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Reducing Cardioembolic Risk in the Patient with Atrial Fibrillation

THE DECISION TO INITIATE anticoagulation is shared between the patient and the provider. Once the patient's risk of stroke and bleeding is determined, and if anticoagulation is recommended, the provider and the patient should discuss the risks and benefits of currently approved anticoagulants. The choice of anticoagulant should only be partly based on the cost, type of follow up needed, and any lifestyle limitations that impact this choice.

Other factors that must be considered when selecting anticoagulation therapy include age, cognitive impairment, bleeding risk, ability to follow monitoring requirements, fall risk, co-morbid conditions, potential drug interactions, alcohol consumption, and the patient's previous history of compliance. To minimize the risk of drug interactions or adverse effects, the clinician should review all medications, including prescription and, over the counter medications, as well as herbal products.[1]

The risk of stroke is present with paroxysmal, persistent, or permanent atrial fibrillation. For patients with non-valvular atrial fibrillation, the CHA_2DS_2-VASc score is recommended to determine the patient's risk for stroke.[1] Anticoagulation is recommended for patients with a prior stroke, transient ischemic attack (TIA) or a CHA_2DS_2-VASc score of >2. For patients with mechanical heart valves warfarin is indicated with a target INR (International Normalized Ratio) between 2.0 to 3.0 or 2.5 to 3.5 depending on the location of the prosthetic valve. *Table 1* defines the scoring criteria for CHA_2DS_2-VASc. *Table 2* defines the oral anticoagulation criteria and level of evidence for stroke prophylaxis based on CHA_2DS_2-VASc.[2]

BLEEDING RISK

In addition to assessing stroke risk, the risk of bleeding must be evaluated when considering anticoagulation. Three assessment tools are commonly used to assess the risk of bleeding for individuals: HAS-BLED, HEMORR2HAGES and ATRIA. HAS-BLED bleeding risk includes hypertension, abnormal renal or liver function, stroke, bleeding tendency or predisposition, labile INRs for patients taking warfarin, elderly considered greater than 65 years of age, and drugs including aspirin or NSAIDS or alcohol abuse. The HEMORR2HAGES bleeding risk includes liver or renal disease, alcohol abuse, malignancy, elderly, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke. ATRIA bleeding risk includes severe renal disease with estimated glomerular filtration rate (EGFR) <30 mL/min or dialysis, age 75 years or older, any prior hemorrhage, and the diagnosis of hypertension.

In a retrospective study, the AMADEUS trial applied the three bleeding risk models to 2293 patients who were treated with warfarin and found that HAS-BLED outperformed the other risk assessment tools although it was only modest in predicting the bleeding risk. The HAS-BLED score was better at predicting intracranial hemorrhage.[3] (*Refer to Table 3.)*

With HAS-BLED, a score of ≥3 indicates increased one year risk of bleeding with anticoagulation therapy. If the patient is found to be at high risk of bleeding and the risk and benefits have been weighed in favor of anticoagulation, regular clinical evaluation should be part of the follow up care of this patient.[4]

WARFARIN

Warfarin is indicated for the prevention of thrombosis and thromboembolism. Warfarin is a vitamin K antagonist and inhibits the vitamin K dependent coagulation factors II, VII, IX and X as well as anticoagulant protein C and protein S. It is a racemic mixture, with equal amounts of R and S active isomers. The R and S isomers are bound to plasma proteins and accumulate in the liver. They are metabolized by

TABLE 1. CHA_2DS_2-VASc Scoring System[1]

CHA_2DS_2-VASc SCORE For Patients with Non-Valvular Atrial Fibrillation	POINTS
Congestive heart failure or left ventricular systolic dysfunction	1
Hypertension consistently >140/90 or under treatment with medication	1
A_2 Age ≥75 years	2
Diabetes mellitus	1
S_2 Prior stroke or TIA or thromboembolism	2
Vascular disease (peripheral arterial disease, myocardial infarction, aortic plaque)	1
Age 65-74	1
Sex category (female gender)	1

TABLE 2. CHA_2DS_2-VASc Selected Treatment Guidelines with Level of Evidence[1]

CHA_2DS_2-VASc SCORE	TREATMENT	LEVEL OF EVIDENCE 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation	
0	Reasonable to consider no antithrombotic therapy	IIa	B
1	No antithrombotic therapy, oral anticoagulant or aspirin may be considered	IIb	C
Prior stroke , TIA or score ≥2	Oral anticoagulation recommended: includes		
	Warfarin INR 2-3	I	A
	Dabigatran	I	B
	Rivaroxaban	I	B
	Apixaban	I	B
Moderate to severe CKD with score ≥2	Treat with reduced doses of dabigatran, rivaroxaban or apixaban	IIb	C
End stage CKD (Crcl <15 ml/min) or on dialysis	Reasonable to treat with warfarin INR 2-3	IIa	B
Following coronary revascularization (percutaneous or surgical) score ≥2	Reasonable to use clopidogrel 75 mg QD concurrently with oral anticoagulants but without aspirin	IIb	B

different CYP 450 pathways. The S isomer is metabolized mainly by CYP 2C9 and is 3-5 times more potent than the R isomer. It has greater clinical application when there are other medications that inhibit clearance of the S-warfarin and increase the anticoagulant effect of warfarin. Warfarin is water soluble and generally absorbed rapidly in the small bowel, but age, co-morbid disease, other medications and environmental factors can all have an effect on metabolism. The R isomer is metabolized mainly by CYP 3A4, but also by 1A1, 1A2, 2C8, 2C9, 2C18, 2C19. The effective half-life of warfarin is 20 to 60 hours.[5-7]

DOSAGE

In 2012 the American College of Chest Physicians (ACCP) Guidelines recommended that warfarin be initiated in a healthy outpatient at 10 mg daily for two days and then adjusted based on the INR. (Grade 2C).[8] Although the 10 mg loading dose may be beneficial for younger patients, it may increase the INR too rapidly in the elderly. The 2008 ACCP Guidelines suggested initial doses of 5 mg or less in the elderly and those with co-morbid diseases.[6] Physiologic changes that occur with aging affect the pharmacokinetics of medications. Gastric acid production is decreased and gastric motility slows resulting in a decrease in the rate that the medications are absorbed. Drug distribution may change due to decreases in lean body mass, decrease in total body water and an increase in body fat. The function of the kidneys and liver also decline, all of which can affect the body's ability to clear the medication resulting in a prolonged half-life of the drug.[9] Additionally, it is important to pay attention to other medications that the patient takes that may cause drug interactions. For example, medications that inhibit CYP 2C9 inhibitors are especially important as they may increase the risk of bleeding when combined with warfarin.

