New Anticoagulants for Thrombo-embolic Disease: Clinical Implications

Allison R. Campbell1, Richard McKnight1 and Harakh V. Dedhia2*

1Department of Pharmacy, West Virginia University Hospitals, 1 Medical Center Dr, Morgantown, WV26501, USA
2Section of Pulmonary- Critical Care Medicine, 4062, HSC-N, West Virginia University Health Science Center, 1 Medical Center Drive,Morgantown, WV26506-9166, USA

Abstract

The medical community and patients have long awaited new oral anticoagulants, a substitute for warfarin. Finally, 2 drugs have received limited approval and many more are in various developmental stage. Recently, as a result of the RE-LY study, a phase 3 clinical trial, the FDA approved an oral anticoagulant Dabigatran (Pradaxa), a direct thrombin inhibitor, for prevention of stroke in patients with non-valvar atrial fibrillation. A major advantage is that there is no need for frequent monitoring of coagulation or dose adjustment. Results of the RE-LY study (NEJM) showed that dabigatran 150 mg twice a day has decreased incidence of systemic embolization and stroke but similar rates of major hemorrhage when compared to warfarin. This drug can be used in both outpatient and inpatient settings and has already been approved in 75 countries including many European countries. It is being investigated for many clinical conditions, including prevention and treatment of DVT and pulmonary embolism. The European Medicines Agency approved dabigatran in 2008 for the prevention of thrombo-embolic disease and expanded the indication in 2011.

Additional oral Xa inhibitors; apixaban, edoxaban, betrixaban are in different stages of development and likely to get approval for different indications in the near future. Although the market for oral anticoagulants is billions of dollars, safety, clinical, and economic issues will influence the acceptance and use of these drugs. The costs of these drugs is likely to be higher than warfarin, however, elimination of frequent coagulation tests will help reduce overall costs. Important limitations for these new classes of drugs, is the absence of simple, easily available, cost effective reversal agents.

This article reviews the clinical trials, pharmacokinetics, side effects and potential clinical applications of these new oral thrombin inhibitors.

Introduction

Occurrence of acute venous thrombo-embolic (VTE) events is seen commonly in clinical practice [1]. Atrial fibrillation (AF) is also a common clinical condition and can have significant consequences mainly with development of stroke. It is estimated that over 2.3 million US adults suffer from AF and risk increases with advancing age [2]. Treatment with parenteral heparin followed by an oral vitamin K antagonist is very effective and has long been standard therapy. Major limitations of conventional long term anticoagulation include a narrow therapeutic window, the potential side effect of major bleeding, and variable individual dose response. Because of these issues, the medical community and patients have long awaited new oral anticoagulants, a substitute for warfarin. Recently, new oral thrombin inhibitors have been introduced in clinical practice, and as a result, the American College of Cardiology Foundation has updated their practice guidelines for management of AF and has added dabigatran to the recommendation [3]. In 2011, the European Medicines Agency adopted the new indication for prevention of stroke and systemic embolism in adult patients with non- valvar atrial fibrillation with one or more risk factors [4].

In September 2008, Canada and the European Commission approved the oral direct factor Xa Inhibitor rivaroxaban 10 mg. taken daily for the prevention of venous thromboembolism in patients undergoing elective total knee or hip replacement surgery [5]. Another Xa inhibitor, rivaroxaban demonstrated comparable outcomes to warfarin in preventing stroke and non-CNS embolic events in patients with atrial fibrillation, while not increasing the incidence of bleeding. The FDA has approved application for this indication as well.

This article will review the new and upcoming drugs in the management of acute VTE and prevention of emboli and stroke in patients with AF.

Basic Hemostasis And Coagulation Pathway

Before going in to detail regarding the new drugs, it is important to understand the basics of hemostasis pathways. Thrombosis can develop as a result of a myriad of risk factors and underlying disease states and has the potential to contribute to a patient’s morbidity and mortality. The patients at highest risk for thrombosis can be understood through Virchow’s triad, which describes the underlying pathophysiology through three separate mechanisms. These mechanisms include trauma to the endothelial layer of the vessels, hypercoagulability of the blood, and poor blood flow or stasis [4]. When injury to the endothelial layer occurs, tissue factor is released in the blood and initiates the extrinsic pathway of the coagulation cascade through the activation of factor VII. When calcium is present, the factor VIIa-tissue factor complex converts factor X to its activated form (Xa). Factor Xa will then form a complex with Factor Va in the presence of calcium to convert prothrombin to thrombin (Factor IIa). The production of thrombin allows for the final step of the coagulation cascade to occur, which is the conversion of fibrinogen to fibrin (Figure 1) [5,6].

