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Abstract

Although Coumadin® (warfarin) has been the standard outpatient anticoagulant for long-term prevention of thrombosis for many decades, it presents with significant challenges for both patients and health care providers in optimizing standards of care including dietary and drug restrictions, regular monitoring of the patient's International Normalized Ratio (INR), and difficulty maintaining therapeutic levels. Despite its unmistakable effectiveness, there has been an interest from the medical community in developing potential alternative drug therapies. As a result, within the past three years the U.S. Food and Drug Administration (FDA) has approved the use of three new oral anticoagulant drugs (dabigatran, rivaroxaban, and apixaban) specifically targeting thrombin or factor Xa that have overcome many of the barriers seen in warfarin therapy. The use of these new oral anticoagulants is of particular interest in patients who have failed warfarin therapy or for whom warfarin therapy is contraindicated, in situations when monitoring is not feasible or interactions are problematic, or if patient INR control is poor. All of these novel agents are currently approved for prevention of thrombosis in patients with nonvalvular atrial fibrillation, and with ongoing clinical research these agents may present health care providers with additional therapeutic options in a greater variety of disease states. For the comparative purposes of this article, we have combined all of the recent clinical evidence and major landmark trials for each of these new agents as well as benefits and drawbacks of therapy in specific patient populations when compared to warfarin.

Introduction

Warfarin, a vitamin K reductase antagonist (VKA), has been the standard outpatient anticoagulation medication for decades. Indications for use include: prophylaxis and treatment of embolism development, prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and reduction in thromboembolic events such as stroke or systemic embolization after a myocardial infarction (MI). While numerous injectable forms have entered the market over the years, only recently have new oral agents become available.[1] Warfarin has several drawbacks that establish a need for these new anticoagulants. Due to warfarin's mechanism of action interfering with bio-synthesis of vitamin K dependent clotting factors, it takes several days to reach effective levels of anticoagulation. For this same reason, the effects of warfarin take days to wear off. Warfarin therapy also requires constant monitoring of INR to be sure the patient has the correct level of anticoagulation. Vitamin K is the antidote to warfarin's action and is present in many beverages and food products, creating many potentially significant dietary interactions. Drug-drug interactions are very common with warfarin therapy as well.

In certain patient populations there is an obvious need for these new anticoagulants and the goal of this article is to bring forth information from current research to see where these new medications will fall into place in regard to anticoagulation therapy. Along with the American Heart Association (AHA)/American Stroke Association (ASA) recommendations made for a new approach to anticoagulation therapy, there is a greater emphasis on the pharmacist's role in drug recommendation to maximize the benefits of patient care while simultaneously minimizing the potential for adverse events. Therefore, continuing education, especially concerning updates to current guidelines with regard to the most recent additions for stroke prevention, is essential in order for pharmacists to make decisions based not only on effective treatment strategies, but also on cost analysis and individual patient variations. In this article, three of the new oral anticoagulation medications will be compared to warfarin in regard to efficacy, safety, cost and monitoring.

Dabigatran (Pradaxa®)

Dabigatran (Pradaxa®) is a direct thrombin inhibitor with an FDA-approved indication for the reduction in risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The clinical effects of dabigatran can be seen within a few hours, whereas warfarin takes up to two to three days to reach full effect. Atrial fibrillation is an increasingly common arrhythmia with an incidence of greater than 2.3 million people in the United States and greater than 4.5 million people in Western Europe. It is a sign of underlying heart disease and poses a significant threat, primarily in the form of stroke. Stroke associated with atrial fibrillation is generally ischemic due to clot embolization originating in the left atria and is 4.5 times more likely in this patient population.[2] In the RE-LY trial, over 18,000 patients with atrial fibrillation from 967 centers and 44 countries were randomized to warfarin, dabigatran 150 mg twice daily, or dabigatran 110 mg twice daily.[2] The primary endpoint of the study was reduction in stroke or systemic embolism, and patients were treated for an average of two years. Patients included in the study experienced atrial fibrillation and were at risk for cardiovascular or thromboembolic events. The average age of the study population was 72, mean CHADs score of 2.1, history of myocardial infarction (17 percent), heart failure (32 percent) and

