REVIEW ARTICLE

Review of New Oral Anticoagulants

Lindsay Frye, DO; Heather Katz, DO; Natasha Bray, DO; Barry Berman, MD
Broward Health Medical Center, Fort Lauderdale, FL

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New oral anticoagulants have been developed over the past several years. These include the factor Xa inhibitors and direct thrombin inhibitors. These anticoagulants have been tested for safety and efficacy against standard therapies including subcutaneous enoxaparin or oral warfarin. The following is a review of pertinent trials comparing the new oral anticoagulants to standard therapy.

INTRODUCTION

Disorders of venous thromboembolism (VTE) have plagued physicians for hundreds of years. For the past half century the only oral treatment available for prevention and treatment of these diseases was warfarin. While warfarin is certainly effective, it is cumbersome requiring diet restrictions, close monitoring of international normalized ratio (INR), and avoidance of medications that potentially interact with its metabolism. The beneficial effects of warfarin in preventing VTE are undeniable, however, so are its bleeding risks. Practitioners have had to closely weigh the risk of bleeding with the potential therapeutic effects of anticoagulation with warfarin which can be quite difficult in certain patients.

Over the past decade, pharmaceutical companies have been developing new oral anticoagulants which affect different steps in the coagulation cascade than the traditional vitamin K antagonists. For the first time, there is a choice with regards to oral anticoagulation therapy. This leaves us to wonder, what is desired in the 'perfect oral anticoagulant'? Some desirable characteristics include: once daily oral dosing, predictable pharmacokinetics, low rates of interactions with other medications, no need for routine monitoring, low risk of bleeding, reliable and readily available reversal agents, affordable, low side effect profile, and no need for renal/hepatic dose adjustments. The new oral anticoagulants are more costly than warfarin, however it is difficult to compare the cost/benefit analysis. The need to monitor warfarin and the risks of suboptimal or supratherapeutic anticoagulation with warfarin need to be weighed against the cost and risks of the new agents. Patient characteristics are the strongest predictors of the cost/benefit ratio of each anticoagulant.

Currently there are more oral anticoagulants than before and each has its own unique desirable qualities. There are no head-to-head studies comparing these new medications to each other. Therefore, it is impossible to determine which agent is the best. However, many of the new oral anticoagulants have had promising results when compared to warfarin. The new oral anticoagulants' pharmacokinetic properties include rapid onset/offset of action, few drug interactions, and predictable pharmacokinetics, and eliminate the requirement for regular laboratory monitoring. The following is a summary of the major trials examining each new oral anticoagulant. Individually, each new oral anticoagulant was evaluated for the following indications: stroke prevention in non-valvular atrial fibrillation (AFIB), deep vein thrombosis (DVT) prevention after orthopedic surgery, and treatment of DVT or pulmonary embolism (PE).

DABIGATRAN

Dabigatran etexilate, Pradaxa®, is a direct thrombin inhibitor. The indications studied include anticoagulation for non-valvular atrial fibrillation, prevention of venous thromboembolism and treatment of deep vein thrombosis or pulmonary embolism. The usual dosage is 150 mg by mouth twice daily however, since dabigatran is excreted primarily through the urine, patients with a creatinine clearance of 15-30 mL/min use a lower dose of 75 mg by mouth twice daily. Use with caution in patients greater than 75 years old, have renal issues or have a bleeding risk. The half life of dabigatran is 12–17 hours, and due to its predictable pharmacokinetics does not need to be routinely monitored.

Address correspondence to: Lindsay Frye, DO, Broward Health Medical Center, 1600 S Andrews Avenue, Fort Lauderdale, FL 33316; Phone: (717) 491-7938; E-Mail: lfrye@browardhealth.org

The trials that demonstrate the efficacy and safety of dabigatran are summarized below.

Stroke Prevention in Non-valvular Atrial Fibrillation

The Randomized Evaluation of Long term anticoagulant therapy, RE-LY, trial was a randomized, partially blinded (warfarin was open, dabigatran was closed) phase III study, non-inferiority trial that compared the efficacy and safety of two different doses of dabigatran, 110 mg and 150mg, to warfarin with a dose adjusted INR of 2-3, in patients with non-valvular atrial fibrillation[1]. 18,113 patients with atrial fibrillation and at increase risk of stroke were enrolled in the study[1]. The primary endpoint, stroke or systemic embolism, occurred in 1.53% of patients given 110 mg of dabigatran twice daily, in 1.11% of patients given dabigatran 150 mg twice daily and in 1.69% of patients given warfarin[1]. The study revealed that both doses of dabigatran were non-inferior to warfarin in reducing rates of stroke or systemic embolism, however dabigatran 150mg twice daily was statistically superior[1]. Both the 110 mg and 150mg dose of dabigatran (0.12%, 0.10% of patients respectively) showed a significantly lower annual rate of hemorrhagic strokes than warfarin (0.38%)[1]. Major bleeding occurred in 2.71% of patients receiving dabigatran 110 mg twice daily, 3.11% in patients receiving 150 mg of dabigatran twice daily and 3.36% in patients receiving warfarin with the lower dose having statistically less major hemorrhage and the higher dose with similar rates[1]. There was a statistically significant increase in dyspepsia and gastrointestinal bleeding in the dabigatran groups compared to the warfarin group[1].