*Corresponding author: Harakh V. Dedhia, Professor, Section of Pulmonary-Critical Care Medicine, 4062, HSC-N, West Virginia University Health Science Center, 1 Medical Center Drive, Morgantown, WV26506-9166, USA Tel: 304 293 3724; Fax: 304 293 3724; E-mail: hdedhia@hsc.wvu.edu

Received August 08, 2011; Accepted September 28, 2011; Published October 01, 2011


Copyright: © 2011 Campbell AR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Not only does the production of thrombin allow for the conversion of fibrinogen to fibrin, it is a key compound to initiate the intrinsic pathway of the coagulation cascade. Thrombin converts factor XI to its activated form. If thrombin is unavailable to activate factor XI, activated factor XIIa can also lead to the production of factor XIa. In the presence of calcium, factor XIa then converts factor IX to factor IXa. Factor IXa can activate factor VIII and together they form a complex that in the presence of calcium can activate factor X, which will then contribute by leading to further activation of the common pathway. Again, the final product formed is fibrin, which is a key component of thrombus formation (Figure 1) [5-7]. The thrombin remains the final enzyme in the clotting mechanism and hence the new research in anticoagulants is directed toward its inhibition (blockage).

The characteristics of an ideal anticoagulant include selective targeting on the coagulation cascade including effects on a recently formed clot, rapid onset of action, ease of administration (oral being the natural route), no individual dose adjustment, safe therapeutic window, minimal food or other drug interactions, no laboratory monitoring, and no dose adjustment for renal or liver failure. Also in case of significant bleeding, it should be easy to reverse the anticoagulatory effect. Even though such drug remains to be discovered, we should look at the new agents in this light.

**Warfarin**

Prior to the development of this new class of oral direct thrombin inhibitors, warfarin was the main oral option available for more than fifty years for patients requiring anticoagulation. Even though it has been used over fifty years, it is still one of the most difficult medications to manage and continues to maintain safety concerns. Mechanistically, warfarin inhibits the enzyme vitamin K epoxide reductase in the liver, which inhibits the vitamin K-dependent clotting factors (VII, IX, X and II).

Although warfarin is an effective anticoagulant, several factors prevent it from being an ideal agent. Warfarin has a very slow onset requiring patients to receive dual therapy with another agent at the time of initiation. In addition, dosing with warfarin is unpredictable requiring several factors such as sex, weight, race, diet, etc. to be considered when dosing a patient. Even when every factor is considered, there is still variability in dosing requiring frequent routine monitoring. Another major reason why warfarin is far from an ideal agent is the extensive amount of drug, food, and disease state interactions. Since warfarin is metabolized by the cytochrome P450 system, medications inhibiting or inducing CYP2C9 will affect warfarin’s metabolism.

According to an article published by Anderson et al. [8], differing genotypes of patients in fact may predict approximately one half of inter-individual dose variability. Genotypes of the cytochrome p450 isoform CYP2C9 and the vitamin K epoxide reductase complex subunit 1 VKORC1 jointly determine warfarin dose requirements[9-20] The *2 (R144C) and *3 allele (I359L) variants of CYP2C9 cause reductions in enzymatic activity of 30% and 80%, respectively, and increase bleeding risk [21]. Ten VKORC1 single nucleotide polymorphisms, many tightly linked, and 5 inferred haplotypes determine low, intermediate, and high-dose requirements [9-20] 

**Thrombin inhibitors (TIs)**

Due to the increasing need for alternatives to the currently available agents, the new class of agents are in the various stages of development, known as direct thrombin inhibitors, causing the thrombin Inhibition. These agents prevent the final step of the coagulation cascade, which is the production of fibrin. Within the last twenty years, lepirudin, argatroban, and bivalrudin all became available as intravenous formulations. Compared to IV heparin, these direct thrombin inhibitors are believed to have a less variable anticoagulant response and are advocated in the setting of heparin-induced thrombocytopenia [7,20,22-23] However, there are several drawbacks to these agents, which include the need for a continuous infusion, monitoring of the aPTT, cost, and until recently, the lack of available oral alternative to transition patients.

