New Options in Anticoagulation for the Prevention Of Venous Thromboembolism and Stroke

Lisa R. Clayville, PharmD; Katherine Vogel Anderson, PharmD; Shannon A. Miller, PharmD; and Erin L. St. Onge, PharmD

INTRODUCTION
Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a national health problem that affects more than 200,000 Americans each year. VTE causes significant morbidity and mortality, surpassed only by coronary heart disease and stroke. Atrial fibrillation, the most common arrhythmia, is responsible for one-third of embolic stroke in the U.S. VTE and atrial fibrillation more commonly affect the elderly population; therefore, the incidence of both conditions can be expected to increase as the elderly population increases in number.

Warfarin (Coumadin, Bristol-Myers Squibb) has been the mainstay of therapy for the primary and secondary prevention of VTE and for the prevention of stroke secondary to atrial fibrillation. Despite warfarin’s proven efficacy, its use is complicated by the need for routine monitoring and numerous drug and dietary interactions. Fondaparinux (Arixtra, GlaxoSmithKline) and enoxaparin (Lovenox, Sanofi-Aventis) are additional options used for VTE prevention; however, their use is limited by their parenteral formulation and cost. Additional agents for VTE and stroke prevention are necessary. An ideal anticoagulant agent would be orally administered and have few monitoring parameters, drug interactions, and adverse events. In this article, we review several oral anticoagulants that have recently been approved or are in advanced clinical development that meet these criteria.

VITAMIN K ANTAGONISTS
Vitamin K antagonists (VKAs) are the gold standard for long-term anticoagulation. Named for the organization that discovered it—the Wisconsin Alumni Research Foundation (WARF)—warfarin was approved in the U.S. in 1954. Warfarin produces its anticoagulant effect by interfering with the synthesis of vitamin K–dependent coagulation factors (II, VII, IX, and X). By inhibiting the enzyme vitamin K epoxide reductase (Figure 1), warfarin blocks the formation of vitamin K₁H₂. Without vitamin K₁H₂, the activation of vitamin K–dependent clotting factors is impossible. As a result, factors II, VII, IX, and X circulate in their inactive form and are unable to perpetuate the clotting cascade.

The benefit of warfarin is well established, but its use is hampered by numerous limitations. These include a slow onset of action, a narrow therapeutic window, numerous food–drug interactions, and inconsistencies in laboratory testing. In addition, warfarin acts as a procoagulant when it is first initiated, thereby increasing the risk of thrombosis until steady-state concentrations are achieved. These limitations mandate routine coagulation monitoring to ensure that the International Normalized Ratio (INR) is therapeutic and that the patient is receiving adequate anticoagulation.

In recent years, the relationship between patients’ genetic profiles and their responses to initial doses of warfarin has received much attention and debate. In 2007, the FDA announced labeling changes to encourage health care practitioners to consider genetic testing before initiating warfarin therapy. The vitamin K epoxide reductase (VKORC1) test can determine a person’s sensitivity to the drug. Patients with sensitivity typically require lower initial doses of warfarin than those with “resistant,” or usual, genotypes.

The cytochrome P450 (CYP) 2C9 test can also be used to estimate a patient’s rate of warfarin metabolism. Patients with a genetic variation in the CYP2C9 isoenzyme may metabolize warfarin more slowly and thus may need lower doses initially. Laboratory testing to detect these variants is not widely available; more research is needed to validate the necessity of these tests before their routine use is recommended.

POTENTIAL REPLACEMENTS FOR WARFARIN
The many limitations of VKAs have prompted extensive research to find a long-term replacement for warfarin. The most advanced clinical studies are focused on activated factor II (thrombin) and factor X. Both of these targets are logical choices. Factor X is centrally located at the convergence of the extrinsic and intrinsic coagulation pathways and, upon activation, can generate up to 1,000 thrombin molecules. Thrombin converts fibrinogen to fibrin and activates various other clotting factors, leading to the formation of a stabilized fibrin clot (Figure 2). Inhibiting either of these two targets may lead to an agent that can replace warfarin.

Direct Thrombin Inhibitors
Activation of thrombin is a key step in the formation of a stabilized fibrin clot. Intravenous (IV) formulations of direct thrombin inhibitors (DTIs) are currently used in anticoagulation but not for preventing VTE or stroke caused by atrial fibrillation or joint replacement surgery. Oral DTIs are potential...
alternatives to VKAs because of thrombin’s location in the clotting cascade, predictable pharmacokinetics, and low potential for interactions and adverse events. Two products, dabigatran etexilate capsules (Pradaxa, Boehringer Ingelheim) and AZD0837 (AstraZeneca), are described next.

**Dabigatran Etexilate (Pradaxa)**

Dabigatran etexilate, an oral DTI, has been approved in Europe and Canada for stroke and VTE prevention secondary to atrial fibrillation and joint replacement surgery, respectively. In October 2010, the FDA approved dabigatran etexilate for stroke prophylaxis with atrial fibrillation. It is the second oral product in this class to be developed. Ximelagatran (Exanta, AstraZeneca) was the first; however, its long-term use resulted in idiosyncratic liver toxicity and death, prompting its withdrawal from the market in the early 2000s.8

Dabigatran is a highly polar compound that is not orally available. As such, the prodrug dabigatran etexilate has been developed, which is rapidly absorbed and completely converted to dabigatran by hydrolysis. To provide optimal absorption in an acidic environment, each dabigatran etexilate capsule contains tartaric acid pellets, coating the drug, thereby creating an acidic microenvironment.9,10

Dabigatran is excreted renally and is not associated with the CYP 450 isoenzyme system, allowing for a low probability of drug–drug interactions.9-11 This agent is a substrate for the p-glycoprotein (p-GP) system; thus, it has been suggested that the dose can be decreased for patients who are also taking amiodarone (Cordarone, Wyeth/Pfizer), clarithromycin (Biaxin, Abbott), or verapamil (Calan, Pfizer). Coadministration of dabigatran with quinidine, a potent p-GP inhibitor, is contraindicated.