In 2013, RELY-ABLE trial was released. The purpose of this trial was to evaluate the long term safety of dabigatran at the dosages used in the RE-LY trial. It was a randomized, phase II safety study that enrolled 5,851 patients greater than or equal to 18 years old with atrial fibrillation who had participated in the RE-LY trial[2]. The results of the trial showed that during the 2.3 years of continued treatment after the RE-LY trial, there was no significant difference in stroke or mortality comparing dabigatran 150mg twice daily to 110 mg twice daily[2]. Dabigatran 150mg twice daily did have a higher rate of major and minor bleeding.[2] Net clinical benefit was examined between the two doses of dabigatran and was found to be similar: high dose dabigatran demonstrated superior efficacy in preventing embolic stroke while increasing major bleeding, and low dose dabigatran was less effective at preventing embolic stroke with lower bleeding risks[2].

Prevention of Venous Thromboembolism

The RE-MODEL trial was a randomized, double blinded study that compared oral dabigatran to subcutaneous enoxaparin for the prevention of VTE after total knee replacement. 2101 patients were involved in the study[3]. Dabigatran 150 mg or 220 mg by mouth once daily starting 1-4 hours after surgery for 6–10 days was compared to enoxaparin 40 mg subcutaneous daily, starting the evening before surgery for 6 -1 0 days[3]. The primary endpoint (DVT, symptomatic PE, or death) occurred in 40.5% of patients given dabigatran 150 mg daily, 36.4% in patients given dabigatran 220 mg and 37.7% in patients receiving enoxaparin[3]. Both doses of dabigatran were found to be statistically non-inferior to subcutaneous enoxaparin with regards to efficacy[3]. Major bleeding was similar between each group[3].

A similar randomized, double blind trial known as RE-NOVATE, compared dabigatran to enoxaparin for prevention of VTE after total hip replacement with anticoagulation lasting 28–35 days. 3,494 patients were enrolled in this study[4]. VTE or death from any cause occurred in 8.6% of those taking dabigatran 150 mg, 6.0% of those taking dabigatran 220 mg and 6.7% of those given enoxaparin[4]. The similar results among the 3 groups proved once again that dabigatran was not statistically inferior to enoxaparin for the prevention of VTE in the setting of hip replacements. The rates of minor and major bleedings with the dabigatran 150 mg, 220 mg or the enoxaparin 40 mg was comparable in all 3 study groups, 1.3%, 2.0% and 1.6%, respectively[4].

The RE-NOVATE II trial in 2011 was a randomized, double blind study that compared dabigatran 220 mg daily for 28-35 days verses enoxaparin 40 mg subcutaneously for 28-35 days for thromboprophylaxis after total hip arthroplasty. 2,055 patients age 18 years or older scheduled for a total hip arthroplasty were involved in this study[5]. VTE or death from any cause occurred in 7.7% of those given dabigatran and 8.8% of those given enoxaparin which was not statistically different[5]. Risk of bleeding was statistically similar in both groups[5].

The RE-MOBILIZE trial, that consisted of 2,615 patients scheduled for elective total knee replacement, compared dabigatran 150mg or 220 mg daily for 12–15 days versus enoxaparin 30 mg subcutaneous twice daily for 12-15 days for prevention of venous thromboembolism after knee arthroplasty[6]. This randomized, double blind study showed that combined incidence of VTE and death was higher in patients treated with both doses of dabigatran (33.7%, 31.1%) compared to enoxaparin (25.3%)[6]. Although inferior to enoxaparin in VTE events or death, major bleeding events were seen more frequently in those receiving enoxaparin[6].

Treatment of DVT/PE

The RE-COVER trial was a randomized, double blind study involving 2,539 patients, that compared dabigatran 150 mg twice daily to dose-adjusted warfarin with a target INR of

2-3 as treatment in the setting acute VTE[7]. Both groups were initially treated with 5 days ofparenteral anticoagulation with low molecular weight or unfractionated heparin[7]. Symptomatic VTE and VTE related deaths occurred in 2.4% of patients given dabigatran 150 mg twice daily and in 2.1% of patients given dose-adjusted warfarin[7]. Dabigatran was non-inferior to warfarin in the prevention of recurrent or fatal VTE in patients with acute VTE[7]. Patients on dabigatran also had significantly lower rates of major and clinically relevant non-major bleeding events, 5.6%, compared to 8.8% in those taking warfarin[7].