---

**Figure 1:** Normal coagulation cascade.
Mechanism of Action

Both rivaroxaban (a selective factor Xa inhibitor) and dabigatran (a direct thrombin inhibitor) interrupt the coagulation cascade by inhibiting the formation of fibrin, which in turn disrupts the process of platelet aggregation and the formation of thrombi. Dabigatran binds to the active site of both free and clot-bound thrombin and competitively inhibits the conversion of fibrinogen to fibrin [22-24]. The effect of newer drugs on the clotting cascade is shown in Figure 2.

Pharmacokinetics

With an oral bioavailability of 80 – 100%, rivaroxaban is rapidly absorbed with peak concentrations reached 2 – 4 hours after tablet ingestion. Rivaroxaban is highly protein bound (>90%) with a moderate volume of distribution of roughly 50 liters. With the 10mg dose, two-thirds will encounter metabolic degradation of which half will be eliminated renally and half will undergo fecal elimination. The remaining third is eliminated unchanged in the urine, lending to an elimination half-life of 7 – 11 hours. Metabolism primarily occurs in the liver through the Cytochrome P450 enzymes, specifically CYP3A4 and CYP2J2 [23].

Unlike Rivaroxaban, dabigatran is formulated as a prodrug, the dabigatran etexilate ester, which is hydrolyzed to form its active moiety. Dabigatran requires an acidic environment for absorption and is therefore formulated with tartaric acid pellets which provide the necessary milieu. Since dabigatran etexilate is a substrate of the efflux pump p-Glycoprotein, it has a low bioavailability of around 3 – 7%. Depending on the fasting state of the patient, the maximum serum concentration occurs anywhere from 1 – 3 hours following drug administration. The volume of distribution of dabigatran is 50 – 70 liters and is approximately 35% protein bound. Dabigatran is metabolized to four acyl-glucuronides that have similar activity as dabigatran. Dabigatran is eliminated primarily in the urine and the has a half-life of 12 to 17 hours [24].

Clinical Efficacy

Rivaroxaban

In December 2010, the EINSTEIN program published the results for two of the three trials for rivaroxaban, which were the acute deep-vein thrombosis (DVT) study and the continued treatment study [25]. The Acute DVT Study was a randomized, open label trial of patients with an acute DVT that compared the efficacy and safety of oral rivaroxaban with the current standard of enoxaparin and a vitamin K antagonist. The patients on rivaroxaban received 15mg twice daily for three weeks, followed by 20mg daily for the duration of therapy. In the standard therapy arm, patients were prescribed enoxaparin 1 mg/kg of body weight twice daily and a vitamin K antagonist. The enoxaparin was discontinued once the international normalized ratio (INR) was ≥ 2.0 for two consecutive days and the patient had at least five days of enoxaparin. The INR was monitored at least once a month and dose adjustments were made as necessary to maintain an INR of 2.0 – 3.0. The primary efficacy outcome was the development of recurrent VTE, which was defined as a recurrent DVT or the development of a pulmonary embolism, either fatal or non-fatal. Of the 1718 patients receiving rivaroxaban, 36 patients or 2.1% developed a recurrent VTE, while 51 or 3% of the 1705 patients receiving standard therapy developed a recurrent thrombo-embolic clot. This demonstrated that rivaroxaban was noninferior to standard treatment (P < 0.001). From a safety standpoint, there was no difference seen between the two therapies. The primary safety outcome of major bleeding or clinically relevant non major bleeding (as defined by bleeding requiring medical intervention, contact to a physician, an interruption in treatment, or affecting daily activities) was 8.1% in both treatment arms (P = 0.77) [25].

Figure 2: Site of action of the thrombin inhibitors on the coagulation cascade.
The Continued Treatment study was a double-blind trial evaluating patients with a diagnosed VTE who had received six or twelve months of therapy with either rivaroxaban or standard treatment [25]. The patients were randomly assigned to receive continued treatment for an additional six to twelve months with either 20mg rivaroxaban daily or placebo. The primary efficacy endpoint was recurrent VTE, defined in the same fashion as the Acute DVT study. With a relative risk reduction of 82%, the primary endpoint occurred in 8 of the 602 (1.3%) patients on rivaroxaban vs. 42 of the 594 (7.1%) patients taking placebo (P < 0.001). The primary safety outcome in this trial was major bleeding and occurred in 4 of the patients on rivaroxaban and none in the placebo arm (P = 0.11) [25].