Inducers of p-GP, such as rifampin (Rifadin, Sanofi-Aventis) and St. John’s wort, may reduce the availability of dabigatran.10,11 Antacids and histamine H2 blockers do not affect the absorption of dabigatran. Although proton pump inhibitors (PPIs) may reduce the area-under-the-curve (AUC) concentration slightly, this was not found to be clinically relevant in early pharmacokinetic studies.10,11 Dabigatran etexilate may be taken without regard to meals.10,11

With an elimination half-life of 12 to 14 hours, dabigatran etexilate may be given once or twice daily, depending upon the indication.9-11 A decreased dose is recommended for patients with a creatinine clearance (CrCl) of 30 to 50 mL/minute; dabigatran is contraindicated for patients with a CrCl of less than 30 mL/minute.10,11

Although there is no recommendation for laboratory monitoring while patients are taking dabigatran, dabigatran etexilate affects ecarin clotting time (ECT), thrombin time (TT), INR, and activated partial thromboplastin time (aPTT) in a dose-independent and inconsistent manner.9-10 Therefore, laboratory values for therapeutic monitoring are not yet standardized, and these values are not reported in clinical trials. To date, there is no known antidote for dabigatran.10,11

Five published phase 3 clinical trials have compared the efficacy of dabigatran with that of warfarin and enoxaparin in the setting of stroke prevention secondary to atrial fibrillation and VTE prevention following joint replacement surgery (Table 1).12-17

*RE-LY.* The Randomized Evaluation of Long-Term Anticoagulation Therapy non-inferiority trial enrolled 18,113 patients with atrial fibrillation plus one risk factor. Patients were randomly assigned to receive either warfarin or dabigatran for stroke prophylaxis.12,13 Patients in the dabigatran group were blinded to receive a dose of 110 mg or 150 mg twice daily. Patients in the warfarin group were unblinded and were treated to an INR range of 2 to 3. Stroke or systemic embolism was the primary endpoint, which occurred at rates of 1.69% per year for warfarin and 1.53% per year with dabigatran 110 mg (P < 0.001 for non-inferiority) and 1.11% per year for dabigatran 150 mg.
New Options in Anticoagulation for Preventing VTE and Stroke

(P < 0.001 for superiority).

Rates of major bleeding were 3.36% with warfarin and 2.71% with dabigatran 110 mg (P = 0.003) and 3.11% with dabigatran 150 mg (P = 0.31). Hemorrhagic stroke occurred at rates of 0.38% per year with warfarin and 0.12% per year with dabigatran 110 mg (P < 0.001) and 0.1% per year with dabigatran 150 mg (P < 0.001). Dabigatran patients tolerated both doses well, but they experienced a significantly higher incidence of dyspepsia (P < 0.001) compared with those receiving warfarin.

There were no reports of hepatotoxicity in either dabigatran group, in contrast to previous studies that compared ximelagatran and warfarin.12 The rate of myocardial infarction (MI) was greater in both dabigatran groups; however, because this was also seen in earlier ximelagatran/warfarin studies, this finding might not be relevant.12 Given these results, the authors concluded that in patients with atrial fibrillation, dabigatran 110 mg was associated with rates of stroke similar to those associated with warfarin but with less risk of major hemorrhage. Dabigatran 150 mg was associated with lower rates of stroke and rates of hemorrhage similar to those associated with warfarin.12

RE-MODEL. This randomized, double-blind, non-inferiority trial (N = 2,076) compared dabigatran etexilate 150 or 220 mg once daily with enoxaparin 40 mg subcutaneously once daily for the prevention of VTE following total knee replacement.14 Patients receiving dabigatran started with half of a dose one to four hours following surgery, then continued with full-dose treatment once daily thereafter. Patients receiving enoxaparin started full-dose treatment the evening before surgery. Both groups continued treatment for six to 10 days and were observed for three months.

The primary endpoint was a composite of total VTE and mortality during treatment, and the primary safety outcome was the incidence of bleeding events.15 The primary endpoint occurred in 37.7% of the enoxaparin group and in 36.4% of the dabigatran 220-mg group (P = 0.0003 for non-inferiority) and in 40.5% of the dabigatran 150-mg group (P = 0.017 for non-inferiority).

There was no significant difference in major bleeding among the three treatment groups (1.3%, enoxaparin; 1.5%, dabigatran, 220 mg; and 1.3%, dabigatran 150 mg). None of the reported bleeding events were fatal.14

Specific aspects of tolerability were not reported in this trial, but adverse drug events led to discontinuation of treatment at a rate of 3.7% in both dabigatran groups and at a rate of 4.6% in the enoxaparin group.

The median duration of treatment was eight days for both dabigatran groups and seven days for enoxaparin. There was no difference in the incidence of elevated liver enzymes in any of the groups.14

Based on these results, the authors concluded that dabigatran etexilate 150 or 220 mg was at least as effective as enoxaparin with a similar safety profile following knee replacement surgery.14 RE-MODEL did not have a study site in North America. The FDA-approved dose of enoxaparin in the setting of knee replacement is 30 mg subcutaneously (SQ) every 12 hours.