TABLE 3. HAS-BLED bleeding risk scores[4]

LETTER	CLINICAL CHARACTERISTICS	POINTS AWARDED
H	Hypertension*	1
A	Abnormal renal and liver function * (1 point each)	1 or 2
S	Stroke*	1
B	Bleeding*	1
L	Labile INRs*	1
E	Elderly >65 years*	1
D	Drugs or alcohol *(1 point each)	1 or 2

Definitions: * Hypertension SBP>160 mmHg; abnormal renal function Sr.Cr. ≥200 umol/L [2.26mg/dL], chronic dialysis or renal transplant; abnormal liver function chronic hepatic disease (eg: cirrhosis) or bilirubin ≥2 X ULN in association with aspartate aminotransferase/alanine aminotransferase/ alkaline phosphatase >3X ULN; prior stroke particularly lacunar; bleeding history or predisposition (anemia); labile INRs defined as <60% time in therapeutic range (INR 2-3); elderly >65 years; drugs (antiplatelet agents, NSAIDs), and alcohol excess described as ≥8 units per week.

CONTRAINDICATIONS

Warfarin is contraindicated in pregnant women, patients with hemorrhagic tendencies or blood dyscrasias, recent or scheduled surgeries involving the central nervous system, eyes, traumatic surgery, ulceration and bleeding of the gastrointestinal tract, genitourinary or respiratory tracts, cerebrovascular hemorrhage, dissecting aorta or cerebral aneurysms, pericarditis and pericardial effusions, bacterial endocarditis, inadequate laboratory facilities, unsupervised patients with senility, alcoholism, psychosis or lack of patient cooperation, spinal puncture and other diagnostic or therapeutic procedures with potential uncontrollable bleeding, regional lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin.[7]

REVERSIBILITY

Risk of bleeding, however, should not be the sole criterion to withhold anticoagulation with a vitamin K antagonist.[7] Warfarin can be reversed with vitamin K, fresh frozen plasma, and prothrombin complex concentrate (PCC). In the event that the INR is between 4.5 and 10 and there is no evidence of bleeding, the 2012 ACCP Guideline recommend against the routine use of vitamin K, but instead the warfarin dose is held with a repeat INR in 1 to 2 days, and the dose adjusted as indicated by the INR.[8] Foods that are rich in vitamin K, such as green vegetables, also accelerate the reduction in the INR. It is important to determine the cause of the high INR by assessing: sudden dietary changes, alcohol intake, acute illness, post procedure, fever, diarrhea, vomiting, taking too much warfarin or taking a new medication that interacts with warfarin. For patients with an INR greater than 10.0 and no evidence of bleeding, the guidelines recommend oral prescription vitamin K.[8] If the INR is elevated and the patient is bleeding, he or she should be sent to the emergency room for evaluation, support and treatment.

RECOMMENDATIONS FOR FOLLOW UP

Clinical practices must have services available for anticoagulation management. Policies that include patient education, systematic INR testing, tracking, follow up and good communication with the patient with results and dosing decision are recommended. The INR testing is generally obtained weekly until stable within the therapeutic range. The 2014 ACC/AHA Guidelines recommend that once the INR has been consistently stable, it should then be tested at least monthly as long as it remains stable. The 2012 ACCP guidelines also recommend using algorithms or computerized dosing programs. (Grade 2C).[8] However, individual judgment or institutional policy may require more frequent testing of the INR to assure a therapeutic range. The frequency of the monitoring is based on the individual's co-morbid disease factors.

PATIENT EDUCATION

It is important to inform the patient that warfarin is a blood thinner and is for stroke prevention only. It will not control the atrial arrhythmia. Patients should be informed of the potential for drug interactions with prescription as well as over the counter and herbal products. They should be encouraged to discuss any new medication, including short term antibiotics with a healthcare professional. Any decision for dosage change is based on the patient's INR and the potential for drug interaction.

Informing the healthcare professional of any change in general health is important to minimize the risk of alteration in INR. The patient should be informed about the effect of an acute illness, such as a cold, flu, fever, vomiting, diarrhea, minor or major surgery, or procedure can have on the metabolism of warfarin. The patient should inform the healthcare professional about their health changes so that the dose may be adjusted if indicated. Over the counter pain medications such as aspirin containing products, and non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen sodium and celecoxib, etc.) can increase the risk of bleeding and should be avoided unless under the careful supervision of the healthcare provider.

Patients should be informed of the interaction with warfarin and foods with vitamin K. There are numerous foods with vitamin K in varying amounts. Avoidance of vitamin K would be extremely difficult and teaching the patient to be consistent with the level of vitamin K may be most effective. The web site http://www.ptinr.com is an informative patient education site with a lengthy list of vitamin K foods divided into categories of high, moderate and low vitamin K foods. Instructing the patient to be consistent with the level of vitamin K in their daily diet will help to maintain stability of the INR.

Warfarin can only be regulated by a blood test called an INR. The goal range of the INR is between 2.0 and 3.0. The test is usually performed weekly until stable and then less frequently depending on the policy of the healthcare providers practice as well as the individual needs of the patient. Recommending that warfarin is taken around the evening dinner hour allows for results from INR testing done earlier in the day to be incorporated into any dose adjustments in a timely fashion.

