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Abstract

Anticoagulants are a well-known class of agents essential for the prevention of blood clots, which may further develop into deep vein thrombosis, pulmonary embolism or stroke. Individuals at a high risk of clotting, such as those with atrial fibrillation, multiple risk factors or recent hip/knee surgery, are in need of long-term anticoagulation therapy. The purpose of this review is to highlight the pros and cons for each available anticoagulant as well as discuss pivotal clinical trials that evaluated the safety and efficacy of these agents. Warfarin, the oldest anticoagulant, requires the patient to attend frequent appointments with a health care professional in order to test their international normalized ratio (INR). Newer anticoagulants, including dabigatran, rivaroxaban and apixaban, do not require frequent INR testing and have a quicker onset of action than warfarin, providing convenience for the patient. However, many health care professionals prefer warfarin because the INR may indicate its efficacy, its dosages can be easily changed and it is typically more affordable. Additionally, dabigatran may be chosen because it is the only one of these drugs that has a reversal agent, which can be utilized in the case of major bleeding or emergent surgery. There are many opportunities for pharmacists to impact patient outcomes in the anticoagulation therapy setting. From clinics to the community pharmacy setting, the pharmacist's role in patient counseling and education is crucial in reducing mortality. Additionally, drug development is a growing market as reversal agents are needed for many of these newer anticoagulation therapies.

Key Terms

Warfarin; Apixaban; Dabigatran; Rivaroxaban; Idarucizumab; Pharmacist, Anticoagulation; Vitamin K, Pulmonary Embolism; Deep Vein Thrombosis; Factor Xa; INR; Myocardial Infarction; Stroke

Introduction

Thromboemboli often follow the abnormality of at least two of the three factors included in Virchow's triad.[1] The triad includes hypercoagulability, stasis and vascular endothelial injury damage as the three most important anomalies in determining a patient's risk of developing a blood clot. A $CHADS_2$ score is used in atrial fibrillation patients to assess their risk for stroke and eligibility for anticoagulation therapy.[2] Factors in this assessment include **c**ongestive heart failure (1 point), **h**ypertension (1 point), **a**ge 75 years and older (1 point), **d**iabetes mellitus (1 point), and prior **s**troke or transient ischemic attack (2 points). Anticoagulation therapy should be considered in patients scoring one point and should be recommended in patients scoring two or more points. Some thromboembolic disorders are congenital, innate or recurring.[1] Risks factors of clot formation also include pregnancy, obesity, immobility for long periods of inactivity, smoking, oral contraceptives, trauma, surgeries, autoimmune disorders, hormone therapy, inflammatory disorders, age, heart valve replacements, postsurgery, congenital heart defects and other coagulation and heart-related disorders.[1,3,4] With many risk factors, and the commonality of their prevalence, the need for an easily managed anticoagulant therapy is important for many patients.[4]

As described by the Virchow's triad, clot formation predominantly occurs when the triad is compromised which is especially common after stasis and/or venous injury, two usual events that occur post-op.[5] Following vascular injury, factors of the coagulation process become exposed and initiate the clotting cascade allowing platelets to adhere to vascular endothelium and become activated. Upon activation, successive platelets aggregate via platelet adhesion receptors resulting in thrombus formation.

The aggregation of clotting factors and platelets causes a blood clot which, if large enough, can cause blockage of blood flow through the vessel.[5] These clots can form in the peripheral extremities causing deep vein thrombosis (DVT) or can become dislodged and enter the lungs causing pulmonary embolism (PE). In the United States, venous thromboembolism (VTE) causes more than 300,000 admissions to hospitals every year, and PEs are responsible for death in approximately 12 percent of hospitalized patients claiming the lives of 50,000 to 250,000 patients every year.[4] In a study conducted by O'Reilly, Burgess and Zicat including 5,999 patients undergoing total knee replacement (TKR), total hip replacement (THR) or bilateral TKR while on DVT prophylaxis, the prevalence of DVT was 25.6 percent, 8.9 percent and 36.9 percent, respectively.[6] In the same study, symptomatic PE was present in 1.9 percent of all patients, and the prevalence of fatal in-hospital PE was 0.05 percent.

Anticoagulant therapy is common in patients with atrial fibrillation (AF), a common type of heart arrhythmia.[7] Arrhythmias include the heart beating too fast, too slow or irregularly; more specifically, AF is caused by an irregular conduction of the atrial chambers allowing them to fibrillate. Atrial fibrillation increases the risk of stroke, which may be reduced with anticoagulation therapy. To prevent these serious outcomes, anticoagulant therapy can be very beneficial.

The goal of this article is to summarize the various anticoagulant therapies and emphasize the value of reversal agents, especially the new reversal agent, idarucizumab (Praxbind), for the anticoagulant dabigatran (Pradaxa®).

Warfarin

Warfarin was approved in the United States in 1954, making it one of the oldest drugs still used therapeutically today.[8] Warfarin was discovered in the 1920s after a bout of cattle disease named "sweet clover disease."[9] During the Great Depression, moldy hay, which unknowingly contained molds such as Penicillium nigricans and Penicillium jensi, was fed to cattle causing severe hemorrhagic bleeding resulting in death of the cattle. Two veterinary surgeons, Schofield and Roderick, found that avoiding the moldy sweet clover hay prevented the bleeding effects in cattle. Roderick later discovered that the acquired coagulation disorder was caused by a "plasma prothrombin defect" and, for the next 10 years, farmers avoided feeding their cattle sweet clover hay in fear of the bleeding disorder. Eventually Karl Link and his student, Wilhelm Schoeffel, isolated the causative agent that is now known as dicoumarol. Dicoumarol was found to be formed by oxidation of natural coumarin in the moldy hay. In 1945, Link used the derivative as a rodenticide that killed rodents by causing internal hemorrhage. After success as a rodenticide, the transition to a compound with clinical application under the name "Coumadin" began.