stroke (20 percent); half of the patients had no previous exposure to warfarin treatment. Regarding the primary endpoint, 198 patients in the warfarin group had a stroke or systemic embolism. The 150 mg dabigatran group had 133 patients experience a stroke or systemic embolism. The 110 mg dabigatran group had 182 patients experience stroke or systemic embolism. These results were analyzed and the conclusions were made that dabigatran 110 mg twice daily is noninferior to warfarin therapy (P<0.001), and that dabigatran 150 mg twice daily is noninferior to warfarin therapy (P<0.001). Compared with warfarin, major bleeds were less for dabigatran 110 mg twice daily (2.74, P=0.002), but similar for 150 mg twice daily (3.22, P=0.32). A potential limitation to the study was that patients and investigators were not blinded to which medication was being given. They were, however, blind to the dose of dabigatran given. In a sub-group analysis of the RE-LY study, dabigatran was compared to warfarin in patients with atrial fibrillation who had previously experienced a transient ischemic attack (TIA) or stroke.[3] A total of 3,623 patients from the original RE-LY study had previously had a TIA or stroke and were included in the analysis. The breakdown by group was: 1,195 patients from the 110 mg dabigatran twice daily group, 1,233 from the dabigatran 150 mg twice daily group, and 1,195 from the warfarin group. In these sub-groups, stroke or systemic embolism occurred in 65 of the warfarin patients, 55 of the dabigatran 110 mg patients, and 51 of the dabigatran 150 mg patients. The results from this sub-group analysis were consistent with the original RE-LY study in that 110 mg dabigatran twice daily was noninferior to warfarin therapy and that 150 mg dabigatran twice daily was also superior to warfarin therapy in preventing stroke and systemic embolism. The rates of major bleeds were also consistent with the original RE-LY study. One other study showing the same results was conducted using the RE-LY study's original data to compare two subpopulations: patients who were naïve to warfarin or other vitamin K reductase antagonists (VKA) and patients who were VKA-experienced.[4] The VKA naïve group represented 50.4 percent of the patients in the original warfarin group. Stroke and systemic embolism rates were similar in the dabigatran 110 mg and both VKA-naïve and VKA-experienced cohorts (P=0.65; P for interaction=0.72). The dabigatran 150 mg group had significantly lower risk of stroke and embolism in both the VKA-naïve and the VKA-experienced group (P=0.005, P=0.007, respectively; P for interaction=0.84). The authors of the study concluded both doses of dabigatran produced beneficial effects regardless of previous VKA exposure. Based on clinical trials, the standard 150 mg twice daily dose is superior to warfarin therapy in attempt to prevent stroke and embolism in patients with atrial fibrillation. Also, the standard dose, 150 mg twice daily, of dabigatran carries a very similar risk for causing a bleed when compared to warfarin treatment. Only the 150 mg strength received FDA approval for use.

Cost is also a major aspect of comparing medications used to treat the same disease state. A decision-analysis model was developed to compare multiple anticoagulation therapies. This cost-effective study utilized data from multiple trials, including the RE-LY trial, and analyzed cost and quality-adjusted survival.[5] Results were broken up into high, medium, and low risk for atrial fibrillation patients to develop a stroke or embolism. Dabigatran 150 mg twice daily was the most cost-effective in individuals that were at high risk of hemorrhage or stroke unless the INR was well-controlled on warfarin. Warfarin was cost-effective in moderate risk patients unless INR control was poor. Aspirin monotherapy was cost-effective for low risk patients.

Finally, there are notable advantages and disadvantages of dabigatran treatment compared to warfarin. Advantages include a wider therapeutic window, fewer food and drug interactions than warfarin and frequent monitoring is not necessary for dabigatran use.[6] Possible disadvantages include the lack of an antidote for dabigatran, compliance issues due to twice daily dosing, more strict storage requirements, and dabigatran dose may need to be lowered or discontinued due to low renal function. Proper storage of dabigatran requires the patient leave the capsules in the original bottle, immediately close the bottle after a capsule was taken out, and to discard any capsules that have not been taken in four months. Hemodialysis is a possible option for the reversal of dabigatran effects but has only shown to remove up to 60 percent of the drug from the blood stream in two to three hours. Overall, dabigatran is just as effective as warfarin and has shown to have less severe adverse effects. It can be considered first-line anticoagulation therapy in atrial fibrillation patients that have adequate compliance and proper renal function.[7]