In 2013, the RE-COVER II trial was a randomized, double blind, double dummy, phase III, non-inferiority study with 2,568 patients that was done to confirm the results of RE-COVER I. After 6 months, 2.3% of patients on dabigatran had recurrent fatal or non-fatal VTE compared with 2.2% of patients on warfarin[8]. This proved once again that dabigatran was non-inferior to warfarin for treatment of acute VTE. Rates of bleeding favored dabigatran, 15.6% over warfarin, 22.1%[8].

RIVAROXABAN

Rivaroxaban, Xarelto® is a factor Xa inhibitor which has come onto the market in recent years. It reaches peak plasma concentrations within 2-4 hours with a half life of 5-9 hours. It is about 50% excreted by renal route requiring dose adjusted in patients with renal insufficiency, and should be avoided in patients with severe renal insufficiency. It is currently FDA approved for VTE prophylaxis post orthopedic surgery, treatment of DVT/PE, and stroke prevention in non-valvular afib. Rivaroxaban dosage in prevention of non-valvular afib is 20mg by mouth daily. The usual dose for DVT prophylaxis is 10mg by mouth daily. Treatment dose for DVT/PE includes 15mg by mouth twice daily for the first 21 days followed by 20mg by mouth daily. The 15mg and 20mg doses should be taken with food. There is no need for routine blood monitoring.

The following summarizes the trials analyzing the efficacy and safety of rivaroxaban.

Stroke Prevention in Non-valvular Atrial Fibrillaion

The study which prompted the FDA to consider Rivaroxaban for the prevention of strokes and embolic phenomena in non-valvular atrial fibrillation is the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolization Trial in Atrial Fibrillation (ROCKET-AF). This was a multicentered, randomized, double blind, double dummy, event driven trial which included 1,178 participants in 45 countries[9].

To be included in this study, participants must have atrial fibrillation documented on electrocardiogram and have had a history of stroke, TIA, systemic embolization or a CHADS2 score of at least 2[9]. Trial participants were assigned to either a 20mg once daily oral dose of rivaroxaban or a 15mg once daily oral dose if creatinine clearance of 30-49 ml/min, or warfarin dose adjusted to a target INR 2-3[9]. The mean duration of therapy was 590 days[9].

The primary efficacy endpoint which included stroke (ischemic or hemorrhagic) and systemic embolization occurred in 1.7% per year of rivaroxaban patients and 2.2% per year in warfarin patients which significantly met criteria for non-inferiority[9]. The principal safety outcome of the trial was major and clinically relevant non-major bleeding. The principal safety outcome occurred in 14.9% per year of rivaroxaban patients and 14.5% per year of warfarin patients, which was not a significant difference[9]. Decreases in hemoglobin of more than 2 grams/dL and blood transfusions occurred more frequently in rivaroxaban group[9]. However, rates of intracranial bleeding and fatal bleeding were significantly less frequent in the rivaroxaban arm[9]. Conversely, GI bleeding occurred more frequently in the rivaroxaban group[9].

Prevention of Venous Throboembolism

Rivaroxaban was examined for prevention of VTE in 2008 in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (RECORD 1 trial). This was a randomized multinational double blinded trial enrolling 4,591 patients[10]. This study included patients undergoing elective total hip arthroplasty. After surgery, patients were randomized to receive either 10mg oral rivaroxaban daily versus 40mg subcutaneous enoxaparin daily[10]. Primary outcomes included any DVT, non-fatal PE, and death from any cause up to 36 days[10]. Safety outcomes included major and clinically significant non-major bleeding[10]. The primary efficacy outcome occurred in 0.8% of patients in the rivaroxaban group and 3.4% of patients in the enoxaparin group which met the non-inferiority margin[10]. The combined incidence of major and clinically relevant non-major bleeding occurred in 3.2% of rivaroxaban group and 2.5% in the enoxaparin group[10]. Incidence of hemorrhagic wound complications and the number of blood transfusions were similar in both treatment arm[10].

RECORD 2 was another trial analyzing VTE prevention in 2,509 patients undergoing total hip arthroplasty[11]. This trial examined extended duration rivaroxaban (31-39 days) versus short term enoxaparin (10-14 days) in patients post hip arthroplasty[11]. The same doses of each medication were used as in RECORD 1 and primary efficacy outcomes were the same as well. In this trial, extended dose rivaroxaban was found to be significantly more effective at preventing venous thromboembolism than short dose enoxaparin[11].

RECORD 3 and 4 published in 2008 and 2009 respectively analyzed rivaroxaban in prevention of VTE in patients receiving total knee arthroplasty. The RECORD 3 trial enrolled 2,531 patients undergoingtotal knee arthroplasty and randomized them to receive either rivaroxaban 10mg by mouth daily starting 6-8 hours post surgery or enoxaparin 40mg subcutaneously daily starting 12 hours before surgery[12]. Primary outcomes which included DVT, PE, or death from any case 13-17 days after surgery occurred in 9.6% of patients in the rivaroxaban arm and 18.9% of patients in the enoxaparin arm demonstrating non-inferiority of rivaroxaban[12]. The combined incidence of major and clinically relevant non-major bleeding events was similar in the two groups[12].