Warfarin, the generic of Coumadin, is an anticoagulant that functions by competitively inhibiting the vitamin K epoxide reductase (VKOR) complex which works by reactivating inactive vitamin K to active vitamin K, thus depleting active vitamin K.[10] With decreased active vitamin K, synthesis of active clotting factors is reduced causing diminished coagulation effects of the blood.

Warfarin is approved for prophylaxis and treatment of thromboembolic complications, which include valvular and nonvalvular atrial fibrillation; mechanical prosthetic cardiac valves; prophylaxis and treatment of venous thrombosis and its extension, including PE; and as adjunct therapy in reducing the risk of systemic embolism following a myocardial infarction (MI).[8,10]

Warfarin is dosed anywhere between 1 mg and 10 mg daily.[8] Dosing varies on hepatic impairment, vitamin K intake, chronic heart failure (CHF), age, and functional variants of CYP2C9 (*2 or *3 alleles) or VKORC1 (-1639 polymorphism).[10] Full therapeutic effects of warfarin are typically seen five to seven days after beginning therapy which generally requires bridging therapy overlap with low molecular weight heparin (LMWH) or unfractionated heparin for at least five days and with an international normalized ratio (INR) of 2 or higher for at least 24 hours.

The major adverse reactions of warfarin are fatal and nonfatal hemorrhage from any tissue or organ, and the most severe are spontaneous intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding.[10] Warfarin use should be avoided as the monotherapy in treating heparin induced thrombocytopenia (HIT) as warfarin initially inhibits the synthesis of Protein C, the body's own anticoagulant factor, and possibly accelerates the thrombotic process. Warfarin is considered pregnancy category D or X as warfarin crosses the placenta, and incidents of teratogenic effects have been reported in exposure after the first trimester, and central nervous system (CNS) events to the fetus have been observed while taking warfarin in any trimester. In most cases, warfarin is contraindicated in pregnancy, except in women with mechanical heart valves where the possible benefits of warfarin should be weighed against the risks and risks/benefits of switching to another anticoagulation therapy.

Warfarin has a narrow therapeutic index, and several factors, including other medications and alterations in diet, can play a role in the extent of clotting factor inhibition; therefore, anticoagulation must be carefully monitored.[8] An INR increased by 2 to 3.5 times normal should be achieved to balance between preventing thrombosis and avoiding major bleeding complications.[11] International normalized ratio should be monitored at least every one to four weeks depending on INR consistency or variations including recent warfarin dose, medication, disease and diet changes.[8] When other products that affect warfarin are initiated, discontinued or taken irregularly, additional INR testing should be performed. It is also important to note that whole blood clotting and bleeding times are not effective in measuring and monitoring warfarin therapy, and an INR greater than 4 generally does not provide an additional benefit and is often associated with increased bleeding risk.[10]

Before starting a new prescription or over-the-counter medication, a patient should discuss the risks with a trusted health care professional as some medications can affect INR and require more frequent blood testing.[12] Patients should avoid aspirin, unless instructed otherwise by a physician, as this may increase a patient's bleeding risk. Other medications that can interact with warfarin include antibiotics, pain medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), and acid reflux medications such as cimetidine.

Some foods may also alter the effects of warfarin.[10] Excessive acute consumption of alcohol (binge drinking) should be avoided in patients taking warfarin as it decreases the metabolism of oral anticoagulants and increases prothrombin time (PT) and INR, whereas, chronic alcohol use may increase the metabolism of anticoagulants and decrease PT and INR. Patients taking warfarin should maintain a consistent diet because the effects of warfarin are decreased with an increase of vitamin K intake. Foods, especially green leafy vegetables, are high in vitamin K, and changes in ingestion of these foods may alter warfarin effects. Patients should do their best to take their warfarin medication at the same time every day to maintain consistency in their therapy.

In cases of warfarin overdose, patients may have extensive bleeding requiring reversal. In excessive bleeding, warfarin should be discontinued and vitamin K_1 may need to be administered parenterally.[8] Urgent warfarin reversal may also require fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC). The 2015 American Heart Association/American Stroke Association (AHA/ASA) Guidelines on intracerebral hemorrhage (ICH) compares FFP, PCC and re-

combinant activated factor VIIa (rFVIIa) as potential therapies with the use of vitamin K in reversal of warfarin induced over-anticoagulation.[13] Congruent recommendations are found in the 2012 CHEST Guidelines on Evidenced-Based Management of Anticoagulant Therapy. The CHEST Guidelines advise the administration of vitamin K in over-anticoagulated patients as follows: patients with an INR between 4.5 and 10 and no evidence of bleeding should not be given vitamin K, patients with an INR of 10 or higher with no evidence of bleeding should be given oral vitamin K, and patients with major bleeding associated with warfarin should undergo rapid reversal of anticoagulation with PCC rather than plasma and with vitamin K 5 mg to 10 mg administered by slow intravenous injection.[2]

Dabigatran

Dabigatran etexilate (Pradaxa), is a direct thrombin inhibitor.[14] It was approved by the U.S. Food and Drug Administration (FDA) in 2010 for use in DVT, PE, nonvalvular atrial fibrillation and postoperative thromboprophylaxis. Dabigatran etexilate is a prodrug which is converted into its active form, dabigatran. Dabigatran reversibly inhibits thrombin which is both free and fibrin-bound, preventing thrombin's endogenous activity of cleaving fibrinogen to fibrin, activating clotting factors V, VII, XI, XIII and promoting platelet aggregation. The inhibition of these functions leads to the inhibition of clot formation.