Rivaroxaban (Xarelto®)

Rivaroxaban (Xarelto®) is an orally active, direct competitive inhibitor of Factor Xa in the coagulation cascade. The major role of active Factor X is the generation of thrombin via proteolysis of prothrombin precursors, thereby providing the final common link of the intrinsic and extrinsic clotting pathways. Factor Xa can additionally amplify the production of thrombin molecules through its role in the prothrombinase complex that consists of Factor Xa, Factor V, free calcium (Ca^{2+}), and various phospholipids. Factor Xa inhibitors can more efficiently prevent clots than directly inactivating free thrombin molecules because it is calculated that one molecule of Factor Xa is capable of generating approximately 138 molecules of thrombin.[8]

Available in three different strengths: 10 mg, 15 mg and 20 mg tablets, rivaroxaban is renally and hepatically cleared with high oral bioavailability. This novel anticoagulant has numerous benefits over traditional therapies like warfarin, such as lack of routine monitoring, less food and drug interactions and more predictable pharmacokinetics. Since rivaroxaban allows for fixed doses, it has the potential to increase patient adherence due to simpler medication regimens. Rivaroxaban has a quick onset of action with its full anticoagulant effects occurring two to four hours after administration versus warfarin's two to three days. As a result, rivaroxaban does not require bridging therapy pre and post-surgery and should be discontinued at least 24 hours before a procedure.

Rivaroxaban also has a shorter terminal half-life of five to nine hours compared to warfarin's terminal half-life of approximately 40 hours.[9,10] Thus, warfarin's anticoagulant effects can last much longer, and overdose can lead to prolonged bleeding events such as intracranial or gastrointestinal hemorrhaging. Unlike warfarin, there is currently no antidote available for rivaroxaban. Consequently, in emergency cases of severe bleeding or required surgery, there is no way to immediately reverse its effects. Since rivaroxaban is a relatively new drug, there is little data and limited studies available on counteracting its effects. One such study done in 2011 suggested the use of prothrombin complex concentrate (PCC) to overcome the anticoagulation effects of rivaroxaban. PCC contains high amounts of blood coagulation factors II, VII, IX, and X and promotes the generation of thrombin used in clot formation. The randomized, double-blinded, placebo-controlled crossover study performed in 12 healthy volunteers compared rivaroxaban 20 mg twice daily and dabigatran 150 mg twice daily. Rivaroxaban significantly prolonged prothrombin time (PT) (15.81.3 versus 12.30.7 seconds at baseline; P<0.001), which was rapidly reversed by the infusion of 50 units/kg of PCC on day 3 (PT=12.81.0; P<0.001) versus an equal volume of saline placebo, which had no effect on the prolonged PT. For dabigatran there was no significant difference between placebo and PCC administration in neutralizing a prolonged thrombin time (TT).[11]

As an alternative to warfarin, rivaroxaban was FDA approved in 2011 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[9] The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a randomized, double-blinded, multinational trial that compared fixed-dose rivaroxaban to dose-adjusted warfarin in prevention of stroke or systemic embolism. The study randomized 14,264 patients to receive 15 or 20 mg rivaroxaban daily with a meal or warfarin (titrated to INR 2.0-3.0). Inclusion criteria included moderate-to-high-risk of stroke (mean $CHADS_2$ risk score=3.3) and nonvalvular atrial fibrillation. The primary endpoint was time to first stroke or embolism, which occurred in 188 patients in the rivaroxaban group (1.7 percent) and 241 in the warfarin group (2.2 percent). Hazard ratio was 0.79 for the rivaroxaban group, 95 percent confidence interval (CI) 0.66-0.96, and p<0.001 for noninferiority. The study also concluded that there was no significant difference between the rivaroxaban and warfarin groups for risk of major or minor bleeding events; however, the rivaroxaban group had lower rates of intracranial hemorrhage (0.5 percent versus 0.7 percent). ROCKET-AF proved that rivaroxaban was safe, efficacious, and noninferior to warfarin for stroke and embolism prevention.[12] A limitation of ROCKET AF was that patients on warfarin were in the therapeutic INR range only 55 percent of the time. One study done by Melamed et al. defined poor anticoagulation control as time in therapeutic range (TTR)<60 percent, good control between 60 percent and 70 percent, and excellent anticoagulation control>75 percent.[14] Another study done by Morgan et al. found that when warfarin TTR>70 percent there were the greatest benefits in stroke prevention.[15] Therefore, poor anticoagulation control with warfarin may not be a good comparator for all clinical situations. This inadequate warfarin control may not be necessarily due to poor study design, but instead due to complications of managing warfarin itself, such as diet influences and drug interactions. Even within the guidelines of a well-designed study, INR ratios still fall outside of the therapeutic range one-third of the time.[16] Warfarin has been proven successful as an anticoagulant, however poor quality of anticoagulation control in clinical practice may limit its effectiveness.[17]