RECORD 4 trial enrolled 3,148 patients who were randomized to receive once daily 10mg rivaroxaban dose initiated 6-8 hours post knee replacement versus enoxaparin 30mg subcutaneous twice daily dose initiated 12-24 hours after surgery[13]. The primary efficacy outcome which was DVT, PE, or any cause of death within 17 days of surgery occurred in 6.9% of patients in rivaroxaban group, and 10.1% in enoxaparin group demonstrating that rivaroxaban was significantly superior to enoxaparin in preventing venous thromboembolism post knee surgery[13]. Major bleeding was similar between the two treatment groups[13].

Due to the RECORD 1-4 trials, the FDA approved rivaroxaban for administration 6-10 hours post surgery for prevention of venous thromboembolism post hip/knee surgery.

Treatment of DVT/PE

With oral rivaroxaban being shown to prevent DVT in patients after surgery, it was next the aim of investigators to examine rivaroxaban's efficacy in treatment of DVT and PE. The EINSTEIN investigators examined three trials which analyzed the efficacy of rivaroxaban in treatment of DVT and PE.

EINSTEIN DVT was a randomized open label study enrolling 3,449 participants[14]. Patients included had an acute objectively confirmed DVT without signs or symptoms of PE[14]. Patients were treated with Rivaroxaban 15mg by mouth twice daily for three weeks then switched to rivaroxaban 20mg by mouth daily versus standard therapy during which patients were treated with subcutaneous lovenox 1mg/kg body weight with simultaneous warfarin therapy until INR reached 2-3 for at least 2 consecutive days with at least 5 days of treatment with enoxaparin[14].

These groups were analyzed at 3, 6, and 12 months[14]. 3499 patients underwent randomization[14]. During the study, the primary efficacy outcome which included symptomatic recurrent VTE, DVT, or non-fatal PE occurred in 2.1% of rivaroxaban patients and 3.0% in standard therapy patients which met the non-inferiority margin[14]. The principal safety outcome which included major and clinically relevant non-major bleeding occurred in 8.1% of rivaroxaban patients and in 8.1% of standard therapy with no statistical difference[14].

The EINSTEIN PE study was a randomized, open-label, event driven, non-inferiority trial which examined the efficacy and safety of rivaroxaban as compared with vitamin K antagonists in patients who had an acute symptomatic pulmonary embolism with or without DVT[15]. The primary efficacy outcome was symptomatic recurrent VTE. The principal safety outcome was major or clinically relevant non-major bleeding. Patients were randomized to standard therapy of enoxaparin 1mg/kg body weight subcutaneous injection twice daily with simultaneous dose adjusted warfarin until therapeutic INR (2-3) was achieved for 2 consecutive days with at least 5 days treatment with enoxaparin[15]. 4832 patients were enrolled in the study[15]. The primary efficacy outcome occurred in 2.1% of the rivaroxaban group versus 1.8% in the standard- therapy group demonstrating that rivaroxaban is non-inferior to standard therapy in the treatment of PE[15]. The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group which was found to be statistically similar[15].

There was another group that was analyzed called the Extended Treatment group in which 1,197 patients were enrolled. The purpose of this group was to explore the long term benefit to risk ratio of anticoagulation with rivaroxaban in prevention of VTE. These patients were enrolled in either the Acute DVT study or the Acute PE study or were enrolled from outside the study. These patients completed 6-12 months of either rivaroxaban therapy or warfarin therapy for a confirmed DVT[14,15]. They were then randomized to either rivaroxaban 20mg by mouth daily or placebo for a following 6-12 months[14,15]. The primary efficacy outcome in this group was symptomatic recurrent VTE and was seen in 1.3% of the rivaroxaban group and 7.1% in the placebo group[14,15]. Major and non-major bleeding occurred in 0.7% of the rivaroxaban group and none occurred in the placebo group.[14,15]

APIXABAN

Apixaban, also known as Eliquis, is a Factor Xa inhibitor. The indications for use include anticoagulation for non-valvular atrial fibrillation, prevention of venous thromboembolism and treatment of deep vein thrombosis or pulmonary embolism. The usual does for apixaban is 5 mg by mouth twice daily. The dose is decreased to 2.5 mg by mouth twice daily in patient with at least 2 of the following: greater than 80 years old, less than 60 kg, or creatinine of greater than 1.5mg/dL. Apixaban is adjusted for creatinine of greater than 1.5mg/dL, and if the patient has severe hepatic impairment apixaban should be

avoided. The half-life of apixaban is 12 hours. Apixaban does not require routine blood monitoring.