RE-NOVATE. To compare the efficacy of dabigatran and enoxaparin for preventing VTE after hip-replacement surgery, investigators enrolled 3,494 patients in a double-blind non-

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Table 1  Dabigatran (Pradaxa) Clinical Trials

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>N</th>
<th>Study Duration</th>
<th>Study Drug Dosage</th>
<th>Primary Endpoint, n/N (%)</th>
<th>Absolute Difference, %, (95% CI)</th>
<th>PValue</th>
<th>Major Bleeding, n (%)</th>
<th>Clinically Relevant Non-Major Bleeding, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY12,13 Atrial fibrillation</td>
<td>18,113</td>
<td>2.0 years</td>
<td>DE 110 mg b.i.d. DE 150 mg b.i.d. W (INR 2–3)</td>
<td>182/6,015 (1.53) 143/6,076 (1.11) 199/6,022 (1.69)</td>
<td>–0.16 (NR) –0.58 (NR)</td>
<td>&lt; 0.001 a &lt; 0.001 b</td>
<td>322 (2.71) 375 (3.11) 397 (3.36)</td>
<td>NR</td>
</tr>
<tr>
<td>RE-MODEL14 Knee replacement</td>
<td>2,101</td>
<td>6–10 days</td>
<td>DE 150 mg q.d. DE 220 mg q.d. Enox 40 mg q.d.</td>
<td>213/526 (40.5) 183/503 (36.4) 193/512 (37.7)</td>
<td>2.8 (–3.1 to 8.7) –1.3 (–7.3 to 4.6)</td>
<td>&lt; 0.017 a &lt; 0.003 a</td>
<td>9 (1.3) 10 (1.5) 9 (1.3)</td>
<td>48 (6.8) 40 (5.9) 37 (5.3)</td>
</tr>
<tr>
<td>RE-NOVATE15 Hip replacement</td>
<td>3,494</td>
<td>28–35 days</td>
<td>DE 150 mg q.d. DE 220 mg q.d. Enox 40 mg q.d.</td>
<td>75/874 (8.6) 53/880 (6.0) 60/897 (6.7)</td>
<td>1.9 (–0.6 to 4.4) –0.7 (–2.9 to 1.6)</td>
<td>&lt; 0.001 a &lt; 0.001 a</td>
<td>15 (1.3) 23 (2.0) 18 (1.6)</td>
<td>55 (4.7) 48 (4.2) 40 (3.5)</td>
</tr>
<tr>
<td>RE-MOBILIZE16 Knee replacement</td>
<td>2,615</td>
<td>12–15 days</td>
<td>DE 150 mg q.d. DE 220 mg q.d. Enox 30 mg b.i.d.</td>
<td>219/649 (33.7) 188/604 (31.1) 163/643 (25.3)</td>
<td>8.4 (3.4 to 13.3) 5.8 (0.8 to 10.8)</td>
<td>&lt; 0.01 a &lt; 0.02 a</td>
<td>5 (0.6) 5 (0.6) 12 (1.4)</td>
<td>22 (2.5) 23 (2.7) 21 (2.4)</td>
</tr>
<tr>
<td>RE-COVER17 Acute VTE</td>
<td>2,539</td>
<td>6 months</td>
<td>DE 150 mg b.i.d. W (INR 2–3)</td>
<td>30/1,274 (2.4) 27/1,265 (2.1)</td>
<td>0.4 (–0.8 to 1.5)</td>
<td>&lt; 0.001 b</td>
<td>20 (1.6) 24 (1.9)</td>
<td>51 (4.0) 87 (6.8)</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; CI = confidence interval; DE = dabigatran etexilate; Enox = enoxaparin; INR = International Normalized Ratio; N = total number of subjects; n = number of events; NR = not reported; q.d. = once daily; VTE = venous thromboembolism; W = warfarin.

a = rates are % per year; b = for non-inferiority; c = for superiority; d = the margin for non-inferiority was less than 9.2%.

continued on page 93
in inferiority trial. Patients received either dabigatran 220 or 150 mg once daily or enoxaparin 40 mg SQ once daily for 28 to 35 days. As in RE-MODEL, patients receiving dabigatran were given half of a dose one to four hours after surgery and a full dose once daily thereafter. Patients who received enoxaparin were started on full-dose treatment the evening before surgery.

The primary outcome was a composite total VTE and death from all causes during treatment, occurring at the following rates: 6.7% with enoxaparin and 6% with dabigatran 220 mg (P < 0.001 for non-inferiority) and 8.6% for dabigatran 150 mg (P < 0.001).23 Bleeding, the primary safety outcome, did not differ statistically among the groups; however, there was one fatal bleeding episode in each dabigatran group and no fatal bleeding episodes with enoxaparin.24

Adverse-event profiles were similar among all three groups, resulting in discontinuation of treatment in 6% of patients receiving dabigatran 220 mg and enoxaparin and in 8% of patients receiving dabigatran 150 mg.

The median duration of treatment was 33 days. No difference was observed in the frequency of liver enzyme elevations.25 The RE-NOVATE authors stated that dabigatran was as effective as enoxaparin in reducing the risk of VTE following hip replacement surgery and had a similar safety profile.26 This trial did not have a North America study site; the FDA-approved dose of enoxaparin used for hip replacement is either 30 mg SQ every 12 hours or 40 mg SQ once daily.

RE-MOBILIZE. This randomized, double-blind, active-controlled, non-inferiority study compared dabigatran etexilate 150 or 220 mg once daily with the approved North American enoxaparin dose of 30 mg SQ twice daily for the prevention of VTE following total knee replacement.27 Patients who were assigned to either dabigatran group received half of a dose six to 12 hours after surgery, followed by a full dose once daily thereafter. Patients receiving enoxaparin began therapy the morning following surgery.

The primary efficacy outcome was a composite of total VTE events and all-cause mortality during treatment, whereas the primary safety outcome was the incidence of bleeding events. Data on 1,896 patients were analyzed.28 The incidence of VTE and death during treatment occurred in 31.1% of the dabigatran 220-mg patients, 33.7% of the dabigatran 150-mg group, and 25.3% of the enoxaparin group (P = 0.02 and P < 0.001 vs. enoxaparin, respectively).