Since there have been limited studies comparing anticoagulation control of rivaroxaban versus dose-adjusted warfarin, it is difficult to say which offers more efficacious anticoagulation effects. Rivaroxaban is not considered first-line therapy for stroke prevention in atrial fibrillation patients and should only be taken into consideration as an alternative treatment choice for those patients contraindicated for or not well-controlled on warfarin. Currently, the guidelines on stroke prevention from the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommend dabigatran as a second-line alternative to warfarin for patients with moderate-to-high risk of stroke. Therefore, rivaroxaban would be likely considered a third-line or fourth-line choice for anticoagulation and stroke prevention.[13]

Rivaroxaban is also indicated for treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The EINSTEIN-DVT trial was a randomized, open-label, noninferiority study examining the safety and efficacy of rivaroxaban compared to traditional therapy for treatment of DVT. The study included 3,449 patients with acute DVT and without PE who were randomized to receive either rivaroxaban 15 mg twice daily for three weeks, followed by 20 mg once daily versus subcutaneous injections of enoxaparin followed by warfarin or acenocoumarol, another VKA, for up to 12 months. The primary outcome was recurrent venous thromboembolism (PE and/or DVT). The primary safety outcome was major or clinically relevant minor bleeding. The primary outcome occurred in 2.1 percent of the rivaroxaban group and 3.0 percent of the standard-therapy group (hazard ratio=0.68; 95 percent CI 0.44-1.04; p<0.001). The EINSTEIN -DVT trial demonstrated that rivaroxaban alone was as safe and effective as standard therapy for treatment of acute, symptomatic DVT. Based on these results, rivaroxaban is indicated for outpatient treatment of DVT compared to standard heparin and VKA therapy.[18]

The EINSTEIN-PE trial was a randomized, open-label, noninferiority trial with 4,832 patients randomized to rivaroxaban or enoxaparin followed by a VKA. This study was similar to the EINSTEIN-DVT trial except inclusion criteria were patients with PE with or without DVT. Primary outcomes and safety were the same. In the rivaroxaban group, the primary outcome of recurrent venous thromboembolism (VTE) was 50 and 44 in the standard-therapy group (2.1 percent versus 1.8 percent). Frequency of minor bleeding events in the rivaroxaban group was observed in 10.1 percent versus 11.4 percent of the patients for the standard therapy group and 1.1 percent to 2.2 percent for major bleeding. This study

demonstrated noninferiority of rivaroxaban for acute and long-term treatment of PE with a better side effect profile.[19]

Rivaroxaban is approved for DVT prophylaxis, which may lead to PE in patients who have undergone knee or hip surgery replacement. The RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) clinical trial program included three studies, RECORD 1-3, for patients undergoing orthopedic surgery. The RECORD trials were randomized, double-blinded studies looking at the safety and efficacy of rivaroxaban compared to enoxaparin for prevention of DVT and accompanying PE in patients who have had hip or knee replacement surgery. Depending on the assigned treatment group, patients were also given placebo injections or placebo tablets. Rivaroxaban was given at least six to eight hours after wound closure and enoxaparin was started 12 hours preoperatively and restarted six to eight hours after wound closure.