Four studies were credited with the approval of dabigatran by the FDA. The first study, Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER) was a randomized, double-blind, double-dummy, noninferiority trial comparing oral dabigatran to warfarin.[15] Patients enrolled in the study had acute venous thromboembolism and were initially treated with parenteral anticoagulation medication for a median of nine days prior to the initiation of oral therapy with either dabigatran or warfarin. Dabigatran was dosed at 150 mg twice daily while warfarin was dosed per patient to achieve an INR between 2.0 and 3.0.

The study included 2,550 patients with 1,275 patients in each treatment arm.[15] Patients were started on oral therapy, assessed seven days later, and then continually checked once monthly for a total of six months. The primary outcome was the incidence of venous thromboembolism and related death. Within the six month treatment period, 30 patients in the dabigatran arm and 27 in the warfarin arm experienced the primary outcome. This was not a statistically significant difference, determining dabigatran's noninferiority to warfarin.

Treatment of Acute Venous Thromboembolism with Dabigatran or Warfarin and Pooled Analysis (RE-COVER II) was a randomized, double-blind, double-dummy trial that was designed after the conclusion of the RE-COVER study to confirm the findings.[16] The patients in the trial had been diagnosed with an acute venous thromboembolism and had been treated with heparin for five to 11 days prior to initiation of the study. Dabigatran was dosed at 150 mg twice daily, and warfarin was dosed per patient to achieve an INR between 2.0 and 3.0. The primary outcome of the study was the recurrent incidence of venous thromboembolism and related death. Results of the study showed noninferiority of dabigatran to warfarin due to the 30 positive outcomes (recurrent venous thromboembolism and/or related death) of the dabigatran group and the 28 of the warfarin group. These treatment arms were not statistically significant proving noninferiority of dabigatran to warfarin.

The Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism (VTE) is an article compiling the results of the RE-MEDY and RE-SONATE trials.[17] RE-MEDY, a randomized and double-blind trial, treated patients with dabigatran 150 mg twice daily or with warfarin dosed per patient to achieve an INR between 2.0 and 3.0. The primary efficacy outcome was venous thromboembolism or related death. The study included 2,866 patients who had been diagnosed with VTE and treated with anticoagulation therapy for three months prior to initiation of the study. Within the study, 26 patients experienced a VTE or VTE-related death in the dabigatran arm and 18 patients in the warfarin arm. Although the dabigatran treatment group produced more VTE or related deaths, the two treatment arms were not statistically significant, concluding that dabigatran was noninferior to warfarin.

RE-SONATE, another randomized and double-blind trial, compared the treatment of 150 mg of dabigatran twice daily to placebo.[17] The study included 1,343 patients previously diagnosed with a VTE and treated with anticoagulation therapy for three months prior to trial initiation. The patients were selected through expert opinion to be included in the RE-SONATE trial over the RE-MEDY trial if they were considered low-risk patients who were thought to be able to withstand placebo treatment. The primary outcome of the study was recurrent VTE or related death. Recurrent venous thromboembolism occurred in three patients in the dabigatran group and 37 of the patients in the placebo group. These results were statistically significant, concluding that dabigatran is more effective than placebo at preventing a recurrent VTE. Additionally, major bleeding occurred in 36 patients in the dabigatran group and only 12 patients within the placebo group (95 percent confidence interval (CI), 1.52 to 5.60 and P=0.001).

Dabigatran dosing for DVT and PE is identical and instructs to administer one 150 mg capsule twice daily, directly following five to 10 days of parenteral anticoagulation therapy.[14] Dabigatran is also dosed at 150 mg twice daily for the treatment of nonvalvular atrial fibrillation. For the postoperative thromboprophylaxis following hip and knee replacements, 110 mg of dabigatran is administered one to four hours after completion of surgery. If the patient is not started on dabigatran the day of surgery, it should be initiated when homeostasis is achieved and should be given 220 mg once daily. The maintenance dose is also 220 mg once daily and can be given for up to 28 to 35 days.

Most common side effects associated with the use of dabigatran include hemorrhage and gastrointestinal symp-

toms such as dyspepsia or gastritis-like symptoms.[14] Less common adverse drug reactions include wound discharge, hematuria, anemia, hematoma, increased serum alanine aminotransferase (ALT), anaphylaxis and angioedema. Therefore, an allergy to dabigatran presents a large risk to patients. Additionally, it is important to determine the patient's renal function prior to the initiation of therapy and periodically throughout treatment or when clinically indicated. No exact recommendation for the frequency of renal function is provided. Routine coagulation tests, on the other hand, are not required but can be used if the medical team wishes to determine the levels of dabigatran in the blood and the level of therapy the patient is receiving. Such tests include activated partial thromboplastin time (aPTT), ecarin clotting test (ECT) or thrombin time (TT).