PATIENT SELF-TESTING

Point of Care (POC) INR measurements undoubtedly simplify anticoagulation treatment.[5] Patients who test their own INR have instant results and can either discuss with the healthcare provider for direction on treatment or be taught how to adjust their own warfarin dose based on the results. This is an effective method of monitoring for those patients who travel, those who want the freedom to monitor their own INRs, as well as for patients who are home bound due to illness or other reasons. A meta-analysis of 11 trials including data from 6417 people showed that self-monitoring and self-management of oral anticoagulation is safe with a reduction in thrombotic events in patients less than 55 years old and also those with mechanical heart valves. The elderly group, 85 years of age and older, showed no significant adverse effects.[10] As a result of the positive outcomes, international guidelines were published in 2005.[11] There are several companies that manufacture the monitors and the prices range from $1500 to $2000 dollars for the equipment. The equipment and testing materials (test strips and cuvettes) may be covered by Medicare and Non-Medicare insurance companies. A prescription from the healthcare provider is necessary to obtain insurance coverage.

ADDITIONAL ORAL ANTICOAGULANTS

Although warfarin has been used for over 60 years for oral anticoagulation, the variable therapeutic blood levels, food and drug interaction and laboratory follow up have made it less than ideal as a long term treatment for many patients. In recent years, three alternative oral anticoagulants have been used successfully, including dabigatran, a direct thrombin inhibitor, and rivaroxban and apixaban, factor Xa inhibitors. The three agents offer predictable pharmacokinetics and pharmacodynamics. These medications have unique indications and contraindications.

DABIGATRAN

Dabigatran is a concentration dependent, highly selective, and reversible direct thrombin inhibitor.[12] It competitively binds to the active site of thrombin, inhibiting the conversion of soluble fibrinogen into insoluble strands of fibrin resulting in the inhibition of clot formation. In addition, by directly inhibiting thrombin, dabigatran also reduces thrombin's ability to catalyze other coagulation reactions resulting in less amplification of the coagulation cascade.

Given the very poor bioavailability of dabigatran, it is administered as a prodrug, dabigatran etexilate, which is rapidly hydrolyzed after absorption by nonspecific esterases to active dabigatran.[12,13] Other selected pharmacokinetic and pharmacodynamics parameters for dabigatran etexilate are shown in *Table 4*.

Based on the results of the pivotal Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was approved by the Food and Drug Administration (FDA) for use in the United States to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[14,15] In the RE-LY trial more than 18,000 patients with atrial fibrillation and one additional risk factor (i.e. history of cerebrovascular accident (CVA) or transient ischemic attack (TIA), left ventricular ejection fraction (LVEF) < 40%, heart failure Class II or higher within the previous 6 months, age > 75 years, or age of 65-74 years with either diabetes mellitus, hypertension or coronary artery disease, were randomized to open-label therapy with warfarin to achieve an international normalized ratio (INR) of 2.0-3.0, or dabigatran etexilate at blinded doses of either 150 mg or 110 mg twice daily. Key exclusion criteria were a severe heart valve disorder, increased risk of hemorrhage, CVA within 14 days or severe CVA in the previous 6 months, active liver disease, pregnancy, indication for anticoagulation other than atrial fibrillation, or a creatinine clearance (CrCl) < 30 mL/min. Patients were, on average, 71 years of age and had an average CHADS2 score of 2.1. Those randomized to warfarin had a mean time within the therapeutic range of 64%. After a median follow-up of 2 years, dabigatran etexilate 150 mg twice daily significantly reduced the risk of the primary endpoint (stroke or systemic embolism) by 34% versus warfarin (1.11%/year versus 1.69%/year respectively) with a number need to treat (NNT) of 172 patients per year with dabigatran etexilate to prevent one stroke or systemic embolism. Dabigatran etexilate 110 mg twice daily had similar efficacy compared to warfarin. In regards to safety, major bleeding (bleeding resulting in reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or symptomatic bleeding in a critical area or organ) was similar between warfarin and the 150 mg twice daily dose of dabigatran etexilate, but significantly lower in the 110 mg twice daily dose of dabigatran etexilate (2.71%/year versus 3.36%/year; NNT to prevent one major bleeding episode of 153 patients per year). Of particular significance was that both the 110 mg and 150 mg twice daily doses of dabigatran etexilate resulted in less intracranial hemorrhage than warfarin with a NNT of 196 and 227 patients per year, respectively, to prevent one intracranial hemorrhage. In contrast, dabigatran etexilate 150 mg twice daily (but not 110 mg twice daily) had a significantly higher risk of gastrointestinal bleeding than warfarin with a number need to harm (NNH) of 204 patients per year to result in one additional gastrointestinal hemorrhage.[15] While there was some initial concern about a slight, but statistically significant, increase in myocardial infarction with dabigatran 150 mg twice daily versus warfarin in the original trial dataset, a subsequent reanalysis with additional data determined that this difference was not statistically significant.[16] However, additional cohort studies, systemic reviews, meta-analyses and an FDA review have continued to provide conflicting results.[17-21] If there is an elevated risk it is small and probably on the order of about a 0.3% per year absolute increase in events.[19] Lastly, the benefits of dabigatran were most apparent in patients enrolled at centers with INR control below the median of 67%.[22]

Despite the noninferiority of dabigatran etexilate 110 mg twice daily when compared to warfarin in the RE-LY trial, the FDA approved only the 150 mg twice-daily regimen. This was based on an analysis by the FDA

TABLE 4. Selected Pharmacokinetic Properties of Non-Warfarin Oral Anticoagulants[14, 34, 43, 47]

Parameter	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	3.7%	80-100% (10 mg dose)* 6-90% (20 mg dose)*	50%	62%
Activation	Esterase-catalyzed hydrolysis	Not needed	Not needed	Not needed
Tmax (hours)	1-2	2-4	3-4	1-2
T½ (hours)	12-17**	5-9**	12**	10-14**
Protein binding	35%	>90%	87%	55%
Metabolism (major)	Conjugation (no CYP450)	CYP 3A4, CYP2J2	CYP 3A4	Hydrolysis (<4% CYP450)
P-gp Substrate	Yes	Yes	Yes	Yes
Renal elimination of unchanged drug	80%	36%	25%	35%
Significant removal by dialysis	Yes (60% within 2-3 hours)	Not expected	Not expected	Not expected
Effect of Food	No significant effect	Doses >10 mg to be taken with dinner to enhance absorption	No significant effect	No significant effect