Bleeding events were uncommon during treatment (0.6% with dabigatran 220 mg and 150 mg and 1.4% with enoxaparin). None of the bleeding events were fatal.29 All three treatments were well tolerated, and no cases of hepatotoxicity in any treatment arm were documented.

The median length of therapy for all groups was 14 days. On the basis of these results, the RE-MOBILIZE authors determined that dabigatran showed inferior efficacy to the twice-daily North American enoxaparin regimen.30 Of note, there has not been a prospective study comparing enoxaparin 30 mg SQ twice daily, started after surgery, with enoxaparin 40 mg SQ once daily, started the evening before surgery, in the setting of total knee replacement. Consequently, data comparing dabigatran with enoxaparin should be interpreted carefully. It should not be assumed that the enoxaparin regimens used in these studies are equivalent.

RE-COVER. Comparing the efficacy of dabigatran with that of warfarin in acute VTE, RE-COVER, a randomized, double-blind, non-inferiority trial, enrolled 2,564 patients with acute VTE.31 Initially, these patients had been given parenteral anticoagulation. Dabigatran patients received 150 mg twice daily, and warfarin doses were titrated to an INR of 2 to 3.

The primary outcome was a six-month incidence of recurrent VTE and related death. Safety outcomes included bleeding events, acute coronary syndrome (ACS), other adverse events, and results of liver function tests.32 In the dabigatran group, 2.4% of patients had recurrent VTE, compared with 2.1% in the warfarin group. The absolute risk difference between the groups was 0.4% (P < 0.001 for non-inferiority).

Twenty patients in the dabigatran group and 24 patients treated with warfarin experienced a major bleeding episode, with a hazard ratio (HR) of 0.82 and a confidence interval (CI) of 0.45 to 1.48. One fatal bleeding event occurred in each group.33 The incidence of ACS and abnormal liver function tests was similar in the two groups.

In terms of adverse events, 9% of patients in the dabigatran group and 6.8% of patients in the warfarin group discontinued treatment (P = 0.05). Of the adverse events reported, there were no significant differences between the groups except for the occurrence of dyspepsia, which was more common with dabigatran (2.9%) compared with warfarin (0.6%) (P < 0.001).

The incidence of GI bleeding was also common with dabigatran (53 vs. 35 warfarin patients); however, the incidence of any bleeding was lower for patients taking dabigatran (16.1%) than for those taking warfarin (21.9%) (HR, 0.71; CI, 0.59–0.85).34 For treating acute VTE, a fixed dose of dabigatran was judged to be as effective as dose-adjusted warfarin, with a similar safety profile.35

ADDITIONAL STUDIES. As of January 2011, six dabigatran trials were ongoing:

1. RELY-ABLE is an open-label extension trial in which dabigatran patients who participated in RELY will be observed over the long term.36
2. RE-NOVATE II is comparing dabigatran 220 mg once daily with enoxaparin 40 mg SQ once daily for VTE prevention in patients who have undergone hip replacement.37
3. RE-COVER II is similar to RE-COVER I; dabigatran 150 mg twice daily is compared with warfarin for the treatment of acute VTE.38
4. RE-MEDY is a randomized, double-blind study that is comparing dabigatran 150 mg twice daily with warfarin doses, titrated to an INR of 2 to 3 for VTE prevention.39
5. The objective of RE-SONATE is to compare dabigatran with placebo for secondary VTE prevention. Enrolled patients must have completed six to 18 months of treatment with a vitamin K antagonist before enrollment.39
6. RE-DEEM is a phase 2 study comparing dual-antiplatelet therapy (aspirin plus clopidogrel) with four different doses of dabigatran plus dual antiplatelet therapy for the secondary prevention of cardiac events in ACS patients.40,41

AZD-0837, a Direct Thrombin Inhibitor

Currently in development, AZD-0837 (AstraZeneca) is a prodrug of ARH-067637,42 a competitive, reversible inhibitor of free

Vol. 36  No. 2 • February 2011  •  P&T®  93
New Options in Anticoagulation for Preventing VTE and Stroke

and bound thrombin. It is a follow-up compound to ximelagatran (Exanta) without the associated liver toxicity. The half-life of AZD-0837 is nine hours. An extended-release formulation has been developed to allow for once-daily dosing.

AZD-0837 is converted to its active form through metabolism by CYP 2C9, 2C19, and 3A4. Coadministration of AZD-0837 and ketoconazole (Nizoral, Janssen), a potent CYP 3A4 inhibitor, results in a two-fold increase in the AUC concentration of AZD-0837, whereas coadministration with grapefruit juice, a weaker CYP 3A4 inhibitor, does not result in any differences.

The immediate-release form of AZD-0837 has not been found to interact with digoxin. Food does not have any effect on the AUC concentration of ARH-06737, although the drug’s time to peak concentration (Cmax) is delayed by two hours when taken with a meal. AZD-0837 is eliminated by both renal and hepatic pathways, and it affects coagulation markers ECT, TT, and aPTT; however, monitoring guidelines have not yet been established. Therefore, these values are not reported in clinical trials.

Data for AZD-0837 are limited and are derived from two dose-finding studies. In a phase 2 randomized, dose-guiding study by Lip et al. to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of extended-release AZD-0837, 955 patients with atrial fibrillation and one or more risk factors were enrolled. Patients received AZD-0837 150 mg, 300 mg, or 450 mg once daily; AZD-0837 200 mg twice daily; or warfarin adjusted to an INR of 2 to 3.

All AZD-0837 groups had either a similar or lower incidence of bleeding than the warfarin patients (5.3%–14.7% vs. 14.5%, respectively; P value reported). Of the AZD-0837 groups, those receiving 150 mg and 300 mg had the fewest clinically relevant bleeding events.