The trials that demonstrate the efficacy and safety of apixaban in these situations are summarized below. Stroke Prevention in Non-valvular Atrial Fibrillation

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was a randomized, double blind study that compared apixaban 5 mg by mouth twice daily for up to 39 months to dose adjusted warfarin with an INR of 2.0-3.0 in preventing stroke and systemic embolism in patients with atrial fibrillation[16]. A lower dose of apixaban, 2.5 mg by mouth daily, was used in patients who have two of the following criteria: 80 years or older, have a body weight of 60 kg or less or a serum creatinine level of 1.5 mg/dL or more[16].

18,201 patients were involved in the study[16]. They had atrial fibrillation and at least one additional risk factor for stroke[16]. 1.60% of patients on warfarin had a stroke or systemic embolism compared to 1.27% of patients on apixaban[16]. This was statistically significant thus, apixaban was superior to warfarin in preventing stroke or systemic embolism[16]. The rate of hemorrhagic stroke was statistically lower in patients on apixaban (0.24% per year) compared to those receiving warfarin (0.47% per year)[16]. The rate of ischemic stokes was similar within the two groups, 0.97% for those assigned to apixaban and 1.05% for those assigned to warfarin[16]. Death occurred less frequently in patients on apixaban (3.52% per year) compared to warfarin (3.94% per year)[16]. There was less major bleeding in the apixaban group (2.13% per year) than in the warfarin group (3.09% per year)[16].

The AVERROES trial was a randomized, double blind study that compared apixaban to acetylsalicylic acid (ASA). The data and safety monitoring board recommended early termination of the study because apixaban was clearly superior to ASA in preventing stroke or systemic embolism exceeding 4 standard deviations[17]. Apixaban 5 mg by mouth twice daily for up to 36 months or the end of the study was compared to ASA 81-324 mg by mouth once daily for 36 months or the end of the study for prevention of ischemic or hemorrhagic stroke in patients with atrial fibrillation[17]. 5,599 patients 50 years or older with atrial fibrillation and increased risk for stroke who are not suitable for vitamin K antagonist therapy were included in this study[17]. Events occurred 1.6% per year in patients taking apixaban versus 3.7% taking ASA[17]. There was no significant difference between major bleeding events when comparing the two groups, 1.4% per year with those taking apixaban and 1.2% with those taking ASA[17].

Prevention of Venous Thromboembolism

The ADVANCE-1 trial, was a randomized, double blind study of 3,195 patients scheduled for elective total knee replacement[18]. This trial compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after surgery for 10–14 days compared to enoxaparin 30 mg subcutaneous every 12 hours, 12-24 hours after surgery for 10–14 days in patient who had elective total knee replacements[18]. VTE and death from any cause occurred in 9.0% of patients given apixaban compared to 8.8% of patients given enoxaparin[18]. Although the rate of events was similar, the statistical criteria for non-inferiority was not met by apixaban however, apixaban was superior to enoxaparin in major bleeding[18].

The ADVANCE – 2 trial was a randomized, double blind study preformed to try to prove non- inferiority of apixaban compared to enoxaparin in prevention of VTE after total knee replacement[19]. 3,057 patients that were scheduled for elective total knee replacement were involved in this trial[19]. This trial compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after surgery for 10–14 days to enoxaparin 40 mg subcutaneously 12 hours preoperatively and then once daily starting 12–24 hours after surgery and continued for 10–14 days[19]. 15.1% of patients given apixaban and 24.4% of patients given enoxaparin had a venous thromboemoblic event proving that apixaban 2.5 mg by mouth twice daily was superior to enoxaparin 40 mg subcutaneous daily for prevention of VTE(19). Major bleeding events were similar in both groups occurring in 0.6% of patients in the apixaban group and 0.9% in the enoxaparin group[19].

The ADVANCE – 3 trial was a randomized, double blind study that compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after wound closure for 35 days to enoxaparin 40 mg subcutaneously 12 hours preoperatively and then once daily starting 12–24 hours after wound closure and continued for 35 days for prophylaxis for VTE after hip replacement surgery[20].

5407 patients scheduled for total hip replacement was involved in this trial[20]. 1.4% of the apixaban group and 3.9% of the enoxaparin group had asymptomatic or symptomatic DVT, non-fatal PE, or death[20]. Major VTE was seen in 0.5% of those treated with the apixaban group and 1.1% of those treated with enoxaparin[20]. Symptomatic VTE or death related to VTE during the 60 day follow up never occurred in the apixaban group and occurred in 0.2% of patients treated with enoxaparin[20]. It was found that apixaban 2.5 mg by mouth twice daily was superior to enoxaparin 40 mg subcutaneous daily for all VTE and major VTE in patients after total hip replacement[20]. Major bleeding was similar between the two groups and occurred in 0.8% of those in the apixaban group and 0.7% in the enoxaparin group[20].