A recently published trial (ROCKET AF), evaluated the use of rivaroxaban for the prevention of stroke in patients with AF [21,26] This multicenter double-blind, double-dummy study enrolled 14,264 patients with the diagnosis of persistent or paroxysmal AF and randomized them to receive either once daily rivaroxaban (n= 7111) or dose-adjusted warfarin (n = 7125) with an INR goal of 2.0 to 3.0 [12]. In addition, patients also needed to have a significant risk for stroke to be included in the trial, which included either a prior history of stroke, transient ischemic attack (TIA) or systemic embolism or at least two of the following risk factors: heart failure, hypertension, age ≥ 75 years old, and diabetes mellitus (i.e. A CHADS2 score ≥2) [12]. Rivaroxaban was dosed according to the patient’s creatinine clearance. Specifically, if the patient’s creatinine clearance was 30 – 49 milliliters per minute, the patient received 15mg once daily. However, if the clearance was greater than 50 milliliters per minute, patients were given 20mg once daily [26].

The primary efficacy composite endpoints were occurrence of ischemic and hemorrhagic strokes and or systemic thrombo-embolic events. This non-inferiority trial will have achieved a statistical power of 95% if 363 events occurred [26]. Of the 13,962 patients that were included in the as-treated analysis, 188 rivaroxaban patients experienced a primary event compared to 241 warfarin patients, 1.7% vs. 2.2% per year, respectively; p<0.001 noninferiority [12]. Non-inferiority between the two agents was also determined in the intention-to-treat analysis, 2.1% per year for rivaroxaban vs. 2.4% per year for warfarin (p<0.001) [26].

In comparing the bleeding rates, the primary safety endpoint (major and non-major clinically relevant bleeding) occurred in 1475 of 7111 rivaroxaban patients and 1449 of 7125 warfarin patients (14.9% vs. 14.5% per year, respectively; P=0.44) [26]. Rivaroxaban was associated with fewer intracranial hemorrhages than warfarin (55 vs. 84, respectively; P=0.02) but showed a higher incidence of gastrointestinal bleeding (224 vs. 154, respectively; P<0.001) [26]. Overall, it appears that rivaroxaban is non-inferior in efficacy and safety when in comparison to warfarin in the setting of stroke prevention for patients with AF[26].

Dabigatran

In September 2009, the results of the multicenter, randomized controlled RE-LY trial were published comparing the use of dabigatran with warfarin for the prevention of stroke [27]. Inclusion criteria were patients with AF documented through electrocardiography as well as a prior stroke, transient ischemic attack (TIA), an ejection fraction of less than 40%, class II or greater symptoms of heart failure by the New York Heart Association, and an age of at least 75 years old. Patients between the ages of 65 and 74 years old could be included if they also had a corresponding diagnosis of diabetes mellitus, hypertension, or coronary artery disease. Patients were randomized to receive blinded 110 mg or 150 mg of dabigatran twice daily or unblinded warfarin adjusted for INR, which was checked at a minimum of once a month. The primary endpoint was to determine if dabigatran was non-inferior to warfarin for preventing stroke or systemic embolism. The primary safety endpoint was major hemorrhage [13].

Of the 18,113 patients enrolled, the primary endpoint of stroke or systemic embolism occurred in 182 patients receiving 110 mg of dabigatran, 134 patients receiving the 150 mg dose of dabigatran, and 199 patients receiving warfarin. Therefore, dabigatran was found to be non-inferior to warfarin at both doses (P<0.001). In addition, the 150 mg dose of dabigatran was found to be superior to warfarin in preventing the development of emboli, 1.11% vs. 1.69% (P<0.001) [13].

Beyond efficacy, both doses of dabigatran also proved non-inferior to warfarin in major hemorrhage. Major bleeding was seen in 3.36% of patients per year in the warfarin arm. Similarly, patients on 110 mg dabigatran twice daily experienced a major bleed at a rate of 2.71% per year (P=0.003), and patients on the 150 mg twice daily dose had a major bleed at a rate of 3.11% per year (P=0.31). When the bleeding events were further evaluated by type of bleed, it was found that both dabigatran doses were associated with fewer hemorrhagic strokes than warfarin, but there was a significantly higher rate of gastrointestinal bleeding for the 150 mg dose of 27 Hence, a caution in patients with a history of GI bleed may be warranted.

Recently, the American College of Cardiology Foundation (ACCF) recommended Dabigatran as, “useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure” (Class I recommendation) [3].

**Interactions**

Due to the hepatic metabolism of rivaroxaban by CYP3A4, several drug interactions exist with this agent. The CYP3A4 inhibitors, such as the azole antifungal, HIV protease inhibitors, and macrolides all have the capacity to increase rivaroxaban serum concentrations. Likewise, the inducers of CYP3A4 (i.e. rifampin, phenytoin, carbamazepine, etc.) may reduce the serum concentrations of rivaroxaban and should be concomitantly used with caution [23].