Tmax = time to maximum concentration; T1/2 = half-life
* Bioavailability with 10mg is with or without food; bioavailability with 20mg dose is 66% in fasting state and 90% with food
** T1/2 displayed is for healthy individuals; half-life prolonged in patients with severe renal dysfunction

that concluded that even in patients over the age of 75 years, those with moderate renal impairment, or those with a previous hemorrhage that they were unable to establish an improved benefit-risk profile of the lower dose over the higher dose.[23] In addition, based on pharmacokinetic and pharmacodynamics modeling versus actual clinical trial efficacy and safety data, the FDA also approved a dose of 75 mg twice daily for patients with a CrCl of 15-30 mL/min.[24] There are no dosing recommendations for patients with a CrCl less than 15 mL/min or on dialysis.[14] Whether there is a potential role for the monitoring of plasma dabigatran concentrations to tailor therapy and more effectively optimize benefit and minimize risk has recently been raised. A pre-specified analysis of the RE-LY trial revealed that ischemic stroke was inversely related to trough dabigatran concentrations whereas major bleeding increased with dabigatran exposure.[25] However, the utility and practicality of tailoring dabigatran therapy based upon plasma concentrations remains unknown at this time.

Dabigatran etexilate is contraindicated in patients with active pathological bleeding, a history of a serious hypersensitivity reaction to the drug, or a mechanical prosthetic heart valve.[14] Dabigatran etexilate is generally well tolerated with the most common adverse effects consisting of gastrointestinal disturbances such as dyspepsia, nausea, or vomiting.[14,15] These occurred in about 11% of patients in the RE-LY trial randomized to dabigatran versus 6% in the warfarin group. In addition, discontinuation rates at 2 years were significantly greater with dabigatran (around 21%) versus warfarin (16.6%).[15]

Although dabigatran etexilate has much less risk for drug-drug interactions (and no significant food-drug interactions) than warfarin, it is susceptible to interactions with P-glycoprotein (P-gp) inducers and inhibitors.[26] This may be magnified in patients with moderate or severe renal impairment. While current drug-drug interactions studies have not resulted in many changes to approved dose recommendations by the FDA it should be noted that concurrent administration of dabigatran etexilate and P-gp inducers (e.g., rifampin) should be avoided. In addition, in patients with moderate renal impairment (CrCl 30-50 mL/min) consideration should be given to either reducing the dose of dabigatran etexilate to 75 mg twice daily if the patient is also receiving concomitant therapy with dronedarone or systemic ketoconazole (strong P-gp inhibitors) or avoiding it all together. Other P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) in this setting do not require a dose adjustment of dabigatran etexilate. However, in patients with severe renal impairment (CrCl 15-30 mL/min) it is recommended that the concomitant use of P-gp inhibitors and dabigatran etexilate be avoided.[14] Ultimately, time and further study will further clarify the extent and significance of other potential drug-drug interactions with dabigatran, specifically strong P-gp inhibitors such as cyclosporine, itraconazole, tacrolimus and selected HIV-protease inhibitors.

Unlike warfarin, the pharmacodynamic effect of dabigatran with oral dosing is generally considered to be consistent and the routine monitoring of clotting times is not necessary.[27] In pharmacokinetic and pharmacodynamic studies, dabigatran affected the INR, activated partial thrombin test (aPTT), ecarin clotting time (ECT), and the thrombin time (TT). The INR is not a reliable indicator of dabigatran activity and may or may not be affected. The most specific measure of dabigatran activity is the ECT, but at this time the test is not readily available.[14] The aPTT provides an approximation of dabigatran's anticoagulant effect with information available from the manufacturer (package insert) depicting the average time course of dabigatran's effect on aPTT expected with various degrees of renal function and currently approved dosing regimens.[14] This information can be used to estimate the time to get to a particular aPTT, or in other words a level of recovery. However, it must be noted that there may be quantitative differences between various methods used to measure the aPTT. As a result the advantage of not needing routine laboratory monitoring to assess the degree of anticoagulation with dabigatran over warfarin is also a disadvantage in specific situations as rapid reliable measures of its anticoagulant effect are not available. In addition, a specific reversal agent for dabigatran is not currently available although a humanized antibody fragment (idarucizumab) is in development and has received the FDA's breakthrough therapy designation.[28] While dabigatran can be dialyzed with a removal of about 60% over 2-3 hours, this may not be practical in unstable patients.[29,30] The use of prothrombin complex concentrates (PCC), although suggested, has not shown an effect to date.[31] In addition, it is not known if other measures such as the use of activated prothrombin complex concentrates (aPCC) or recombinant Factor VIIa will be of clinical utility. The use of protamine sulfate and vitamin K are not expected to have any effect on dabigatran's anticoagulant activity whereas, early administration of activated charcoal after ingestion can reduce the absorption of dabigatran etexilate.[14,29] Subsequently, for a return to normal hemostasis, one must currently rely upon the body's own elimination of the drug after discontinuation. Drug levels and effects should decrease by about 50% 12-18 hours after the most recent dose, and levels reduced to 25% at 24 hours in patients with CrCl > 50 mL/min. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to dabigatran etexilate, warfarin should be discontinued and dabigatran etexilate initiated when the INR is less than 2.0. When converting from dabigatran etexilate to warfarin, the starting time of warfarin is based on creatinine clearance. If the creatinine clearance is > 50 mL/min warfarin should be started 3 days before discontinuing dabigatran etexilate. If CrCl is between 30-50 mL/min warfarin should be started 2 days before discontinuing dabigatran etexilate, and if CrCl is between 15-30 mL/min, warfarin should be started 1 day before discontinuing dabigatran etexilate. The INR will reflect warfarin's activity only after dabigatran etexilate has been discontinued for at least 2 days. If converting to a parental anticoagulant from dabigatran etexilate, treatment should be initiated 12 (CrCl > 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose of dabigatran etexilate. If converting from a parental anticoagulant to dabigatran etexilate the first dose should be 0-2 hours before the time the next dose of the parental anticoagulant is due or if on a continuous