Praxbind, generic name idarucizumab, is a monoclonal antibody which was developed as a reversal agent of dabigatran.[14] Idarucizumab for Dabigatran Reversal (REVERSE AD) was the study that lead to the approval of idarucizumab by the FDA.[18] The RE-VERSE AD was a prospective cohort study that included 90 patients, split into two groups, who all received idarucizumab for the reversal of dabigatran. The first group consisted of patients who were taking dabigatran and experiencing uncontrollable or life-threatening bleeding, while the second group was composed of patients who were in need of emergent surgery. The primary end point of the study was the maximum percentage of reversal for dabigatran by 5 g dose of idarucizumab given IV. The normalized results of the study concluded that 88 to 98 percent of the patients experienced a reversal of dabigatran within minutes. In 79 percent of patients, unbound dabigatran concentrations continued to remain below 20 ng/ml for 24 hours following idarucizumab administration. Within the study, only one patient experienced a thrombotic event after receiving the reversal agent. Due to the emergent need and high efficacy displayed, idarucizumab was approved by the FDA in 2015.[19]

Idarucizumab is indicated as a reversal agent for dabigatran in the incidence of emergent surgery or if the patient has uncontrolled or life-threatening bleeding.[14] The humanized monoclonal antibody fragment binds to both dabigatran and its acylglucuronide metabolites. Its affinity to dabigatran is approximately 350 times greater than that of thrombin, therefore inhibiting dabigatran within minutes.

Idarucizumab adult dosing is 5 g IV as two separate 2.5 g doses, administered no more than 15 minutes apart.[14] If the patient still has elevated coagulation parameters after the initial 5 g dose, an additional 5 g dose may be given. The most common side effects include delirium, headache, hypokalemia, constipation, pruritus, pneumonia and fever. Hypersensitivity symptoms may also occur such as rash, hyperventilation and pruritus.

Rivaroxaban

Rivaroxaban (Xarelto®) was approved as an anticoagulation therapy by the FDA in 2011. It was the first novel oral anticoagulant (NOAC) approved, nearly 50 years after the approval of warfarin.[20] Rivaroxaban is an oral direct factor Xa inhibitor that works by prolonging activated thromboplastin time and increasing levels of anti-factor Xa. This medication is indicated for the treatment and prophylaxis of PE and DVT in patients who have undergone surgeries such as knee or hip replacement and patients diagnosed with nonvalvular atrial fibrillation. Currently, this therapy is being studied in the treatment of acute coronary syndromes.

Rivaroxaban was compared to warfarin in a multi-center, randomized, double-blind, double-dummy, event-driven trial including 14,264 patients with nonvalvular atrial fibrillation with an increased risk of stroke in the ROCKET AF trial.[21] The study recognized that vitamin K antagonists, like warfarin, are beneficial in patient populations with nonvalvular atrial fibrillation and increased risk of stroke. However, the increased monitoring, dosing adjustments, and food and drug interactions, among other requirements, certainly demonstrated a need for a more convenient and manageable patient therapy. Rivaroxaban was targeted in this study as a once daily anticoagulant with the potential to provide a more consistent, predictable and convenient therapy as opposed to warfarin. The study compared rivaroxaban with dose-adjusted warfarin in patients with the previously mentioned indications for the prevention of stroke and systemic embolism.

Patients were identified as having a moderate-to-high risk of stroke if they had a history of previous stroke, transient ischemic attack or systemic embolism (SE) with either heart failure, left ventricular ejection fraction $\leq$ 35 percent, hypertension, diabetes or were at least 75 years of age.[21] Patients were then randomly assigned to either receive a fixed once daily dose of rivaroxaban in the evening (20 mg or 15 mg based on CrCl of 30 to 49 mL/min) or adjusted warfarin (target INR 2.0-3.0). The primary endpoints included hemorrhagic or ischemic stroke and systemic embolism. Secondary endpoints consisted of stroke, SE or death from cardiovascular causes; a composite including the previous or MI; and individual components of the endpoints. Safety endpoints measured were composites of major and minor bleeding. Primary analysis was used to conclude rivaroxaban's noninferiority to warfarin, and secondary analysis was used to conclude superiority.

Over a span of three years, 14,264 patients were randomized.[21] The median age of patients was 73 years, and patients also had substantial comorbid conditions including hypertension, heart failure and diabetes. The per-protocol population demonstrated significant differences in the primary outcome of stroke or systemic embolism ($P<0.001$). In the rivaroxaban group, only 188 events occurred in the 6,958 patients representing 1.7 percent/year, as opposed to 241 events of the 7,004 patients in the warfarin group (2.2 percent/year). Relevant nonmajor bleeding occurred in 1,475 patients in the rivaroxaban group and 1,449 patients in the warfarin group, but the difference was not clinically significant ($P=0.44$). Major bleeding rates also occurred at similar rates between the two treatment groups ($P=0.58$). Fatal

bleeding rates of intracranial hemorrhage were significantly lower in patients of the rivaroxaban group (0.5 percent versus 0.7 percent; P=0.02)). Decreases in hemoglobin and major gastrointestinal bleeding were more common in the rivaroxaban group than in the warfarin group. In evaluation of the secondary outcomes in the as-treated population, MI and death occurred less frequently in the rivaroxaban group than the warfarin group, but the difference was not clinically significant. Results were similar in the intention-to-treat analysis of secondary outcomes. Findings concluded that rivaroxaban was noninferior to warfarin in primary analysis. In the analysis of patients receiving at least one dose of study drug, rivaroxaban was found to be superior to warfarin.

Rivaroxaban dosing is specific for each individual indication. For the treatment of DVT and PE, it is recommended that the patient initially be started on 15 mg twice daily with food for 21 days, and then the patient should have their dose modified to 20 mg daily with food.[22] For the prevention of recurrent DVT and PE after six months of treatment, the suggested regimen is 20 mg once daily with food. For postoperative DVT thromboprophylaxis, it is recommended that therapy be initiated after hemostasis has been established six to 10 hours postoperatively. In knee replacement, the recommended dosage is 10 mg once daily for 12 to 14 days (maximum 35 days). For hip replacement, 10 mg once daily is appropriate for 10 to 14 days (maximum 35 days). In the treatment of nonvalvular atrial fibrillations, 20 mg once daily with the evening meal is recommended. In cases of DVT and PE prophylaxis and treatment, dose reduction is recommended in older adults with CrCl between 30 and 50 mL/min. If the CrCl is <30 mL/min, avoid use of rivaroxaban. In patients with nonvalvular atrial fibrillation, no dosage adjustment is necessary if the CrCl is >50 mL/min. If the CrCl is 15 to 50 mL/min, a dose reduction to 15 mg is recommended. Use is discouraged if the CrCl is <15 mL/min or if the patient has end stage renal disease (ESRD) requiring dialysis. Beer's criteria recommend a dose reduction in patients over the age of 65 years with CrCl between 30 and 50 mL/min and discourage use in patients with CrCl <30 mL/min.