The mean duration of treatment was 138 to 145 days for those taking AZD-0837 and 161 days for those taking warfarin. Patients tolerated all treatments well, but the AZD-0837 patients experienced a higher incidence of GI distress compared with the warfarin group (23% vs. 14%, respectively). GI distress led more AZD-0837 patients (6.7%–12.5%) than warfarin patients (2.1% vs. 0.7%) to discontinue treatment.

There were no differences in liver enzyme elevations among all groups, but a 10% increase in serum creatinine was reported for AZD-0837. This increase resolved upon discontinuation of the drug.

Although the Lip study was not powered to detect a difference in stroke or VTE, the incidence was low among all groups. The authors concluded that AZD-0837 was generally well tolerated at all doses tested and postulated that the 300-mg dose might provide similar suppression of thrombogenesis with a potentially lower bleeding risk when compared with warfarin.

A second multicenter, randomized, parallel-group, dose-guiding study by Olsson et al. compared the safety and tolerability of an immediate-release formulation of AZD-0837 with warfarin. Two hundred fifty patients with atrial fibrillation plus one or more risk factor received either AZD-0837 150 mg or 350 mg twice daily or warfarin, with the dose adjusted to an INR of 2 to 3.

Six cases of total bleeding were reported for AZD-0837 150 mg, 15 cases for AZD-0837 350 mg, and eight cases for warfarin. Liver enzyme elevations were infrequent and similar in all groups. Serum creatinine levels rose by 10% from baseline in both AZD-0837 groups, but this elevation resolved upon cessation of therapy.

The highest number of adverse events was reported with AZD-0837 350 mg. More patients in this group discontinued treatment compared with other groups (13% vs. 5% for AZD-0837 150 mg; 1% for warfarin). The most common adverse events leading to discontinuation of AZD-0837 were diarrhea and nausea (11% vs. 5% for warfarin). Two patients receiving AZD-0837 350 mg withdrew from the study because of rectal bleeding.

The Olsson study was not powered to detect a difference in stroke or VTE, but no such incidents were reported in any of the groups. On the basis of these data, the authors stated that the safety and tolerability of immediate-release AZD-0837 150 mg twice daily was as good as dose-adjusted warfarin and superior to AZD-0837 350 mg twice daily.

Factor Xa Inhibitors

Generation of factor Xa stimulates the conversion of prothrombin to thrombin. Specifically, generation of a single factor Xa molecule can produce upward of 1,000 thrombin molecules. Production of factor Xa is also stimulated through the release of tissue factor. As a result of its position in the clotting cascade, inhibition of factor Xa has become a popular target in the development of new anticoagulants.

Factor Xa inhibitors are attractive treatment alternatives to warfarin because of their rapid onset of action, predictable anticoagulant effects, and low potential for food-drug interactions. Rivaroxaban (Xarelto, Ortho-McNeil/Bayer), apixaban (BMS-562247, Bristol-Myers Squibb), and edoxaban (DU-176b, Daiichi-Sankyo) have completed or are undergoing phase 3 clinical trials. Betrixaban (PRT-054021, Portola), YMI-150 (Astellas), and LY-517717 (Eli Lilly) are in preliminary studies.

Rivaroxaban

Licensed in Europe and Canada, rivaroxaban (Xarelto), an oral, direct factor Xa inhibitor, is indicated for the prevention and treatment of VTE in adults following hip or knee replacement surgery.

This small molecule is an orally bioavailable (approximately 80%), selective, and a direct inhibitor of both free and clot-bound factor Xa. By reversibly binding to factor Xa, rivaroxaban inhibits human free Xa, prothrombinase, and thrombin-bound Xa activity without the assistance of antithrombin.

Rivaroxaban exhibits predictable pharmacokinetics and pharmacodynamics. It is rapidly absorbed and reaches Cmax in two to four hours. Rivaroxaban’s half-life is five to nine hours in young, healthy subjects but may be longer in patients older than 75 years of age, allowing for once-daily or twice-daily administration.

Anticoagulant effects were similar in patients with normal body weight (70 to 80 kg) and increased body weight (more than 120 kg); however, an increased effect was seen in females weighing less than 50 kg.

Rivaroxaban is metabolized via the CYP 450 isoenzymes 3A4 and 2J2, and approximately one-third of the drug (14%–31%) is eliminated unchanged in the urine. Dosage adjustments may be needed in patients older than 75 years of age as well as in those with renal dysfunction (CrCl below 50
New Options in Anticoagulation for Preventing VTE and Stroke

Table 2 Rivaroxaban (Xarelto) Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>N</th>
<th>Study Duration</th>
<th>Study Drug Dosage</th>
<th>Primary Endpoint, n/N (%)</th>
<th>Absolute Risk Reduction, % (95% CI)</th>
<th>Bleeding, Any, n (%)</th>
<th>Bleeding, Major, n (%)</th>
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</thead>
<tbody>
<tr>
<td>RECORD 1&lt;sup&gt;14&lt;/sup&gt;</td>
<td>4,541</td>
<td>35 days</td>
<td>RIV 10 mg q.d. Enox 40 mg q.d.</td>
<td>18/1,595 (1.1)&lt;sup&gt;a&lt;/sup&gt; 58/1,558 (3.7)</td>
<td>2.6 (1.5–3.7) 133 (6)</td>
<td>131 (5.9)</td>
<td>6 (0.3) 2 (0.1)</td>
</tr>
<tr>
<td>RECORD 2&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2,509</td>
<td>31–39 days (RIV) 10–14 days (Enox)</td>
<td>RIV 10 mg q.d. Enox 40 mg q.d.</td>
<td>17/864 (2)&lt;sup&gt;a&lt;/sup&gt; 81/869 (9.3)</td>
<td>7.3 (5.2–9.4) 81 (6.6)</td>
<td>68 (5.5)</td>
<td>1 (&lt;0.1) 1 (&lt;0.1)</td>
</tr>
<tr>
<td>RECORD 3&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2,531</td>
<td>10–14 days</td>
<td>RIV 10 mg q.d. Enox 40 mg q.d.</td>
<td>79/824 (9.6)&lt;sup&gt;a&lt;/sup&gt; 166/878 (18.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.2 (5.9–12.4) 60 (4.9)</td>
<td>60 (4.8)</td>
<td>7 (0.6) 6 (0.5)</td>
</tr>
<tr>
<td>RECORD 4&lt;sup&gt;22&lt;/sup&gt;</td>
<td>3,148</td>
<td>10–14 days</td>
<td>RIV 10 mg q.d. Enox 30 mg b.i.d.</td>
<td>58/864 (6.7)&lt;sup&gt;a&lt;/sup&gt; 82/878 (9.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.19 (0.71–5.67) 160 (10.5)</td>
<td>142 (9.4)</td>
<td>10 (0.7) 4 (0.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistically significant.