infusion of a parental anticoagulant at the time the infusion is discontinued. The manufacturer recommends that if possible, dabigatran etexilate should be discontinued 1-2 days (CrCl > 50 mL/min) or 3-5 days (CrCl < 50 mL/min) prior to invasive or surgical procedures that require that anticoagu-

lation be discontinued. Longer times may be considered for major surgery (e.g. cardiac, abdominal, neurosurgery), spinal puncture, or placement of a spinal or epidural catheter or port.[14,32] In regards to perioperative bridging, the more predictable anticoagulant effects and shorter half-life of dabigatran should simplify management, but the best strategy at this time remains unknown. Less than 1 in 5 patients in the RE-LY trial receiving dabigatran etexilate who underwent surgery or invasive procedures received periprocedural bridging.[32] In an analysis of patients in the RE-LY trial who underwent a surgical or invasive procedure similar rates of periprocedural and thrombotic events were observed between dabigatran etexilate and warfarin with patients receiving dabigatran etexilate having a shorter period of interruption of therapy.[32] In addition, among 1270 patients in the RE-LY trial who underwent 1983 cardioversion procedures, rates of stroke and systemic embolism as well as major bleeding within 30 days post-procedure were similar between groups.[33]

Patients should be informed about the need for strict adherence with dabigatran etexilate as well as taking it with a full glass of water. In addition, it is important to stress that breaking, chewing, or emptying the capsules should not be done as this will result in an increased exposure of up to 75%.[14] If a dose is missed the patient may take the missed dose as long as it is not within 6 hours prior to the next scheduled dose. Furthermore, dabigatran etexilate must be stored in the manufacturer's original packaging to reduce the risk of exposure to moisture or humidity as this will lead to product breakdown and loss of potency. Once a bottle of dabigatran etexilate is opened it must be used within 4 months, and if dispensed in a blister package, it should be taken as soon as removed.[14] Both of these restrictions make the use of medication organizers problematic with dabigatran etexilate.

RIVAROXABAN

Rivaroxaban is a selective, competitive, reversible, oral direct factor Xa inhibitor that reduces the rapid generation of thrombin that occurs during the propagation phase of the coagulation cascade.[27] It does not reduce the activity of thrombin that has already been generated. In contrast to dabigatran, rivaroxaban has much better bioavailability (absorption), but it is dose-dependent with doses > 10mg requiring administration with food to increase the bioavailability.[34,35] In addition, its absorption is dependent on the site of release within the gastrointestinal tract with significant reductions in absorption when released in the proximal small intestine or further downstream. As a result, it should not be administered in a manner (e.g., feeding tube) that will deposit the drug distally to the stomach (e.g. proximal small intestine).[34] Rivaroxaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4, making it more susceptible to drug interactions than dabigatran, and similar to dabigatran, it requires dose adjustments in patients with moderate renal dysfunction.[34,35] Other selected pharmacokinetic and pharmacodynamics parameters for rivaroxaban are shown in *Table 4*.

Based on the results of the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was approved by the FDA to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[34,35] In the ROCKET AF trial, more than 14,000 patients with atrial fibrillation and a moderate-to-high risk of stroke (i.e., history of CVA, TIA, systemic embolism, or at least 2 of the following risk factors: heart failure or LVEF < 35%, hypertension, age > 75, or diabetes mellitus) were randomized in a double blind fashion to rivaroxaban 20 mg daily (15 mg daily if CrCl was 30-49 mL/min) or adjusted-dose warfarin to achieve an INR of 2.0-3.0. Key exclusion criteria were hemodynamically significant mitral valve stenosis, prosthetic heart valve, active or increased risk of hemorrhage, severe disabling CVA within the previous 3 months, TIA or other CVA within 3 or 14 days respectively, significant liver disease, pregnancy, or a CrCl <30 mL/min. The median age of patients was 73 years with an average CHADS2 score of 3.5 (much higher than the 2.1 in the RE-LY trial with dabigatran). Those randomized to warfarin had an average time within the therapeutic range of 55% (lower than the 64% in the RE-LY trial). After a median follow-up of 1.9 years the primary analysis (per-protocol) established rivaroxaban as non-inferior to warfarin in regards to the primary endpoint of stroke (ischemic or hemorrhagic) or systemic embolism (1.7%/year versus 2.2%/year). The intention-to-treat analysis also demonstrated rivaroxaban as non-inferior to warfarin in regards to the primary endpoint of stroke or systemic embolism (2.1%/year versus 2.4%/year), but not superior. In regards to safety, major (clinically overt bleeding resulting in death, reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or involvement of a critical anatomic site or resulting in permanent disability) and non-major (overt bleeding requiring intervention via a physician visit, temporary interruption of study drug, pain, or impairment of daily activities) clinically relevant bleeding events were not significantly different between groups. However, rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.5%/year) than warfarin (0.7%/year) with a number need to treat with rivaroxaban to prevent one intracranial hemorrhage of 500 patients/year. In contrast major bleeding from a gastrointestinal site occurred in 3.2% of patients assigned to rivaroxaban versus 2.2% of those assigned to warfarin; a difference which was statistically significant.[25] The non-inferiority of rivaroxaban to warfarin did not differ according to the time spent within the therapeutic range for different quartiles of treatment centers, but the study has been criticized for the overall low amount of time patients spent within the therapeutic range compared to other trials.[26,27]

The recommended dose of rivaroxaban for nonvalvular atrial fibrillation is 20 mg once daily with the evening meal in patients with a CrCl > 50 mL/min. In patients with a CrCl of 15-50 mL/min the recommended dose is 15mg once daily with the evening meal. However, it should be noted that patients with a CrCl of < 30 mL/min were excluded from the ROCKET AF trial. There are no dosing recommendations for patients with a CrCl less than 15 mL/min. In patients unable to swallow, whole tablets rivaroxaban may be crushed and mixed with applesauce immediately prior to use followed by food immediately after administration. In patients with a nasogastric tube or gastric feeding tube it can be crushed and suspended in 50 mL of water and administered. Enteral feeding should immediately follow this. The drug is stable in applesauce or water for up to 4 hours, and there is no adsorption from a water suspension to PVC or silicone nasogastric tubing.[34] Rivaroxaban is contraindicated in patients with active pathological bleeding or those with a history of a serious hypersensitivity reaction to the drug, and its use is not recommended in patients with prosthetic heart valves.[34] Rivaroxaban is

generally well tolerated without a significant difference in non-hemorrhagic adverse events than warfarin in the ROCKET AF trial.[36]