There is strong evidence to support the use of rivaroxaban in patients with atrial fibrillation and at least one additional stroke risk factor.[20] Newer agents like rivaroxaban are indicated for this condition due to the fact that routine lab monitoring is not required, which has become a key advantage for this therapy. It has been proven to be as effective as warfarin in this indication. Common side effects of rivaroxaban include bleeding, nausea and fatigue.[22] Renal function should be monitored at baseline and regularly during therapy.[20] Rivaroxaban has a black box warning stating that patients with nonvalvular atrial fibrillation may have an increased risk of thrombotic events if therapy is discontinued without adequate tapering of therapy through use of additional anticoagulation. Additionally, this warning states that patients who are receiving neuraxial anesthesia or are undergoing spinal puncture have an increased risk of epidural or spinal hematoma while taking rivaroxaban. This medication is contraindicated in patients with hypersensitivity to rivaroxaban or pathological bleeding. Rivaroxaban therapy is not recommended in those patients who are pregnant or breastfeeding.

One of the disadvantages of rivaroxaban over warfarin, aside from increased cost, is that there is currently no specific reversal agent for rivaroxaban in the event of severe hemorrhage.[23] Upon suspected bleed associated with rivaroxaban, further evaluate the patient for signs and symptoms of blood loss, and consider the need for blood or blood products if necessary. Partial reversal has been seen in healthy volunteers after administration of prothrombin complex concentrates. One study demonstrated that prothrombin complex concentrates (Cofact) nearly neutralized the anticoagulant effects of rivaroxaban in healthy patients. However, further research needs to be targeted in this area.[24]

Apixaban

Apixaban (Eliquis®) is also a factor Xa inhibitor approved by the FDA in 2012.[20] Apixaban is indicated for the prevention of SE and stroke in patient populations with nonvalvular atrial fibrillation. It can also be used for the treatment of DVT and PE, as well as thromboprophylaxis of postoperative DVT. Apixaban provides an advantage over warfarin due to warfarin's narrow therapeutic range, drug-drug and drug-food interactions, and required monitoring.

Apixaban inhibits formation of fibrin clots and platelet activation through direct reversible inhibition of both the free and bound form of factor Xa.[25] It is predominantly metabolized in the liver by CYP3A4/5 enzymes and interacts with p-glycoprotein. Due to its metabolism by this enzyme, there are specific drug interactions with other inducers of CYP3A4 and p-glycoprotein.[20] Avoid apixaban in combination with CYP3A4 inducers like carbamazepine, phenytoin and rifampin. It is not recommended in patients with severe liver impairment, active pathological bleeding, prosthetic heart valves and those pregnant or breastfeeding. Additionally, use of nonsteroidal anti-inflammatory drugs and clopidogrel should be avoided with apixaban due to increased risk of bleeding.

In the ARISTOTLE trial, a randomized, double-blind, double-dummy trial, patients were randomly assigned either apixaban or dose-adjusted warfarin.[26] The objective of this study was to prove the noninferiority of apixaban as compared to warfarin in reducing the incidence of stroke in patients with nonvalvular atrial fibrillation and at least another risk factor. Secondary outcomes were death from any cause and rate of MI. Patients enrolled in this study had at least two documented episodes of atrial fibrillation or atrial flutter by electrocardiogram. Other risk factors included age of at least 75 years, previous incidence of stroke, transient ischemic attack, heart failure, diabetes or hypertension. This trial also measured the safety outcome of major bleeding as well as whether apixaban was superior to warfarin with respect to reduction of stroke and reduction in major bleeding.

Apixaban was given twice daily in either 2.5 mg or 5 mg doses.[26] There was a significant difference in death between the apixaban and warfarin treatment groups. The rate of death in

the apixaban group was 3.52 percent as compared to 3.94 percent in the warfarin group (p=0.047). Stroke or SE occurred in 212 patients in the apixaban group and 265 patients of the warfarin group, showing that apixaban demonstrated a significant lower incidence of the primary outcomes (p<0.001). Hemorrhagic stroke was 49 percent lower in the apixaban group than the warfarin group. Ischemic stroke was 8 percent lower in the apixaban group than the warfarin group. Approximately 84 patients in the apixaban group experienced fatal or disabling stroke as compared to 117 patients in the warfarin group (p=0.01). Secondary outcomes also showed similar differences among treatment groups. Death from any cause (3.52 percent versus 3.94 percent), rate of death from cardiovascular events (1.80 percent versus 2.02 percent) and rate of death from noncardiovascular events (1.14 percent vs. 1.22 percent) was significantly lower in the apixaban group than warfarin group.