b.i.d. = twice daily; CI = confidence interval; Enox = enoxaparin; N = total number of subjects; n = number of events; q.d. = once daily; RIV = rivaroxaban.

Rivaroxaban (Xarelto) Phase 3 Clinical Trials

- RECORD 1 analyzed the thromboprophylaxis potential of rivaroxaban following total hip replacement. The results showed a statistically significant reduction in the total incidence of VTE (1.1% vs. 3.7%; P < 0.001) with no difference in total (P = 0.94) non-major (P < 0.18) bleeding. 69
- RECORD 2 evaluated the long-term prophylaxis of rivaroxaban versus the short-term prophylaxis of enoxaparin following total hip replacement. When given for 31 to 39 days, rivaroxaban was more effective (P = 0.0001) than enoxaparin given for 10 to 14 days. Although there was an increased risk of bleeding in the rivaroxaban group, it was not significant (P = 0.25). 50
- RECORD 3 and RECORD 4 were conducted to assess VTE prophylaxis following total knee arthroplasty. In RECORD 3, there was a significant (P < 0.001) decrease in VTE incidence when rivaroxaban was given for 10 to 14 days versus enoxaparin, and major bleeding rates were similar between groups (0.6% vs. 0.5%, P = 0.77).
- In RECORD 4, rivaroxaban once daily was found to be superior to enoxaparin twice daily (P = 0.0118) in VTE prophylaxis following knee arthroplasty. Safety profiles were similar. 52

A prespecified pooled analysis of the RECORD program was performed in order to determine whether there was an effect on important clinical outcomes. The authors had postulated that the total number of events would be lower in the individual trials. Results of the analysis showed that once-daily rivaroxaban, compared with enoxaparin, significantly improved composite outcomes of symptomatic VTE, cardiovascular events, all-cause mortality, and major bleeding events. 53 Patients receiving rivaroxaban had a 58% reduction in symptomatic VTE and all-cause mortality (0.6% vs. 1.3%; P < 0.001) for the total treatment duration and a 52% reduction in the active treatment pool (0.5% vs. 1%; P < 0.001), with no significant increase in risk of major bleeding (0.4% vs. 0.2%; P = 0.076). 53

In terms of adverse events, the RECORD program showed a nonsignificant reduction in hepatic enzymes (AST and ALT) in the rivaroxaban group. 59-51

Preliminary phase 1 studies reported nonsignificant incidences of headache, diarrhea, fatigue, flatulence, and dizziness with rivaroxaban, but these effects were not quantified in later trials. 20 Interactions typically seen with current anticoagulants and medications, such as digoxin, naproxen (Naprosyn, Roche), aspirin, clopidogrel (Plavix (Bristol-Myers Squibb/Sanoﬁ-Aventis), and abciximab (ReoPro, Eli Lilly) do not affect rivaroxaban. More studies are needed to evaluate the effect of food and other drugs on rivaroxaban’s pharmacokinetics and pharmacodynamics. 29

EINSTEIN: Rivaroxaban is undergoing further phase 3 clinical trials for additional indications. For VTE treatment, the Einstein program (Evaluating oral, direct Factor Xa Inhibitor rivaroxaban in patients with acute Symptomatic deep vein thrombosis or pulmonary embolism) is conducting three additional studies (Einstein-DVT 2, Einstein-PE, and Einstein-
Study Drug Dosage

The extension study compares rivaroxaban 20 mg daily with placebo for six to 12 months. While the PE study is ongoing, data from the DVT and extension studies have been published. In looking for the incidence of current VTE, the researchers noted that rivaroxaban was non-inferior to enoxaparin–warfarin (2.1% vs. 3%; P < 0.001) in the DVT study and superior to placebo (1.3% vs. 7.1%; P < 0.001) in the extension study.

ROCKET–AF. Rivaroxaban 20 mg daily (15 mg daily if the CrCl is 30 to 49 mL/minute) is being compared with warfarin for stroke prevention in patients with atrial fibrillation. This trial (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) is scheduled to last a maximum of four years, depending on the occurrence of adverse events.

MAGELLAN. Rivaroxaban 10 mg daily for 35 days was compared with enoxaparin 40 mg daily for 10 days in 8,000 medically ill patients. This trial (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of VTE in hospitalized medically ill patients comparing rivaroxaban with enoxaparin) has been completed.

ATLAS–ACS TIMI 51. Rivaroxaban 2.5 or 5 mg twice daily taken for six months was compared with placebo for the prevention of post-ACS cardiac events. The Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without ticlopidine or prasugrel in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction trial is completed.

Apixaban
Apixaban (BMS-562247) is another oral, direct factor Xa inhibitor undergoing clinical trials for the prevention and treatment of VTE, stroke prevention secondary to atrial fibrillation, and secondary prophylaxis in acute coronary syndromes.

