran may be useful in heart valve replacement patients. Dabigatran could be especially beneficial in pa-

tients who have a contraindication to warfarin and are in need of long-term anticoagulation. This medication may replace warfarin in patients receiving it as prophylaxis after a VTE. Dabigatran offers an orally available patient option with the possibility of lower patient stroke and hemorrhage risk, while requiring less patient monitoring.

Warfarin therapy leaves patients at a heightened risk for intracranial hemorrhages, which involve both hemorrhagic stroke and subdural or subarachnoid hemorrhages. Although intracranial hemorrhages only occur in 0.3 percent of patients on warfarin, they account for 90 percent of the death and disabilities associated with hemorrhages.¹⁹ In the RE-LY trial, dabigatran was shown to have a similar bleeding risk; however, significantly less intracranial bleeds occurred in both dabigatran groups (0.23 percent in the 110 mg group and 0.3 percent in the 150 mg group) than the warfarin group (0.74 percent).⁴ A review of the RE-LY trial stated that for every 357 patients treated with 150 mg of dabigatran rather than warfarin, one hemorrhagic stroke will be prevented.²⁰ Patients who commonly fall may not be good candidates for warfarin due to the risk of intracranial hemorrhage. Dabigatran could find a pivotal place in therapy by balancing the risk of an intracranial hemorrhage with the prevention of a VTE while still allowing the patient to be on an oral medication.

While dabigatran may be useful in specific patients, widespread use will not occur until more evidence supports it as a warfarin replacement. The cost of the brand-name dabigatran will likely hinder its prescribing until further studies have shown a cost-benefit over traditional warfarin and enoxaparin treatment regimens. While the potential cost to U.S. patients is not yet known, in Ireland, a month supply of 5 mg warfarin is approximately \$3.55 compared to a month supply of dabigatran at \$239.55. Dabigatran has a potential cost advantage in that there is little to no monitoring required, and the novel agent could reduce the cost of treating complications of warfarin misuse. Hindrances to use of dabigatran include potential interaction with drugs such as PPIs and difficulty dosing in renally impaired patients. Dabigatran is advantageous in hepatically impaired patients due to its activation by esterases and 80 percent renal excretion. Dabigatran does not have interactions with vitamin K-containing foods, other medications metabolized by cytochrome P450s or frequent PT/INR monitoring.²¹

Based on current evidence, clinically dabigatran has a great potential for therapy for both post-hospitalization and prevention of clotting in certain populations. With FDA approval and release of this drug, time will provide safety and efficacy data to solidify the place of dabigatran in therapy along current anticoagulation guidelines.

References:

- Haines ST, Witt DM, Nutescu EA. Venous Thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A Pathophysiologic Approach*. 7th Ed. New York: McGraw-Hill Companies, Inc.; 2008. p331-68.
- Sanoski CA, Schoen MD, Bauman JL. The Arrhythmias. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A Pathophysiologic Approach*. 7th Ed. New York: McGraw-Hill Companies, Inc.; 2008. P279-311.
- Majerus PW, Tollefsen DM. Blood Coagulation and Anticoagulant, Thrombotic, and Anti-platelet Drugs. In: Brunton LL, Lazo JS, Parker KL. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 11th Ed. New York: McGraw-Hill, Companies, Inc.; 2006. P1467-88.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med*. 2009;361(12):1139-51.
- Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of Dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost*. 2009; 101: 77-85.
- Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development *Clin Pharmacokinet*. 2009; 48 (1): 1-22
- Sanford M, Plosker GL. *Adis Drug Profile: Dabigatran*. *Drugs*. 2008; 68 (12): 1699-1709.
- Stangier J, Stähle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet*. 2008;47(1):47-59.
- Stangier J, Rathgen K, Stähle H, Reseski K, Kornicke T, et al. Co-administration of the oral direct thrombin inhibitor dabigatran etexilate and atorvastatin. *Am J Cardiovasc Drugs*. 2009; 9 (1): 59-68.
- Stangier J, Stähle H, Rathgen K, Roth W, Shakeri-Nejad K. Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, are not affected by moderate hepatic impairment. *J Clin Pharmacol*. 2008;48: 1411-19.
- Eriksson BI, Dahl OE, Ahnfelt L, Kalebo P, Stangier J, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement. *BISTRO I*. *J Thromb Haemost*. 2004;2(9): 1573-80.
- Stangier J, Stähle H, Rathgen K. Effect of food and pantoprazole on the bioavailability of the direct thrombin inhibitor dabigatran in healthy subjects. *J Thromb Haemost*. 2005; 3 (Suppl. 1):Abstract 1809.
- Stangier J, Eriksson B, Dahl O, Ahnfelt L, Nehmiz G, et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. *J Clin Pharmacol*. 2005;45(5):555-63.
- Eriksson BI, Dahl OE, Büller HR, Hettiarachchi R, Rosencher N, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost*. 2005;3(1): 103-11.
- Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Niek van Dijk C, et al. Dabigatran etexilate versus enoxaparin for preventions of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. *Lancet*. 2007; 370:949-56.
- Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, et al. (The RE-MOBILIZE Writing Committee). Oral thrombin inhibitor dabigatran etexilate vs the North American enoxaparin regimen for the prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty*. 2009; 24 (1):1-9
- Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol*. 2007;100: 1419-26.
- Nieuwlaat R, Connolly SJ. Stroke prevention in atrial fibrillation: better use of anticoagulation and new agents will lead to improved outcomes. *Heart*. 2009;95(2):95-7.
- Gage BF. Can we rely on RE-LY. *N Engl J Med*. 2009;361;(12):1200-2.
- Barry M. Letter to the Editor: A Reply to Gage. *N Engl J Med*. 2009; 361 (27): 2674.