RECORD 1 (hip)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 31 to 39 days or
  - enoxaparin 40 mg subcutaneously once daily for 31 to 39 days
- **Primary endpoint:** any combination of DVT, nonfatal PE, and all-cause mortality 30 to 42 days after surgery
- Primary outcomes occurred in 1.1 percent of patients on rivaroxaban versus 3.7 percent of those on enoxaparin (absolute risk reduction 2.6 percent; 95 percent CI 1.5-3.7; p<0.001). Major venous thromboembolism occurred in 0.2 percent of the rivaroxaban group versus 2.0 percent of patients in the enoxaparin group.
- **Conclusion:** Rivaroxaban was proven to be significantly more effective than enoxaparin for thromboprophylaxis in patients undergoing hip surgery.[20]

RECORD 2 (hip)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 31 to 39 days (long term) or
  - enoxaparin 40 mg subcutaneously once daily for 10 to 14 days (short term)
- **Primary endpoint:** any combination of DVT, nonfatal PE, and all-cause mortality 30 to 42 days after surgery
- Analyses done in the modified intention-to-treat population: 864 patients randomized to the rivaroxaban group and 869 to the enoxaparin group.
  - Primary outcome of total VTE (proximal and/or distal VTE, nonfatal PE, and death from any cause) was 2.0 percent for rivaroxaban and 9.3 percent for enoxaparin (absolute risk reduction 7.3 percent, 95 percent CI 5.2–9.4; p<0.0001). Bleeding events were similar for both groups (6.6 percent for rivaroxaban versus 5.5 percent for enoxaparin; p=0.25).
  - **Conclusion:** Extended anticoagulation (31 to 39 days) with rivaroxaban was significantly more successful than short term (10 to 14 days) enoxaparin for prevention of venous thromboembolism in patients undergoing hip surgery.[21]

RECORD 3 (knee)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 10 to 14 days or
  - enoxaparin 40 mg subcutaneously once daily for 10 to 14 days
- **Primary endpoint:** DVT, nonfatal PE, and or death from any cause 13 to 17 days after surgery
- Primary outcomes observed in 79 of 824 (9.6 percent) patients on rivaroxaban and 166 of 878 (18.9 percent) patients on enoxaparin (absolute risk reduction 9.2 percent; 95 percent CI 5.9-12.4; p<0.001).
- **Conclusion:** Patients undergoing knee arthroplasty showed 10 mg rivaroxaban was superior to 40 mg enoxaparin subcutaneously once daily for thromboprophylaxis.[22]

Currently, rivaroxaban is not recommended as a first-line agent for any health condition and is contraindicated in patients with poor renal function (CrCl<15 mL/min for atrial fibrillation and CrCl<30 mL/min for all other indications) or moderate to severe hepatic impairment (Child-Pugh class B or C).[9] However, among the new novel anticoagulants, such as dabigatran and apixaban, rivaroxaban is the only medication FDA approved for prevention of VTE in post-orthopedic surgery patients. Compared to warfarin, rivaroxaban offers many benefits, such as lack of monitoring due to low patient intervariability, less food and drug interactions, and lower risk of intracranial hemorrhage. Rivaroxaban shows promise as a new anticoagulant; however, further studies and use in clinical practice is needed to fully understand its place among older and more traditional anticoagulation therapies.

Apixaban (Eliquis®)

Apixaban (Eliquis®), another direct Factor Xa inhibitor, provides an attractive alternative therapy for patients at high risk of developing clots compared to warfarin in addition to those who are unable or otherwise unwilling to undergo treatment with a VKA.[23] Although only recently approved for use in the United States by the FDA in December of 2012, apixaban has shown great promise in several large, clinical studies that demonstrate its effectiveness as well as safety compared to more traditional anticoagulant therapies such as warfarin and aspirin.