Treatment of DVT/PE

The AMPLIFY trial, was a randomized, double blind study with 5,395 participants, 5,244 patients were included in the primary efficacy analysis and 5,365 patient were included in the safety analysis[21]. This trial compared apixaban 10 mg by mouth twice daily for one week and then 5 mg by mouth twice daily for 6 months thereafter to standard therapy with enoxaparin 1 mg/kg subcutaneously twice daily, for at least 5 days, with dose adjusted warfarin until INR is 2.0 or greater and then dose adjusted warfarin to an INR of 2.0 – 3.0 for 6 months for the treatment of acute DVT/PE(21). The primary efficacy endpoint of recurrent VTE or death related to VTE occurred in 2.3% of patients taking apixaban and 2.7% of those taking standard therapy[21].

Apixaban therefore proved to be non-inferior to standard therapy of enoxaparin and warfarin treatment[21]. Major bleeding occurred in 0.6% of patients on apixaban and 1.8% of patients on conventional therapy with enoxaparin and warfarin therefore, treatment with apixaban was associated with significantly less major bleeding events compared to treatment with enoxaparin and warfarin[21].

The AMPLIFY-EXT trial was an extension of the AMPLIFY trial looking at long term VTE prophylaxis after treatment of an acute DVT/ PE[21]. This was a randomized, double blind study with 2,486 patients[21]. This trial compared two different doses of apixaban, 5 mg by mouth twice daily or 2.5 mg by mouth twice daily for up to 12 months versus a placebo twice daily for up to 12 months[21]. Patients had to be 18 years or older and had an acute DVT or PE and completed 6-12 months of prior anticoagulation treatment with no symptomatic recurrence[21].

Symptomatic recurrent VTE or VTE related deaths occurred in 1.7% of patients treated with apixaban 2.5 mg by mouth twice daily and 1.7% in patients receiving 5mg by mouth twice daily[21]. In the placebo group, 8.8% of patients encountered a symptomatic recurrent VTE or death from a venous thromboembolic event[21]. Therefore, it was determined that extended anticoagulation with either apixaban 2.5 mg by mouth twice daily or apixaban 5mg by mouth twice daily significantly reduced the risk of recurrent symptomatic VTE and fatal VTE[21]. The rates of major bleeding was low in all groups, 0.2% of patients taking apixaban 2.5 mg by mouth twice daily, 0.1% of patients taking apixaban 5 mg by mouth twice daily and 0.5% of patients taking the placebo pill[21].

EDOXABAN

Edoxaban is a factor Xa inhibitor which is the newest of the new oral anticoagulants to be studied. It is a once daily medication which has been studied in 30 mg and 60 mg doses. It was recently approved by the FDA in January 2015, and is the newest oral anticoagulant on the market. Edoxaban reaches peak plasma levels in 1-2 hours. Edoxaban is mainly excreted renally. Patients with low body weight, moderate-to-severe renal dysfunction, or concomitant use of a potent P-glycoprotein inhibitor should have the edoxaban dose reduced by 50%. So far it has be studied in stroke prevention in atrial fibrillation, VTE prophylaxis, and in treatment of DVT/PE.

Stroke Prevention in Non-Valvular Atrial Fibrillation

The trial which evaluated stroke prevention in non-valvular afib for Edoxaban was called the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). It was a multinational three group, randomized, double blind, double-dummy trial comparing two dose regimens of edoxaban with warfarin[22].

Patients enrolled had non-valvular atrial fibrillation at moderate to high risk of stroke with a CHADS2 score (Congestive heart failure, hypertension, age greater than or equal to 75 years old, diabetes, previous stroke/TIA) of 2 or higher[22]. 21,105 patients were enrolled and were randomized in a 1:1:1 ratio to receive either warfarin dose adjusted to achieve and INR 2-3, high dose edoxaban of 60mg by mouth daily, or low dose edoxaban 30mg by mouth daily with a median follow up of 2.8 years[22]. In either edoxaban group this dose was cut in half if creatinine clearance 30-50 ml/min, body weight of 60kg or less, or if patient was taking potent P-glycoprotein inhibitors[22].

The primary efficacy end point included time to first stroke (ischemic or hemorrhagic) or systemic embolic event which occurred in 1.5% per year in warfarin group and 1.18% per year in the high dose edoxaban group and 1.61% per year in low dose edoxaban group[22]. The high dose edoxaban met superiority margins compared to warfarin whereas low dose edoxaban was found to be non-inferior[22]. The rate of ischemic stroke was 1.25% with warfarin as compared with 1.25% with high-dose edoxaban and 1.77% with low-dose edoxaban which was significantly higher[22].