Since rivaroxaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4 it appears more susceptible to drug interactions than dabigatran, and similar to dabigatran, drug-drug interactions may be amplified in patients with renal dysfunction.[35] It is recommended to avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP 3A4 inhibitors such as ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan as there are significant increases in rivaroxaban exposure. In addition, it is recommended to avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP 3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort. Caution is also recommended in patients with CrCl of 15-80 mL/min who are receiving combined P-gp and moderate inhibitors of CYP 3A4 such as diltiazem, verapamil, dronedarone, and erythromycin. These patients should receive therapy only if the potential benefit justifies the potential risk.[34] However, results from an analysis of the ROCKET AF trial which allowed concomitant use of combined P-gp and weak or moderate inhibitors of CYP 3A4 (e.g. amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin) did not show an increase risk of bleeding in patients with a CrCl of 30 to < 50 mL/min.[37] Again, it should be noted that patients with a CrCl of 15-30 mL/min were excluded from the ROCKET AF trial.[36] As with dabigatran, time and further study will further clarify the extent and significance of potential drug-drug interactions with rivaroxaban.

Similar to dabigatran the pharmacodynamic effect of rivaroxaban with oral dosing is considered consistent and the routine monitoring of clotting times is not necessary. Rivaroxaban dose dependently inhibits factor Xa activity and prolongs prothrombin time (PT), aPTT, and HepTest. There is some indication that the PT could provide a useful and timely measure of rivaroxaban exposure as it is strongly correlated with rivaroxaban concentrations with low inter-individual variability, but the clinical utility of this has not been adequately studied to provide general recommendations.[27] A specific reversal agent for rivaroxaban is not currently available although a universal factor Xa inhibitor antidote is in development and has received the FDA's breakthrough therapy designation.[38] Unlike dabigatran, there is no role for dialysis to remove rivaroxaban because of its high protein binding, but activated charcoal given early after ingestion may be useful. While the use of prothrombin complex concentrates (PCC) was shown in a small study to reverse the anticoagulant effects of rivaroxaban as assessed by both PT and the endogenous thrombin potential, it requires confirmation in larger clinical trials in which the actual physiological response is evaluated.[31] The use of protamine sulfate and vitamin K are not expected to have any effect on rivaroxaban's anticoagulant activity, and it is not known if other measures such as the use of activated prothrombin complex concentrates (aPCC) or recombinant Factor VIIa will be of clinical utility.[34] As a result, similar to dabigatran, for a return to normal hemostasis, one must currently rely upon the body's elimination of the drug after discontinuation. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to rivaroxaban, warfarin should be discontinued and rivaroxaban initiated when the INR is less than 3.0 to avoid periods of inadequate anticoagulation.[34] In the ROCKET AF trial significantly more patients developed a primary event when transitioned from rivaroxaban to warfarin at the end of the trial. It was felt that this was probably related to increased difficulty transitioning from blinded therapy with rivaroxaban to warfarin.[36] Nevertheless, when converting patients from rivaroxaban to warfarin, caution must be exerted. One approach discussed in the manufacturer's package insert is to discontinue rivaroxaban and initiate therapy with both warfarin and a parenteral anticoagulant at the time the next dose of rivaroxaban is due. Since rivaroxaban affects the INR, measurements of the INR during concomitant therapy may not be useful. If converting to a non-warfarin anticoagulant with rapid onset (oral or parenteral), rivaroxaban should be discontinued and the other anticoagulant should be given at the time that the next dose of rivaroxaban would have been administered. If converting from a non-warfarin anticoagulant, rivaroxaban should be started 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and the other drug omitted. If the patient is receiving a continuous infusion of unfractionated heparin, the infusion should be discontinued and rivaroxaban initiated at the same time.[34] In addition, rivaroxaban should be discontinued at least 24 hours prior to invasive or surgical procedures that require anticoagulation be discontinued, and restarted as soon as adequate hemostasis has been established recognizing that the onset of its therapeutic effect is short. When spinal puncture or neuraxial anesthesia is employed patients should not have the epidural catheter removed earlier than 18 hours after the last dose of rivaroxaban, and the next dose of rivaroxaban should not be administered earlier than 6 hours after removal of the catheter (24 hours if traumatic puncture).[34] Similar to dabigatran the more predictable anticoagulant effects and shorter half-life of rivaroxaban versus warfarin should simplify periprocedural management. However, the best strategy at this time remains unknown. Although fewer patients in the ROCKET AF trial underwent cardioversion with rivaroxaban than did those with dabigatran in the RE-LY trial, similar results were observed between rivaroxaban and warfarin.[39]

Patients should be informed about the need for strict adherence with rivaroxaban as well as taking it with an evening meal. If a dose is missed the patient should take the missed dose as soon as possible on the same day and continue their usual regimen the next day.[34]

APIXABAN

Apixaban, like rivaroxaban, is an oral direct, competitive, reversible factor Xa inhibitor.[35] Similar to the other new oral anticoagulant therapies the pharmacodynamic effect of apixaban with oral dosing is considered consistent and the routine monitoring of clotting times is not necessary. Apixaban is metabolized by the CYP 3A4 system and the potential for drug-drug interactions particularly in the setting of significant renal dysfunction exists.[29] However, since it is also metabolized by other oxidative pathways these interactions may not be as pronounced or clinically significant.[35] Other selected pharmacokinetic and pharmacodynamics parameters for apixaban are shown in *Table 4*.