Additionally, both rivaroxaban and dabigatran are substrates of p-glycoprotein, and therefore interact with both inducers and inhibitors of this transporter molecule. The major inducer of this transporter is rifampin, which leads to a decrease in serum concentrations. P-glycoprotein inhibitors, increase serum levels and include medications such as ketoconazole, verapamil, and amiodarone [20,22].

Unlike the vitamin K antagonists, there is no food-drug interactions associated with the DTIs. Therefore, there are no dietary restrictions that need to be addressed when initiating and maintaining patients on these agents, and there is less day-to-day variability regarding serum levels [22,23].

Due to the necessity of an acidic environment for dabigatran, it was concerning that the proton pump inhibitors and H2 antagonists...
could potentially affect the medication’s absorption. However, during the RE-LY trial, trough levels of dabigatran were obtained and were relatively unchanged [27].

Safety, Tolerability

Unlike warfarin, the direct thrombin inhibitors do not require routine laboratory monitoring. At the recommended dose of 150mg twice daily, dabigatran will prolong the aPTT approximately 2 x controls with a median trough aPTT of 52 seconds observed in the RE-LY trial. Utilizing an INR in patients on dabigatran is unreliable, as it may or may not be elevated [22]. Rivaroxaban influences the prothrombin time (PT). With the use of Neoplastin as the assay, the PT is influenced dose-dependently and demonstrates a close correlation to plasma concentrations (r = 0.98). Rivaroxaban’s pharmacodynamics also correlates to plasma concentrations and demonstrate minimal variability among patients based on gender, age, and weight [23].

Due to the nature of the direct thrombin inhibitors, the major safety concern is for bleeding. While warfarin patients can easily and inexpensively receive vitamin K for reversal, the direct thrombin inhibitors have no available antidote. In the event of overdose or unexpectedly receive vitamin K for reversal, the direct thrombin inhibitors have no available antidote. In the event of overdose or

Effect on Special Populations

Renal impairment

Both rivaroxaban and dabigatran require adjustment for patients with renal impairment. Rivaroxaban doses do not require dosage adjustment for patients with a creatinine clearance greater than 30ml/min. There is little data available for patients with a creatinine clearance less than 30ml/min. The drug is recommended to be used with caution in patients with a creatinine clearance of 15 – 29ml/min and should be avoided in patients with a clearance less than 15ml/min. For dabigatran, the full dose of 150mg twice daily is recommended for patients with a creatinine clearance of greater than 30 ml/min. Patients with a creatinine clearance of 15 – 30ml/min are recommended to reduce the dose to 75mg twice daily. If the creatinine clearance is less than 15ml/min, there is no recommendation available and dabigatran should be avoided in these patients [8,9]. In Europe, treatment with dabigatran in patients with severe renal impairment (CrCl< 30ml/ min), is contraindicated [4].

Hepatic impairment

In patients with hepatic disease associated with coagulopathy or a high bleeding risk, rivaroxaban should be avoided. Additionally, the medication should be used with caution in patients with a Child Pugh B classification, regardless of whether there is an associated coagulopathy [23].

Costs Associated with Anticoagulation: Cost Effective Analysis

Due to warfarin’s extremely narrow therapeutic window, strict

<table>
<thead>
<tr>
<th>Target</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Adjusted per INR</td>
<td>150mg BID</td>
<td>10mg Daily</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Renal Adjustment?</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vitamin K</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Bridging required</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FDA labeled indications</td>
<td>1. VTE treatment and prophylaxis</td>
<td>Thrombosis prevention in AF</td>
<td>VTE prophylaxis in the setting of hip and knee replacements.</td>
</tr>
</tbody>
</table>

Table 1: Currently available oral anticoagulants, their doses and reversal.
anticoagulation monitoring is necessary. This is especially prudent when a patient is beginning therapy with warfarin. Additionally, the cost of operating an anticoagulation clinic needs to be considered in the final evaluation. Currently, it is poorly reimbursed and the hospital or healthcare system absorbs the cost.