The rate of MI was lower in the apixaban group, but the difference was not statistically significant (P=0.37).[26] Major bleeding occurred at a statistically significantly higher rate in the warfarin group than the apixaban group (p<0.001). According to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for bleeding, there was a greater reduction in risk of bleeding in the apixaban group. Fewer patients experienced intracranial hemorrhage and overall major bleeding in the apixaban group than the warfarin group. Rates of adverse events were similar among groups. Overall, this study concluded that there was a significant reduction in risk of stroke or SE in treatment with apixaban over treatment with warfarin. No unexpected side effects were noted in the apixaban group. While the authors noted that warfarin is still extremely efficacious in the prevention of stroke in patients with atrial fibrillation, they identified that apixaban did not have many of the issues seen in warfarin therapy. The dose that was most efficacious for the prevention of stroke in these study patients was 5 mg twice daily. This study concluded that apixaban was noninferior to warfarin in preventing the primary outcomes.

Apixaban is normally dosed at 5 mg twice daily for atrial fibrillation.[20] It is recommended that the dose be reduced to 2.5 mg twice daily if the patient is 80 years of age or older, has a bodyweight of 132 pounds or less or has a serum creatinine level of 1.5 mg/dL or above. Currently there is no data for dosing in patients on dialysis with a CrCl < 15 mL/min or patients with liver impairment. For the treatment of DVT and PE 10 mg twice daily for seven days followed by 5 mg twice daily maintenance is recommended.[25] To reduce the risk of recurrence of DVT and PE, 2.5 mg twice daily is recommended for at least six months following treatment for DVT. In postoperative prophylaxis, initiate 2.5 mg twice daily 12 to 24 hours postoperatively in both knee and hip replacement.

The most common adverse effect of apixaban is bleeding. However, clinically relevant bleeding comprises only a small portion of this adverse event.[20,25] Similar to rivaroxaban, there is no specific reversal agent for apixaban at this time.[20] The clinician and patient should monitor for signs of bleeding during treatment. Currently, studies are being conducted to investigate potential reversal agents in patients receiving this therapy.[24] We should expect to see more research on this topic in the future.

Apixaban is best suited for patients who are unable or unwilling to adhere to the monitoring parameters associated with vitamin K antagonists like warfarin.[27] While warfarin requires strict monitoring of specific blood parameters, apixaban does not require such monitoring. This criteria should be considered when selecting the appropriate therapy for patients eligible for anticoagulation therapy.

Role of the Pharmacist

With the recent approval of advanced anticoagulation therapy, the pharmacist must make it a priority to keep up to date on changes.[28] Additionally, the pharmacist must be able to identify the advantages and disadvantages of newer therapies as compared to traditional therapies like warfarin in making patient specific recommendations. Refer to Table 1 as a guide in recommending appropriate anticoagulation therapy. Pharmacists certainly continue to play a large role in management of patients requiring anticoagulation therapy. For pharmacists specifically working in the area of anticoagulation, such as clinics, a national certification exam is available through the National Certification Board for Anticoagulation Providers. Pharmacists will continue to play a crucial role in assessing patients for appropriate therapy and adjusting accordingly to provide exceptional patient care.

Impact of Patient Care and Counseling Points

Anticoagulation therapy provides a large area for pharmacist intervention. Anticoagulation therapy is common, especially in patients suffering from congenital heart defects, heart valve replacements, surgery and other heart and coagulation related disorders.[29] Patients receiving anticoagulation therapy who become pregnant need to take special precautions and be monitored. The cardiologist and the obstetrician of the patient should address her specific and individualized management.

While frequent monitoring is a drawback of warfarin use, some competent, well-controlled patients may be eligible to self-monitor their INR at home.[20] Point-of-care monitors, which are normally used in clinics and physicians' offices, may be provided to patients for home use. Patient self-testing has demonstrated an increase in INR control, decreased thromboembolic events, improved quality of life and patient satisfaction with treatment. Self-testing may not be appropriate in all patients taking warfarin. Patients should not be considered for self-testing if they do not demonstrate competency, are treated with warfarin for less than six months, have atypical INR target ranges, have intellectual impairment, have a known drug or alcohol problem or have language barriers that would impede with communication. It is important to consider these criteria when deciding if a patient is eligible for self-monitoring of INR.

Table 2 identifies important counseling points for pharmacists for each individual therapy. It is crucial to educate these

Table 1. Comparison of Anticoagulation Therapy for Pharmacist Recommendation.[6,10,13-14]

Anticoagulant	Dosing	FDA Approved Indications	Renal dosing	Monitoring
Warfarin	Once daily; with or without food[10]	Prophylaxis and treatment of thromboembolic disorders and embolic complications arising from Afib or cardiac valve replacement; adjunct to reduce risk of systemic embolism after myocardial infarction.[10]	No dosage adjustment necessary.[10] However, patients with renal failure have an increased risk of bleeding complications; monitor closely.	INR should be monitored at least every one to four weeks.[10] When products that affect warfarin are initiated, discontinued, or taken irregularly, additional INR testing should be performed.
Rivaroxaban	Once daily; with food	DVT prophylaxis and treatment; PE prophylaxis and treatment; nonvalvular Afib	DVT & PE: CrCl > 30 mL/min - no dose adjustment Avoid use in CrCl < 30 mL/min Nonvalvular Afib: CrCl > 50 mL/min - no dose adjustment CrCl 15 to 50 mL/min, reduce dose to 15 mg once daily with evening meal. Avoid use if CrCl < 15 mL/min Postoperative thromboprophylaxis: CrCl > 50 mL/min - no adjustment Use with caution in CrCl 30 to 50 mL/min Avoid use in CrCl < 30 mL/min	Routine lab monitoring not required Monitor renal and hepatic function
Apixaban	Twice daily; with or without food	DVT prophylaxis and treatment; PE prophylaxis and treatment; nonvalvular Afib	DVT & PE: No dose adjustment Nonvalvular Afib: sCR < 1.5 mg/dL no adjustment necessary unless > 80 years of age and body weight ≤ 60 kg - reduce dose to 2.6 mg twice daily. sCr ≥ 1.5 mg/dL and either ≥ 80 years of age or body weight < 60 kg - 2.5 mg twice daily	Routine lab monitoring not required Not recommended in severe liver impairment
Dabigatran	Twice daily; with or without food	DVT treatment and prophylaxis; nonvalvular AFib; postoperative thromboprophylaxis	CrCl > 30 mL/min - no adjustment unless CrCl , 50 mL/min and patient is receiving concomitant P-gp inhibitors - avoid coadministration Avoid use if CrCl <30 ml/min	Routine monitoring not required. Can use aPTT, ECT or TT if desired