The oral bioavailability of apixaban is 50% to 85%. Peak plasma concentrations are reached in three hours. The agent’s terminal half-life is eight to 15 hours, and it is metabolized primarily via the CYP 450 isoenzyme 3A4. It is excreted via the kidneys (25%) and feces (70%). It selectively and reversibly inhibits free and prothrombinase-bound Xa activity without the assistance of antithrombin III.

Three phase 2 clinical trials of apixaban have been completed. An additional study is being conducted to evaluate VTE prophylaxis in patients with metastatic cancer.

APROPOS. The Apixaban PROphylaxis in Patients undergoing Total Knee Replacement Surgery study examined the safety and efficacy of apixaban following knee arthroplasty. Twelve hundred seventeen patients received apixaban 5, 10, or 20 mg once daily or divided into two doses; enoxaparin 30 mg SQ twice daily; or warfarin for 10 to 14 days.

All apixaban groups experienced a significantly lower incidence of VTE compared with both enoxaparin (P < 0.02) and warfarin (P < 0.001), leading to a relative risk reduction of 21% to 69% (versus enoxaparin) and 53% to 82% (versus warfarin), respectively. There was no significant difference between groups in terms of bleeding risk; however, there was a dose-related increased risk of bleeding in the apixaban group.

BOTTICELLI–DVT. This dose-ranging study compared apixaban 5 to 10 mg twice daily or 20 mg daily with standard low-molecular-weight heparin/vitamin K antagonist (LMWH/VKA) therapy for 84 to 91 days as initial treatment for acute symptomatic DVT. Standard therapy was defined as enoxaparin 1.5 mg/kg daily, enoxaparin 1 mg/kg twice daily, tinzaparin (Innohep, Celgene) 175 units/kg daily, or fondaparinux (Arixtra, GlaxoSmithKline) plus either warfarin, phenprocoumon (Marcoumar, Organon), or acenocoumarol.

The primary outcomes of recurrent symptomatic VTE or asymptomatic thrombus deterioration, observed via ultrasound or lung perfusion scan, were observed in 4.7% of patients in the apixaban group and 4.2% in the conventional therapy group. There was no significant difference in safety outcomes. The study investigators concluded that apixaban exhibits a similar safety and efficacy profile as standard LMWH/VKA therapy.

APPROISE. The Apixaban for PREvention of Acute Ischemic and Safety Events dose-ranging study investigated bleeding risk associated with apixaban versus placebo in patients with recent STEMI and NSTEMI. Four dosing reg-

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>N</th>
<th>Study Duration</th>
<th>Study Drug Dosage</th>
<th>Primary End Point, n/N (%)</th>
<th>Absolute Risk Reduction, % (95% CI)</th>
<th>Bleeding, Any, n (%)</th>
<th>Bleeding, Major, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE-1 (NM)</td>
<td>3,202</td>
<td>10–14 days</td>
<td>Apixaban 2.5 mg b.i.d. Enox 30 mg b.i.d.</td>
<td>104/1,157 (9) 100/1,130 (8.8)</td>
<td>0.11 (~2.22 to 2.44)</td>
<td>85 (5.3)</td>
<td>108 (6.8)</td>
</tr>
<tr>
<td>ADVANCE-2 (NL)</td>
<td>3,053</td>
<td>10–14 days</td>
<td>Apixaban 2.5 mg b.i.d. Enox 40 mg q.d.</td>
<td>147/976 (15.1) 243/997 (24.4)</td>
<td>9.3 (5.79–12.74)</td>
<td>104 (6.9)</td>
<td>126 (8.4)</td>
</tr>
<tr>
<td>ADVANCE-3 (NL)</td>
<td>3,866</td>
<td>35 days</td>
<td>Apixaban 2.5 mg b.i.d. Enox 40 mg q.d.</td>
<td>27/1,949 (1.4) 74/1,917 (3.9)</td>
<td>2.5 (1.5–3.5)</td>
<td>313 (11.7)</td>
<td>334 (12.6)</td>
</tr>
</tbody>
</table>

* Statistically significant.

b.i.d. = twice daily; CI = confidence interval; Enox = enoxaparin; N = total number of subjects; n = number of events; q.d. = once daily.
New Options in Anticoagulation for Preventing VTE and Stroke

imens were used initially (2.5 mg twice daily, 10 mg daily, 10 mg twice daily, and 20 mg daily); however, the two higher dosing groups withdrew because of excessive bleeding. Results indicated a dose-dependent increase in major or clinically relevant non-major bleeding events.63

ADVANCE. Data on apixaban are available for three phase 3 clinical trials, ADVANCE 1, 2, and 3 (Table 3).64–66 The Apixaban Dose orally Versus Anticoagulation with Enoxaparin program is a series of studies evaluating apixaban versus enoxaparin following either knee or hip replacement surgery.

ADVANCE-1, a non-inferiority trial, compared apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily for 10 to 14 days in 3,202 patients following knee arthroplasty. Similar efficacy data were noted in both groups (VTE incidence, 9% apixaban vs. 8.8% enoxaparin).64

ADVANCE-2 compared apixaban 2.5 mg twice daily with enoxaparin 40 mg once daily for 10 to 14 days in 3,053 patients who underwent knee arthroplasty. Apixaban was shown to be superior to enoxaparin (15.1% vs. 24.4; P < 0.001) as thromboprophylaxis with an absolute risk reduction of 9.3% and a trend toward less bleeding (3.5% vs. 4.8%, P = 0.09).65

ADVANCE-3, a double-blind, double-dummy study in 3,866 patients, evaluated apixaban 2.5 mg twice daily and enoxaparin 40 mg once daily for 35 days. Apixaban was shown to be superior to enoxaparin (1.4% vs. 3.9%, P < 0.001) in decreasing the risk of asymptomatic or symptomatic DVT, nonfatal PE, or death, with an absolute risk reduction of 2.5% and a lower incidence of bleeding (11.7% vs. 12.6%, P = 0.34).66

The following phase 3 apixaban trials are under way:18

- in medically ill patients: ADOPT
- as VTE treatment: Apixaban VTE and Apixaban VTE extension
- as secondary prevention for those with ACS: APPRAISE 2
- as stroke prevention in those with atrial fibrillation: AVERROES (Apixaban VERsus Aspirin to Reduce the Risk Of StrokE) and ARISTOTLE.