When evaluating costs of anticoagulation therapy, one must also understand the associated costs of management of warfarin as well [28-31]. In a study published by Menzin, et al. in 2005, a retrospective cohort design study was performed on the quality and costs associated with anticoagulation services [28]. In this study, 600 patients from 3 different health plans were identified with chronic non-valvular AF receiving warfarin [28]. These patients were identified between 1996 and 1998 and followed for up to one year. The results of the study showed that the mean per patient cost of warfarin monitoring over the one year follow up period averaged from $205-$305 among the 3 different sites. Mean costs for patients treated for one full year were $216-$339.00. Of particular interest in this study was the portion of time that the INR value was within the recommended range (2-3). The INR was in range only 62% of the time, with 25% of the days below range and 13% above range. Additionally, patients had an average of 18 clinic contacts over a mean duration follow up of 10.5 months [28].

Currently there is no monitoring needed of other oral anticoagulants, therefore the costs of management of monitoring for all other agents is not an issue. In order to better grasp the perspective of costs of therapy of dabigatran vs. all other agents, we have assessed the direct costs in US dollars [29-31]. These costs are based on the retail average wholesale price (AWP) of each drug as published in the 2008 Facts and Comparison’s Red Book as shown in Table 2.

Obviously the least expensive agent in anticoagulation is warfarin but to understand the total costs of warfarin therapy it is truly important to realize all costs of monitoring associated with the drug as mentioned earlier.

According to American Healthcare Research and Quality (AHRQ), approximately 4.2 million Americans purchased 27.9 million anticoagulant prescriptions in 2007. This represented 905 million dollars annually of which the average annual expense was 213.16 and the average wholesale price (AWP) of each drug as published in the 2008 Facts and Comparison’s Red Book as shown in Table 2.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>$.66-$6.8 per dose</td>
</tr>
<tr>
<td>Coumadin®</td>
<td>$.93 to $1.50 per dose</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®) 30mg</td>
<td>$2.45 per dose</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®) 40mg</td>
<td>$3.27 per dose</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra®) 2.5mg</td>
<td>$43.50 per dose</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra®) 5mg</td>
<td>$ 118.43 per dose</td>
</tr>
<tr>
<td>Dabigatran 75mg and 150mg</td>
<td>$4.05 per dose</td>
</tr>
</tbody>
</table>

Table 2: Cost comparison of various anticoagulants.
AF or flutter and a risk of stroke. The incidence of bleeding was 0.8%, 3.9%, 3.9%, and 5.5% for betrixaban 40mg, 60mg, 80mg, and warfarin, respectively. The EXPERT trial was the first study to assess the efficacy of betrixaban. In the setting of VTE prophylaxis following a total knee replacement, patients received betrixaban at a dose of 15 or 40 mg daily or enoxaparin 30mg subcutaneously twice a day. The incidence of VTE was 20%, 15% and 10% for betrixaban 15mg, 40mg, and enoxaparin, respectively [34].

In addition to edoxaban and betrixaban, the last two factor Xa inhibitors in the pipeline are YM-150 and LY-517717. In early phases of study, YM-150 has preliminary data to suggest that it may better prevent VTE in patients undergoing hip arthroplasty as well as enoxaparin with no additional bleeding risks. Similarly, an early study with LY-517717 in patients undergoing hip arthroplasty or total knee surgery showed noninferiority at doses of 100mg to 150mg daily when compared to enoxaparin 40mg given subcutaneously daily. Larger trials will be completed to substantiate these results [34].

Conclusion: Summary
Occurrence of VTE and AF remains an ongoing major medical issue and its treatment can be costly and burdensome to patients. One may say that a new era of AF treatment and VTE prevention has arrived. Many new drugs will be introduced in clinical practice in the near future for the prevention and treatment of thrombo-embolic disease [32-36]. Even though current new drugs have limited FDA indications, many clinical trials are on-going in the prevention and treatment of VTE. We anticipate the list of clinical indications will rise in near future.

These newer anticoagulants have some attractive features, including ease of administration and lack of frequent blood tests for INR monitoring, which in turn may lead to better compliance and less burden to the patient. Through a few major trials these drugs look as effective as warfarin but still share the same risk of bleeding. The rapid onset of action makes these agents very attractive when initiating therapy in both the inpatient and outpatient settings. Limitations of these drugs include lack of clinical trials for long term efficacy, safety, complications, and cost effectiveness. Further, there is no available antidote to these drugs. Therefore, a conservative approach to the use of these drugs in the very near future may be more practical rather than a wide spread acceptance of these novel oral anticoagulants until more information is learned. Some clinicians and patients would prefer the potential benefits and lack of frequent monitoring of these newer drugs compare to warfarin.

References