Apixaban is an orally active compound that is available in 2.5 mg and 5 mg tablets with dosing up to 5 mg twice daily. Metabolism of apixaban is primarily achieved through CytochromeP450 3A4 (CYP3A4) activity along with minor contributions from pathways utilizing CYP1A2, CYP2C8, CYP2C9, and CYP2C19 in addition to being a substrate for

P-glycoprotein (PGP). The dose of apixaban should be reduced to 2.5 mg twice daily when concomitantly administered with drugs that are strong inhibitors of CYP3A4 and PGP such as ketoconazole, clarithromycin, ritonavir or strong inducers such as carbamazepine, rifampin, or phenytoin due to increased risk of bleeding or stroke, respectively.[24,25] Administration of these drugs should be avoided if the patient is already receiving the reduced dose of apixaban.

Clinical studies have shown that in patients with mild to moderate hepatic impairment there is no noticeable change in anti-Factor Xa activity. While there have been no studies to date detailing the effects of apixaban in patients with severe hepatic impairment, there is no data providing an understanding of how this level of damage alters its anticoagulant activity. Therefore, since biotransformation that renders apixaban inactive occurs in the liver, this drug is contraindicated in patients that have severe hepatic impairment. Unaltered apixaban is the major component of drug concentrations found in the plasma and there are no active metabolites. Apixaban exhibits both renal and fecal elimination with 27 percent of the drug clearance achieved through urine and 50 percent by gastrointestinal or biliary excretion. No dosing adjustments are necessary for geriatric patients or those with any level of renal impairment.

At therapeutic doses, apixaban displays linear pharmacokinetics with a dose-dependent relationship. The oral bioavailability in doses of up to 10 mg is approximately 50 percent with maximum concentrations being achieved within three to four hours. Direct intravenous administrations of apixaban display a half-life of five hours. When taken orally, apixaban has prolonged absorption throughout the gastrointestinal tract, especially within the distal portions of the small intestines and ascending colon, which contributes to an approximate half-life of twelve hours.[24,25] This characteristic allows for twice daily dosing in order to achieve optimal anticoagulant effects in most patients.

Currently, apixaban is only approved for reducing the risk of strokes or systolic emboli in patients with nonvalvular atrial fibrillation. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial that was conducted from 2006 to 2010 assessed the stroke risk of apixaban compared to warfarin in patients diagnosed with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. As a double-blind, double-dummy, randomized trial enrolling 18,201 patients with atrial fibrillation from 39 countries, ARISTOTLE randomly assigned patients to receive either apixaban 5 mg twice daily or warfarin with a targeted INR value of 2.5 (goal range of 2.0 to 3.0 with 62 percent of time spent in therapeutic range) while comparing the primary outcome of stroke and systolic embolism versus the primary safety outcome of major bleeding.[26] Event rates for primary outcomes were defined as the number of patients who experienced the event divided by the sum of days to the first event across all patients. Safety and efficacy of the experimental group was evaluated through $CHADS_2$ (1, 2, ≥ 3), CHA_2DS_2VASc (1, 2, ≥ 3), and HAS-BLED scores (0-1, 2, ≥ 3), which are typically employed to determine a patient's risk score and assess the likelihood they will experience a major bleeding event.[27] At the point of randomization, patients within each treatment group were equally stratified across all risk levels.

Results of this trial displayed overall noninferiority and superiority of apixaban compared to warfarin in regards to both prevention of primary outcomes (1.27 percent versus 1.6 percent, CI: 0.66-0.95, p= 0.0114) as well as the primary safety outcome of major bleeding (2.13 percent versus 3.09 percent, CI: 0.6-0.8, p <0.0001).[26] Additionally, fewer patients receiving apixaban discontinued treatment compared to those receiving warfarin across all $CHADS_2$ scores, especially in patients with a reported $CHADS_2$ score of three or higher who are considered high risk patients (p for interaction= 0.02), although this was not the case with CHA_2DS_2VASc and HAS-BLED scores.