Edoxaban

Edoxaban (DU-176b), an oral direct factor Xa inhibitor, has been evaluated in two phase 2 clinical trials and is now in phase 3. Similar to the other direct factor Xa inhibitors described, it is rapidly absorbed (median time to peak concentration [Tmax] =1–1.5 hours), highly selective, inhibits both free and clot-bound factor Xa. It exhibits a dual mode of elimination. Its half-life is nine to 11 hours.67,68

Edoxaban has been evaluated as an option for VTE prophylaxis following orthopedic surgery in two separate phase 2 trials. Compared to placebo, edoxaban reduced VTE incidence following knee replacement surgery without a clinically significant bleeding risk.69,70 Compared with dalteparin (Fraxmin, Pfizer) following hip arthroplasty, edoxaban showed a 20% lower incidence of VTE along with a nonsignificant increased risk of bleeding.69,70 In a phase 2 trial involving patients with atrial fibrillation, once-daily edoxaban was associated with fewer bleeding events compared with twice-daily administration.71

ENGAGE-AF TIMI 48. Edoxaban is being evaluated in the phase 3 Effective aNTicoaGulation with FActor Xa next GEneration in Atrial Fibrillation trial. Edoxaban 30 to 60 mg once daily is being compared with warfarin (titrated to an INR of 2 to 3) for the prevention of stroke and systemic embolic events in approximately 16,500 patients.71

Other Factor Xa Inhibitors

Several factor Xa inhibitors are in the early stages of clinical development, including betrixaban, YM-150, and LY-517717.

Betrixaban. PRT-054021 is an orally bioavailable, selective, direct factor Xa inhibitor, which has been evaluated in one phase 2 trial.54,72 With a half-life of approximately 20 hours, betrixaban is administered once daily. This agent effectively inhibits both free and clot-bound Xa activity.72 With no liver metabolism reported and being predominantly excreted unchanged in bile, the chance of food–drug interactions is minimal.72 EXPERT was the first trial evaluating the efficacy of betrixaban, enrolling 215 patients undergoing elective total knee replacement surgery. Patients received either betrixaban 15 or 40 mg daily or enoxaparin 30 mg SQ twice daily as VTE prophylaxis for 10 to 14 days. Overall, the incidence of VTE was 20% with betrixaban 15 mg, 15% with betrixaban 40 mg, and 10% with enoxaparin. There was no statistical difference in bleeding risk between the groups.72

YM-150. YM-150 (Astellas) directly inhibits free, prothrombinase, and clot-bound Xa activity. It has been evaluated in two dose-ranging studies for VTE prophylaxis.68 In the first study, YM-150 at doses of 3, 10, 30, and 60 mg once daily was compared with enoxaparin 40 mg SQ once daily for seven to 10 days in 174 patients undergoing hip arthroplasty. The investigators found a significant difference in VTE incidence favoring the use of YM-150 (32.8% vs. 38.7%, respectively; P = 0.006) with no major bleeding and a low rate of clinically non-major bleeding.73

ONYX-2, a dose-finding trial (Factor Xa Inhibitor YM-150 for the Prevention of Blood Clot Formation in Veins After Sched- uled Hip Replacement), evaluated YM-150 at doses of 5, 10, 30, 60, or 120 mg daily versus enoxaparin 40 mg SQ daily for five weeks (N = 1,017). Results showed a significant dose-related decrease in the rate of VTE with YM-150 (P = 0.0002). Based on these results, the investigators concluded that YM-150 at doses of 30 to 120 mg daily had a similar efficacy to enoxaparin with no change in bleeding risk.74

LY-517717. A selective, direct inhibitor of factor Xa, LY-517717 (Eli Lilly) reaches peak effectiveness in 0.5 to 4 hours following oral administration. Its terminal half-life is approximately 25 hours. The drug is eliminated primarily via the GI tract.58,75,76

LY-517717 was studied to determine its safety and efficacy in VTE prevention in 507 patients undergoing either total knee or hip replacement surgery. Initially, LY-517717 25, 50, or 75 mg once daily was compared with enoxaparin 40 mg SQ daily; however, LY-517717 doses of 100 to 150 mg daily were added after the investigators realized that the lower doses were not sufficiently effective and did not cause excessive bleeding. They noted a significant dose-dependent decrease in VTE rates (19% for 25 mg, 19% for 50 mg, and 16% for 100, 125, and 150 mg vs. 21% for enoxaparin; P = 0.001). A dose of 100 to 150 mg was found to be non-inferior to enoxaparin after hip or knee arthroplasty. Bleeding profiles were similar.76
New Options in Anticoagulation for Preventing VTE and Stroke

CONCLUSION

VTE and stroke are significant causes of morbidity and mortality in the U.S. Although warfarin has been the cornerstone of therapy for the prevention of stroke secondary to atrial fibrillation and for the prevention and treatment of VTE following joint replacement surgery, its use is complicated by its numerous drug and dietary interactions, as well as its constant need for close monitoring.

The development of oral direct thrombin inhibitors and factor Xa inhibitors may give clinicians additional options when choosing an anticoagulant. The evidence surrounding each of these classes appears promising. Future research will further elucidate the role of these medications in managing patients who require anticoagulation.

REFERENCES

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