Primary safety outcome which was annualized rate of major bleeding occurred in 3.43% patients in warfarin group, 2.75% of patients in high-dose edoxaban group and 1.61% patients in low dose edoxaban group with both doses of edoxaban having significantly lower bleeding rates[22]. The annualized rate of hemorrhagic stroke was 0.47% with warfarin, 0.26% with high- dose edoxaban and 0.16% with low-dose edoxaban which was statistically significant[22]. The annualized rate of life-threatening bleeding, intracranial bleeding, and major

bleeding plus clinically relevant non-major bleeding were also analyzed and each found to be significantly lower in both high dose and low dose edoxaban group compared to warfarin[22]. The annualized rate of GI bleeding was found to be statistically higher in high dose edoxaban compared to warfarin, but lowest rates of GI bleed occurred in low dose edoxaban[22].

In summary, this trial demonstrated that high dose edoxaban was superior to warfarin in preventing stroke (ischemic plus hemorrhagic) but carried a higher risk of GI bleed. Low dose edoxaban had the lowest rates of GI bleed, and while being non-inferior to warfarin in combined hemorrhagic and ischemic stroke, tended to be less effective in preventing only ischemic strokes compared to warfarin.

Prevention Venous Thromboembolism

There were three phase III trials which were conducted in Japan which investigated the effect of edoxaban on the prevention of DVT/PE. These were the STARS (Studying Thrombosis After Surgery) trials. The STARS e-3 trial assessed a once daily dose of 30mg Edoxaban versus enoxaparin 20mg subcutaneous injection twice daily after knee replacement in 716 patients[23].

The STARS trial which evaluated patients undergoing hip replacement was called STARS j-5, which studied 610 Japanese patients using the same protocol as STARS e-3[23]. Patients in both studies were initiated on therapy after surgery and were continued on therapy for 11-14 days[23]. The primary endpoint which included symptomatic and asymptomatic DVT and PE occurred in 5.1% of patients taking edoxaban and in 10.7% of patients taking enoxaparin which was found to be statistically significant[23]. The primary safety endpoint which was major and clinically relevant bleeding occurred in 4.6% of patients taking edoxaban vs 3.7% of patients taking enoxaparin which was similar[23].

The STARS trials were limited to a Japanese population, so it is impossible to determine from these studies if the efficacy of edoxaban in preventing DVT/PE can be expanded to a more general population. Also, the dose of enoxaparin of 20mg subcutaneous injection twice daily is not a common dose used outside Japan for the prevention of DVT/PE post orthopedic surgery. The future may bring further trials examining edoxaban for this indication.

Treatment DVT/PE

A recent trial which evaluated edoxaban in the treatment of DVT/PE is called the Hokusai VTE trial. This trial was published October 2013. This trial enrolled 8292 patients in 37 countries[24].

Patients with objectively diagnosed acute DVT or PE were randomized to receive edoxaban 60mg by mouth daily (or 30mg by mouth daily if CrCl 30-50ml per min, or body weight below 60kg) or warfarin dose adjusted to achieve INR 2-3[24]. Prior to randomization, patients were treated with heparin then switched to either edoxaban or warfarin. Treatment was continued for 3-6 months[24]. The primary efficacy outcome which was recurrent symptomatic VTE, occurred in 3.2% of patients in the edoxaban arm, and occurred in 3.5% of patients in the warfarin arm which met statistical significance for non-inferiority[24]. The safety outcome which was major and clinically relevant bleeding occurred in 8.5% of edoxaban patients and 10.3% of warfarin patients which met statistically significant superiority criteria in favor of edoxaban[24]. (*Table 1)*

TABLE 1

	Renal dosing for Non-valvular Afib	Treatment of DVT/PE	Pharmicokinetics
Dabigatran etexilate, Pradaxa® ***COST $356-385 per mth***	·CrCl>30 ml/min: 150mg BID ·CrCl 15-30 mL/min: 75mg BID ·CrCl<15 mL/min: not recommended	·For patients who received parenteral anticoagulant for 5-10 days: 150mg BID	·Direct thrombin Inhibitor
Rivaroxaban, Xarelto® ***COST $297-320 per mth***	CrCl >50mL/min 20mg QD with evening meal CrCl 30-50mL/min 15mg QD with evening meal CrCl 15-30mL/min 15mg QD with evening meal CrCl<15 not recommended	15mg BID for 21 days then 20mg QD	Factor Xa Inhibitor
Apixaban, Eliquis® ***COST $302-326 per mth***	Normal kidney function: 5mg BID Serum Creatinine ≥ 1.5 PLUS either Age ≥ 80 or weight ≤ 60 Kg: 2.5mg BID ESRD: 5mg BID Decrease dose to 2.5mg BID if ESRD and either ≥80 years old or weight ≤ 60kg	10mg BID x 7days then 5mg BID	Factor Xa Inhibitor