Although the ARISTOTLE trial was very well-crafted, there was some discrimination in the ability of the $CHADS_2$ score to accurately predict stroke risk, especially in lower risk patients, even though it is the most commonly used method for assessing a patient's risk level. High $CHADS_2$ scores are directly correlated to high HAS-BLED scores and patients were more likely to experience major bleeding events while on oral anticoagulants. It is hypothesized that this association between bleeding risk and high scores may explain the warfarin treatment paradox (i.e. patients at high risk of stroke are less likely to receive anticoagulation therapy due to a higher risk of bleeding). Since the results of apixaban were generally more beneficial than those seen with warfarin across all patient risk groups, the scores could possibly be less effective for tailoring individual patient treatment for those receiving apixaban. Overall, the authors postulate that additional studies are necessary to determine the optimal method of assessing bleeding risk for atrial fibrillation patients who are receiving anticoagulation therapy.[26]

A previously published trial, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), determined the efficacy of apixaban versus aspirin with or without clopidogrel, which are the two most effective treatment options for atrial fibrillation patients incapable of receiving warfarin therapy. This randomized, double-blind, double-dummy trial recruited 5,600 patients stratified equally to receive either apixaban 5 mg twice daily or aspirin 81 to 324 mg daily in a 1:1 ratio in order to achieve 90 percent power. The trial's primary outcomes and primary safety outcomes are identical to those of the ARISTOTLE trial and were conducted to finish once 226 patients experienced a stroke or systemic emboli.[28] Primary outcomes were monitored using a modified Haybittle-Peto boundary to four standard deviations (SD) once the relative risk (RR) crosses the critical value the first time and three SDs for the second time. If the RR crosses the critical value three times, the safety board may recommend discontinuing the study due to the obvious superiority of apixaban over aspirin.

Table 1. Summary table for comparison of major pharmacology points for dabigatran, rivaroxaban, & apixaban.

Drug	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Prodrug	Yes	No	No
FDA approved dose(s)	150 mg BID	10 mg QD 15 mg BID 20 mg QD	5 mg BID
FDA approved indication(s)	Nonvalvular atrial fibrillation	Nonvalvular A-fib DVT prophylaxis after hip/ knee replacement Treatment of DVT Treatment of PE	Nonvalvular atrial fibrillation
Possible reversal agents	Hemodialysis*	Prothrombin concentrate complex (PCC)*	Prothrombin concentrate complex (PCC)*
Dose adjustments	CrCl 15-30 mL/min-75 mg BID Contraindicated when CrCl<15 mL/min	CrCl 15-50 mL/min-15 mg QD (atrial fibrillation) Contraindicated when CrCl <15 mL/min (atrial fibrillation) Contraindicated when CrCl < 30 mL/min (all indications except A-fib)	2.5 mg BID with 2 or more of the following: age > 80 years, weight <60 kg, sCr > 1.5 mg/dL
Drug interactions	PGP inhibitors or inducers, PPIs	CYP3A4 substrates, PGP inhibitors or inducers	CYP3A4 substrates, PGP inhibitors or inducers
2012 AHA Guideline recommendations [32] Note: Warfarin is Class IA.	Class IB	Class IIa B	N/A

**Not a true reversal agent*

The AVERROES trial was concluded before the projected 226 incidences of strokes/systemic emboli due to achievement of the above-mentioned requirements for superiority of apixaban over aspirin in prevention of primary outcomes (1.6 percent versus 3.7 percent, CI 0.32-0.62, relative risk reduction (RRR)= 57 percent). However, similar incidence of major bleeding was experienced between both treatment groups (1.4 percent versus 1.2 percent, CI 0.74-1.75). [28]

Apixaban is not considered first-line treatment for stroke prevention, but rather as a potential alternative to traditional VKA therapy once more clinical evidence for its use becomes available. Currently, the AHA and the ASA make no recommendations toward apixaban's use over warfarin.

Conclusion

As of 2012, both the AHA and the ASA have updated guidelines to include dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) in treatment algorithms for primary and secondary prevention of stroke with specific agent selection based on level of evidence, risk factors, costs, drug interaction potential, clinical characteristics (e.g. INR) and personal preference.[30, 31] Recommendations for apixaban (Eliquis®) are included below, although they have not been formally endorsed by the AHA/ASA guidelines.

With the conclusion of a considerable number of landmark trials detailing the numerous benefits as well as drawbacks of three recent additions to the previously singular list of oral anticoagulants available on the market, health care providers have begun to see potential alternatives in therapeutic management for nonvalvular atrial fibrillation patients requiring long-term stroke prevention. As more evidence becomes available, these drugs may receive additional therapeutic indications, thereby broadening their use in contemporary medicine.

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