Table 1 (continued). Comparison of Anticoagulation Therapy for Pharmacist Recommendation.[6,10,13-14]

Reversal Agent	Adverse Effects	Interactions	Procedure Considerations
Vitamin K, and in severe bleeding complications PCC or FFP is also used[6,10,13]	Increased risk for bleeding[10]	Many drug and food interactions, but dose can be adjusted for interactions.[10]	Hold 5 days prior to surgery.[10] If urgent procedure, may administer low-dose IV or oral vitamin K. Continue warfarin during minor dental and dermatological procedures or cataract surgery.
No specific reversal agent May consider PCC, activated PCC or recombinant factor VIIa Do NOT use dialysis	Fatigue, nausea, increased bleeding risk	CYP3A4 and P-gp drug interactions	Hold 24 hours prior to surgery Longer cessation may be required based on clinical judgment
No specific reversal agent May consider PCC, activated PCC or recombinant factor VIIa for major bleeding Do NOT use dialysis Activated charcoal may be used if ingestions within 2-4 hours of presentation	Bleeding, nausea, bruising	CYP3A4 and P-gp drug interactions	Hold 24 to 48 hours prior to surgery
Idarucizumab	Hemorrhage, dyspepsia	P-gp drug interactions	CrCl ≥50 mL/minute: Hold 1 to 2 days prior to surgery CrCl <50 mL/minute: Hold 3 to 5 days prior to surgery Consider holding more than 5 days before major surgery spinal puncture, or insertion of a spinal or epidural catheter or port

Table 2. Counseling Guide for Pharmacists in Anticoagulation Therapy.[10,14,22,25]

Anticoagulant Therapy	Indication	Monitoring/ Expectations
Warfarin	The medication is used to treat blood clots and is used to thin the blood so more clots will not form.	The patient may notice more bleeding or bruising. Common side effects include fatigue, nausea or abdominal pain. This medication can cause severe bleeding—it's important to monitor for signs of extreme bruising and bleeding like bloody stools, blood in the urine, excessive dizziness and severe weakness. If the patient falls and/or hits their head, advise patient to seek medical attention immediately. This medication requires frequent blood work monitoring (INR) by the physician. It is important to keep these appointments.
Rivaroxaban	The medication is used to treat blood clots and is used to thin the blood so more clots will not form.	The patient may notice more bleeding or bruising. Spinal or epidural procedures are more likely to have bleeding issues in that area. While this effect is rare, if it does happen it can cause paralysis in some cases. Consult physician. Risk of bleeding is increased with aspirin or NSAIDs. While there is no routine monitoring for this drug, it is important to have regular blood work done. If the patient falls and/or hits their head, advise patient to seek medical attention immediately.
Apixaban	The medication is used to treat blood clots and is used to thin the blood so more clots will not form.	The patient may notice more bleeding or bruising. Other common side effects of this medication include nausea and anemia. Spinal or epidural procedures are more likely to have bleeding issues in that area. While this effect is rare, if it does happen it can cause paralysis in some cases. Consult physician. Risk of bleeding is increased with aspirin or NSAIDs. While there is no routine monitoring for this drug, it is important to have regular blood work done. If the patient falls and/or hits their head, advise patient to seek medical attention immediately.
Dabigatran	The medication is used to treat blood clots and is used to thin the blood so more clots will not form.	The patient may notice more bleeding or bruising. Other common side effects of this medication include upset stomach or heartburn. Spinal or epidural procedures are more likely to have bleeding issues in that area. While this effect is rare, if it does happen it can cause paralysis in some cases. Consult physician. Risk of bleeding is increased with aspirin or NSAIDs. While there is no routine monitoring for this drug, it is important to have regular blood work done. If the patient falls and/or hits their head, advise patient to seek medical attention immediately.

Missed Dose	Other Precautions
If a dose is missed, take the dose as soon as patient thinks of it if on the same day as the missed dose. If it is close to the time of the next dose, skip to missed dose and go back to normal schedule. Do not take extra doses or more than one dose in the same day. Don't stop taking this medication unless directed by a doctor. Stopping the drug increases risk of blood clots.	The patient may notice bleeding of the gums or bleeding while shaving. Recommend a soft bristle toothbrush or electric razor. Inquire about new medications or dietary supplements. Many foods may interact with this medication. Keep the diet consistent to minimize fluctuations in lab values. Avoid excessive consumption of leafy greens, green tea and alcohol.
For dosing 15 mg twice daily and miss a dose, take the missed dose as soon as patient thinks of it to get 30 mg in for the day. In this case, the patient can take two doses at the same time. Return to normal time the following day. For all other doses: If a dose is missed, take the dose as soon as patient thinks of it if on the same day as the missed dose. If it is close to the time of the next dose, skip to missed dose and go back to normal schedule. Do not take extra doses or more than one dose in the same day. Don't stop taking this medication unless directed by a physician. Stopping the drug can increase risk of blood clots.	The patient may notice bleeding of the gums or bleeding while shaving. Recommend a soft bristle toothbrush or electric razor. Take this medication with food and a full glass of water in the evening. There are no food interactions with this medication.
If a dose is missed, take the dose as soon as patient thinks of it if on the same day as the missed dose. If it is close to the time of the next dose, skip the missed dose and go back to normal schedule. Do not take extra doses or more than one dose in the same day. Don't stop taking this medication unless directed by a physician. Stopping the drug can increase risk of blood clots.	The patient may notice bleeding of the gums or bleeding while shaving. Recommend a soft bristle toothbrush or electric razor. Take this medication with or without food. There are no food interactions with this medication.
If a dose is missed, take the dose as soon as patient thinks of it if on the same day as the missed dose. If it is less than 6 hours until the next dose, skip the dose and return to normal schedule. Do not take extra doses or more than one dose in the same day. Don't stop taking this medication unless directed by a physician. Stopping the drug can increase risk of blood clots.	The patient may notice bleeding of the gums or bleeding while shaving. Recommend a soft bristle toothbrush or electric razor. Take this medication with or without food and with a full glass of water. Do not store this medication in a pill box or organizer. It is important to leave this medication in its original container. Throw away any unused capsules after four months.