CONCLUSION

Rivaroxaban, Dabigatran, Apixaban, and Edoxaban are some of the new oral anticoagulants that have been studied in patients with venous thromboembolic diseases including stroke prevention in patients with non-valvular atrial fibrillation, DVT/PE prophylaxis after orthopedic surgery, and treatment of DVT/PE. Antithrombotic agents should be chosen based upon the absolute and relative risk and benefit for a given patient. While warfarin remains standard in patients with valvular atrial fibrillation and patients with end stage renal disease, the new oral anticoagulants are being accepted by several agencies including the American College of Cardiology, the American Heart Association, and Heart Rhythm Society as a viable alternative for other conditions. Bleeding with any anticoagulant remains a concern. Currently, there are trials underway analyzing efficacy and safety of factor Xa inhibitor antidotes including andexanet alpha. Development of agents to help stop or reverse bleeding with new oral anticoagulants may aid in weighing risk/benefit analysis in patients. The only way to adequately risk stratify patients is to understand how these drugs were studied in the various trials until studies emerge comparing the new oral anticoagulants or until we find the 'perfect anticoagulant'.

REFERENCES

1. S. Connolly, M. Ezekowitz, et al (2009)"Dabigatran versus Warfarin in Patients with Atrial Fibrillation." New England Journal of Medicine 361:1139-1151
2. S. Connolly, L. 1.)S. Connolly, M. Ezekowitz, et al (2009)"Dabigatran versus Warfarin in Patients with Atrial Fibrillation."Wallentin, et al (2013) "The Long-term Multicenter Observational Study of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) Study" Circulation 128(3):237-43
3. B. Eriksson, O. Dahl, et al (2007) "Oral Dabigatran Etexilate vs. Subcutaneous Enoxaparin for the Prevention of Venous Thromboembolism After Total Knee Replacement: the RE-MODEL Randomized Trial" Journal of Thrombosis and Haemostasis 5(11):2178-85 4.)B. Eriksson, O. Dahl et al (2004) "Dabigatran Etexilate Versus Enoxaparin for Prevention of Venous Thromboembolism After Total Hip Replacement: a Randomized, Double-blind, Non- inferiority Trial." Lancet 370(9591):949-56
4. B. Eriksson, O. Dahl, et al (2011) "Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non- inferiority trial." Journal of Thrombosis and Haemostasis 105(4):721-9
5. J. Ginsberg, B. Davidson, et al (2009) "Oral thrombin inhibitor dabigatran etexilate vs North
6. American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery" Journal of Arthroplasty 24(1):1-9
7. S. Schulman, C Kearon, et al (2009) "Dabigatran versus warfarin in the treatment of acute venous thromboembolism" The New England Journal of Medicine 361:2342-2352
8. S. Schulman, A. Kakkar, et al (2013) "Treatment of Acute Venous Thromboembolism with Dabigatran or Warfarin and Pooled Analysis" Circulation 129:764-721
9. M. Patel, K. Mahaffey et al (2011) "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation" New England Journal of Medicine 365:883-891
10. B. Eriksson, L. Borris, et al (2008) "Rivaroxaban Versus Enoxaparin for thromboprophylaxis after hip arthroplasty" New England Journal of Medicine 358:2765-2775
11. A. Kakkar, B. Brenner, et al (2008) "Extended duration rivaroxaban versus short-term enoxaparin in the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial" The Lancet 372(9632):31-39
12. M. Lassen, W. Ageno, et al (2008) "Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty" The New England Journal of Medicine 358:2776-2786
13. A. Turpie, M. Lassen, et al (2009) "Rivaroxaban versus Enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial" The Lancet 373(9676)1673-1680
14. The EINSTEIN-DVT Investigators (2010) "Oral Rivaroxaban for Symptomatic Venous Thromboembolism" New England Journal of Medicine 363:2499-2510
15. The EINSTEIN-PE Investigators(2012) "Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism" New England Journal of Medicine 366:1287-1297
16. C. Granger, J. Alexander, et al (2011) "Apixaban versus Warfarin in Patients with Atrial Fibrillation" New England Journal of Medicine 365:981-992
17. 17.) S. Connolly, J. Eikelboom (2011) "Apixaban in Patients with Atrial Fibrillation" The New England Journal of Medicine 364:806-817
18. 18.) M. Lassen, G. Raskob (2009) "Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement" The New England Journal of Medicine 361:594-604
19. M. Lassen, G. Raskob (2010) "Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial" The Lancet 375(9717):807-815
20. M. Lassen, A. Gallus, et al (2010) "Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement" The New England Journal of Medicine 363:2487-2498
21. G. Agnelli, H. Buller (2013) "Oral Apixaban for the Treatment of Acute Venous Thromboembolism" The New England Journal of Medicine 369: 799-808
22. R. Giugliano, C. Ruff (2013) "Edoxaban versus Warfarin in Patients with Atrial Fibrillation" The New England Journal of Medicine 369:2093-2104
23. H. Kawaji, M. Ishii (2012) "Edoxaban for prevention of venous thromboembolism after major orthopedic surgery" Orthopedic Research and Reviews 2012:453-64
24. Hokusai VTE investigators (2013) "Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism" The New England Journal of Medicine 369:1406-1415