Apixaban is approved by the FDA to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation based upon data from two large-scale randomized trials. In the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, apixaban was superior to aspirin for the prevention of stroke of systemic embolism (1.6%/year versus 3.7%/year) in 5599 patients with a NNT to prevent one stroke or systemic embolism of 45 patients per year. Rates of major bleeding, including intracranial hemorrhage were similar. When patients without a history of stroke or TIA were analyzed by CHADS2 score, apixaban was superior to aspirin in patients with a score of 2 or more, and equally safe and effective as aspirin in those with a CHADS2 of 0 or 1.[40] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, over 18,000 patients with atrial fibrillation and at least one additional risk factor for stroke (age > 75 years, previous stroke, TIA, systemic embolism, symptomatic heart failure within the previous 3 months with a LVEF < 40%, diabetes mellitus, or hypertension requiring pharmacologic therapy) were randomized in a double blind fashion to apixaban 5 mg twice daily (2.5 mg twice daily if 2 or more of the following: age > 80 years, weight of < 60 kg, or serum creatinine (SCr) > 1.5 mg/dL) or adjusted-dose warfarin to achieve an INR of 2.0-3.0. Key exclusion criteria were moderate or severe mitral valve stenosis, prosthetic heart valve, CVA within the previous 7 days, reversible cause of atrial fibrillation, doses of aspirin > 165 mg/day, combination therapy with clopidogrel and aspirin, SCr > 2.5 mg/dL, or CrCl < 25 mL/min. The median age of patients was 70 years with an average CHADS2 score of 2.1. Those randomized to warfarin had an average time within the therapeutic range of 62%. After a median follow-up of 1.8 years the rate of the primary outcome of stroke or systemic embolism was 1.27%/year in the apixaban group versus 1.60%/year in the warfarin group establishing both noninferiority and superiority of apixaban over warfarin with a NNT of 303 patients/year to prevent one stroke or systemic embolism. In regards to safety, major bleeding (defined as clinically overt bleeding accompanied by a reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units, or involvement of a critical anatomic site or resulting in death) was significantly lower with apixaban than warfarin (2.13%/year versus 3.09%/year; NNT of 104/year) as was the rate of hemorrhagic stroke (0.24%/year versus 0.47%/year; NNT of 434/year). In addition, the rate of death from any cause was also significantly lower with apixaban than warfarin (3.52% versus 3.94%).[41] However, this last finding is in contrast to the AVERROES trial where apixaban did not reduce rate of death versus aspirin, a much inferior antithrombotic in the setting of atrial fibrillation.

Apixaban is dosed as 5 mg orally twice daily unless the patient meets at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or a SCr ≥ 1.5 mg/dL, in which case the dose is 2.5 mg orally twice daily.[42] It should be emphasized that less than 1.5% of patients in the ARISTOTLE trial had an estimated glomerular filtration rate of ≤ 30 mL/min and that patients with a CrCl < 25 mL/min or SCr > 2.5 mg/dL were excluded from the trial a priori.[41] However, approved product labeling does not recommend avoiding apixaban based on renal dysfunction and even provides dosing recommendations for patients with end stage renal disease (ESRD) maintained on dialysis. This is based on pharmacokinetic and pharmacodynamic data. The recommended dose in patients receiving maintenance hemodialysis is 5 mg orally twice daily unless the patient is 80 years of age or older or weighs 60 kg or less in which case the recommended dose is 2.5 mg orally twice daily.[42] For patients unable to swallow whole tablets, apixaban tablets may be crushed and suspended in 60 mL of 5% dextrose in water and immediately administered through a nasogastric tube.[42] Patients should be informed about the need for strict adherence with apixaban. If a dose is missed the patient should take the missed dose as soon as possible on the same day (without doubling any one dose) and then continue their twice daily dosing. Apixaban is contraindicated in patients with active pathological bleeding or those with a history of a severe hypersensitivity reaction to the drugs and its use is not recommended in patients with prosthetic heart valves.[42] Apixaban is well tolerated without a significant difference in non-hemorrhagic adverse events than warfarin in the ARISTOTLE trial.[41]

Although apixaban is both a P-gp substrate as well as a substrate of cytochrome P450 3A4 its appears to be less susceptible to P-gp and P450 3A4 mediated drug interactions than rivaroxaban probably in part as it is also metabolized by other oxidative pathways as well as being less dependent on renal elimination than rivaroxaban. Nonetheless, specific drug interactions do exist and require modification of therapy. Concomitant use of apixaban with strong dual inducers of P-gp and CYP 3A4 (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) should be avoided. In patients who would generally receive 5 mg of apixaban twice daily the dose should be reduced to 2.5 mg twice daily if co-administered with strong dual inhibitors of P-gp and CYP 3A4 (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). If they would already receive 2.5 mg twice daily then concomitant use should be avoided.[42] Similar to both dabigatran and rivaroxaban further study and experience will provide additional information on these and other potential drug interactions.

The pharmacodynamic effect of apixaban with oral dosing is consistent and the routine monitoring of clotting times is not considered necessary. Apixaban, by its inhibition of factor Xa activity, prolongs the PT, INR, and aPTT. However, these changes are small and subject to a high degree of variability and therefore not useful in monitoring the anticoagulation effect of apixaban. In addition, there is no role for urgent dialysis to remove apixaban in the setting of bleeding or overdose because of its high protein binding. However, activated charcoal given at 2 and 6 hours early after ingestion may be useful. While the use of PCC, aPCC, or recombinant Factor VIIa may be considered it must be noted their efficacy and safety have not been thoroughly evaluated in clinical trials. On the other hand, the use of protamine sulfate and vitamin K are not expected to have any effect on apixaban's anticoagulant activity. As a result, similar to dabigatran and rivaroxaban, for a return to normal hemostasis, one must currently rely upon the body's elimination of the drug after discontinuation. In the case of apixaban this would be at least 24 hours. If the patient is bleeding, along with discontinuation of the drug, early volume and red blood cell replacement, identification of the cause, and use of local measures to stop the bleeding should be implemented.[27]