patients to manage their conditions and reduce their risk of stroke and other cardiovascular events.

Economic Concerns

The cost of these new anticoagulant medications is offset by both adverse effect mitigation and the economic impact of cardiovascular events such as stroke. In 2008, an alarming 780,000 patients experienced a stroke, costing an estimated $65.5 billion. While it is important to note that not all strokes are caused by atrial fibrillation, prevention of stroke secondary to atrial fibrillation through anticoagulation therapy is crucial. The economic burden of bleeding in patients receiving anticoagulation therapy is limited in comparison to the costs associated with stroke. In 2011, studies estimated the cost of these bleeding events to be around $35,000; however, the severity of the bleed will ultimately determine the true impact.

For over a decade, warfarin therapy has consistently been more cost-effective compared to aspirin therapy.[30] Warfarin is cost-effective in patients at least 65 years of age with atrial fibrillation and at least one additional risk factor for stroke. These risk factors include history of transient ischemic attack (TIA), hypertension, diabetes and heart disease. Even in patients without additional risk factors for stroke, the cost-effectiveness of warfarin over aspirin remains high.

Dabigatran is certainly more expensive than warfarin due to a higher acquisition cost, raising the question of whether or not it is a cost-effective option as compared to warfarin.[30] One model studied the cost-effectiveness of dabigatran using $CHADS_2$ score based on the presence or absence of risk factors. Dabigatran 150 mg dosed twice daily was determined to be cost-effective in patients older than 65 years who had at least one point based on their $CHADS_2$ score with no contraindications against dabigatran therapy. However, 110 mg daily was not determined to be cost-effective.

Another model by Shah and Gage estimated the cost of dabigatran at approximately $9 per day.[30] Cost-effectiveness was measured over 20 years of treatment. In patients with a $CHADS_2$ score of 0, aspirin was preferred over dabigatran therapy in terms of cost-effectiveness. In patients with a $CHADS_2$ score of 1 or 2, warfarin was preferred over dabigatran unless the patient was at high risk of bleeding or was rarely within therapeutic range while on warfarin. If the patient had a $CHADS_2$ score of 3 or higher, 150 mg of dabigatran was preferred in terms of cost-effectiveness. This recommendation stands regardless of bleeding risk or time within target INR. Dabigatran dosed at 110 mg twice daily was determined not to be cost-effective in this model. The third model studying the cost-effectiveness of dabigatran compared dosing of 150 mg in patients who had previously experienced a stroke or TIA. This study determined that 150 mg twice daily was not cost-effective as compared to warfarin.

Rivaroxaban's cost-effectiveness was studied in patients at a high risk of stroke.[30] Over a time period of 35 years or until death, it was found that rivaroxaban 20 mg daily is more cost-effective than warfarin therapy if the patient was at least 65 years of age and at a high risk of stroke. The authors noted that this effectiveness was also sensitive to change in risk of stroke.

Apixaban's cost-effectiveness was studied in three separate models.[30] In the first Markov model, the cost-effectiveness of apixaban was studied compared to aspirin in patients 70 years of age with atrial fibrillation, high risk of stroke, low risk of bleeding or not suitable for warfarin therapy. Apixaban was more costly than aspirin in the first year. However, after 10 years the data showed a reversal in this conclusion. Apixaban became more cost-effective over longer periods of time. The second Markov model studied the cost-effectiveness of apixaban compared to warfarin in patients 65 years of age with atrial fibrillation and a $CHADS_2$ score of 2. Apixaban was determined to be more cost-effective over a timeline of 35 years. In a third model, the subject of study was the cost reduction of clinical events such as major bleeding associated with anticoagulation oral therapy. It was determined that the medical cost reduction was significantly more with newer anticoagulation therapy compared to warfarin. The yearly medical cost of these events with dabigatran, rivaroxaban and apixaban were $1,905; $1,995; and $1,598, respectively, versus $2,084 with warfarin.

Future of Anticoagulation Therapy

In the future, pharmacists should expect to see further advancements in anticoagulation. Specifically, studies are currently being conducted to potentially identify a reversal agent for rivaroxaban and apixaban.[24] While there have been numerous advancements in medications in the last two decades, it is expected that there will be an increased focus on disease prevention and patient safety with this therapy. This focus is primarily due to quality care assessments and their direct impact on hospital accreditation and reimbursement. Overall, anticoagulation therapy provides a number of opportunities for drug development, further improvements in disease state management and promotion of health care professional collaboration.

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