When converting patients from warfarin to apixaban, warfarin should be discontin-

ued and apixaban initiated when the INR is less than 2.0.[42] When converting from apixaban to warfarin, several considerations must be made. First, since apixaban affects the INR, measurements of the INR during concomitant therapy will not be very useful. Second, in the clinical trials an increased risk of stoke was observed following discontinuation of apixaban.[42] As a result, if continuous anticoagulation is required when converting from apixaban to warfarin both warfarin and a parenteral anticoagulant should be initiated at the time the next dose of apixaban would be due. If switching between apixaban and other non-warfarin anticoagulants the agent being taken should be discontinued and the other initiated at the time of the next scheduled dose. Apixaban should be discontinued at least 48 hours prior to elective invasive or surgical procedures that have a moderate or high risk of unacceptable or clinically significant bleeding, and at least 24 hours if they have a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. It should be restarted as soon as adequate hemostasis has been established recognizing that the onset of its therapeutic effect is short. When spinal puncture or neuraxial anesthesia is employed patients should not have the epidural catheter removed earlier than 24 hours after the last dose of apixaban, and the next dose of apixaban should not be administered earlier than 5 hours after removal of the catheter (48 hours if traumatic puncture).[42] Similar to dabigatran and rivaroxaban, outcomes post cardioversion were similar in regards to cardiovascular events and major bleeding for apixaban and warfarin.[43] *Table 5* lists the Level of Evidence for currently approved oral anticoagulants.

FUTURE ORAL ANTICOAGULATION THERAPIES

Other emerging oral anticoagulants for the prevention of stroke and systemic embolism in the management of non-valvular atrial fibrillation include the direct factor Xa inhibitors edoxaban and betrixaban. Betrixaban has the advantage over other currently available agents of having both limited renal excretion, a long half-life and minimal metabolism through CYP 3A4.[44] However, it has only been evaluated in a Phase 2 trial at this time. In contrast, edoxaban has been evaluated in a large-scale Phase 3 trial and has recently been submitted to the FDA for approval. The Effective Anticoagulation with Factor

TABLE 5. 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: Level of Evidence [1,2]

Guidelines	Treatment	LEVEL OF EVIDENCE	
Prevention of recurrent stroke in patients with non-valvular AF whether paroxysmal or permanent	Individualize treatment based on risk factors The following are indicated: VKA target INR 2.5 Apixaban Dabigatran The following is reasonable: Rivaroxaban	 I I I IIa	 A A B B
	Combination of oral anticoagulation, warfarin or one of the newer agents with antiplatelet therapy is NOT recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement	IIb	C
	Patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended. The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable	I IIb	A B
	For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms	IIa	B
	In the presence of high risk for hemorrhage (ie: large infarct, hemorrhagic transformation on initial imaging uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days	IIa	B
	Patients with AF and history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with low molecular weight heparin or an equivalent anticoagulant agent if intolerant to heparin, is reasonable depending on perceived risk of thromboembolism and bleeding.	IIa	C
For patients with clinically apparent coronary artery disease, particularly an acute coronary syndrome or stent placement	Combination of oral anticoagulation (ie, warfarin or one of newer agents) with anti-platelet therapy is reasonable to use in this group of patients	IIb	C
Patients with ischemic stroke or TIA and AF unable to take oral anticoagulants	Aspirin alone is recommended Addition of clopidogrel to aspirin compared with aspirin alone might be reasonable	I IIb	A B
Most patients with a stroke or TIA with AF	Reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms	IIa	B
In presence of high risk for hemorrhagic conversion (large cerebral infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension)	Reasonable to delay initiation of oral anticoagulation beyond 14 days	IIa	B

Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF-TIMI 48) trial evaluated two doses of edoxaban (30 mg or 60 mg once daily with dose adjustments based on renal function, weight, or concomitant medications) versus warfarin (dose adjusted to target an INR of 2.0-3.0) for stroke prevention in 21,105 patients with atrial fibrillation.[45,46] Patients 21 years of age or older with atrial fibrillation and a CHADS2 score of 2 or higher were eligible for randomization. Key exclusion criteria included atrial fibrillation due to a reversible cause, estimated CrCl < 30 mL/min, high risk of bleeding, dual antiplatelet therapy, moderate-to-severe mitral stenosis, other indications for anticoagulation therapy, acute coronary syndromes, coronary revascularization, or stroke within 30 days of randomization. Patients were randomized in a double blind fashion to edoxaban 60 mg once daily, edoxaban 30 mg once daily, or adjusted-dose warfarin to achieve an INR of 2.0-3.0. The dose of edoxaban was reduced by 50% at the time of randomization or during the study if the CrCl was 30-50 mL/min, body weight was 60 kg or less, or the patient received verapamil, quinidine, or dronedarone. The median age of patients was 72 years with an average CHADS2 score of 2.8. Those randomized to warfarin had an average time within the therapeutic range of 65%. After a median follow-up of 2.8 years the rate of the primary outcome of stroke or systemic embolism was 1.18%/year in the edoxaban 60 mg once daily group, 1.61%/year in the edoxaban 30 mg once daily group, and 1.50%/year in the warfarin group establishing noninferiority for both doses of edoxaban versus warfarin. In regards to safety, major bleeding (defined as fatal bleeding, symptomatic bleeding in a critical area or organ or clinically overt bleeding accompanied by a reduction in hemoglobin of > 2 gm/dL or requiring transfusion of > 2 units) was 3.43%/year with warfarin, 2.75%/year with edoxaban 60 mg, and 1.61%/year with edoxaban 30 mg both of which were statistically significantly lower than warfarin. The rates of life threatening bleeding, and intracranial bleeding were also significantly lower with both doses of edoxaban versus warfarin. However, the rate of major gastrointestinal bleeding was significantly higher (1.51%/year) with edoxaban 60 mg than warfarin (1.23%). Overall edoxaban, if approved, will represent yet another alternative to warfarin.[47]

While the last several years have seen the emergence of viable alternatives to warfarin therapy for the prevention of stroke in patients with atrial fibrillation, much remains to be resolved with the newer agents particularly regarding long-term efficacy and safety, reversibility, potential drug-drug interactions, head to head comparative data, adherence and persistence with therapy, as well as their management in the peri-procedural setting or concomitant use with other newer antithrombotic agents (e.g., prasugrel, ticagrelor). In addition, there remains a need to continue to improve how we manage anticoagulation with warfarin, including methods to increase the time within therapeutic range and promotion of self-management in appropriately selected patients. Ultimately, the decision regarding which agent to use will be individualized based on many of the aforementioned characteristics as well as cost and patient preference. ■

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