CONTINUING EDUCATION CREDIT

Medication Management of Atrial Fibrillation
Emerging Therapies for Rhythm Control and Stroke Prevention

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Educational Objectives

After completing this program, readers should be able to:

- Identify the use of rate versus rhythm control in the treatment of atrial fibrillation.
- Evaluate the utility of new agents for rhythm control in the treatment of atrial fibrillation.
- Differentiate between therapies for stroke prevention in atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common dysrhythmia in North America, affecting approximately 2.2 million people. The lifetime risk of AF in individuals 40 years of age and older is 26% for men and 23% for women.1 AF is associated with approximately a five-fold increased risk of stroke, and it accounts for 1.5% of strokes in people 50 to 59 years of age and for 23.5% of strokes in those who are 80 to 89 years of age.2-3

Management of AF includes the use of medications to control ventricular rate and to restore or maintain normal sinus rhythm (NSR), as well as the use of antiplatelet or anticoagulant therapy to minimize the risk of thromboembolic events. At this time, no ideal antiarrhythmic or anticoagulant agent exists. Current antiarrhythmic agents are limited by their less than optimal effectiveness, their side-effect profile, and the potential for numerous drug interactions. Warfarin (Coumadin, Bristol-Myers Squibb), which is used to minimize the risk of thromboembolic events, is also limited by its adverse-effect and drug-interaction profile. These factors have led to the development of alternative antiarrhythmic and anticoagulant agents and to the increased use of nonpharmacological strategies for the management of AF.

In this article, we review the general treatment approaches for the management of AF and discuss both newly approved medications and those under investigation for the chronic management of AF.

Treatment Overview

Management of chronic AF involves controlling ventricular rate or heart rhythm. Treatment guidelines are available for the management of AF from the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) and from the European Society of Cardiology and National Collaborating Centre for Chronic Conditions.4-6

Controlling the patient’s ventricular rate can be accomplished with beta blockers, non-dihydropyridine calcium-channel blockers, such as diltiazem (Cardizem, Biovail), verapamil (e.g., Calan, Pfizer), and digoxin (Lanoxin, GlaxoSmithKline). Rhythm control is used to restore or maintain NSR via pharmacological and nonpharmacological strategies. This article addresses treatment from the ACCF/AHA/HRS guidelines.

Rate Control Versus Rhythm Control

The decision for selecting one strategy over the other is based on the presence of symptoms and previous treatment options. Two landmark trials, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation), have provided insight for clinicians who must decide whether to initiate rate-control and/or rhythm-control therapies.

In AFFIRM, 4,060 participants with AF were randomly assigned to receive rate control or rhythm control with cardioversion and antiarrhythmic drugs to maintain NSR. Enrolled participants were 65 years of age or older, or younger than age 65 with risk factors for stroke. Participants in both arms received anticoagulation with warfarin, titrated to an International Normalized Ratio (INR) goal of 2.0 to 3.0. Whether to continue treatment with warfarin in the rhythm-control group was left to the physicians’ discretion if NSR was maintained for four to 12 weeks. There was no difference in five-year mortality rates between rate-control and rhythm-control groups (21.3% vs. 23.8%, respectively); the hazard ratio (HR) was 1.15 with a 95% confidence interval (CI) of 0.99 to 1.34 (P = 0.08).

There was no difference in the rate of risk of ischemic stroke between the rate-control and rhythm-control groups (5.5% vs. 7.1%, respectively; P = 0.79). The risk of stroke overall was highest in patients who stopped anticoagulation therapy and in those with subtherapeutic INRs. Data from this trial suggest that anticoagulation for stroke prevention should be continued even when it appears that NSR has been achieved and maintained.7

The rate of adverse effects (AEs) was significantly higher in

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the rhythm-control group than in the rate-control group for pulmonary events (7.3% vs. 1.7%, respectively; \( P < 0.001 \)), gastrointestinal (GI) events (8% vs. 2.1%; \( P < 0.001 \)), prolongation of the corrected QT (QTc) interval (1.9% vs. 0.3%; \( P < 0.001 \)), and torsades de pointes (0.8% vs. 0.2%; \( P = 0.007 \)).

In the RACE trial, 522 patients with AF were randomly assigned to receive either rate control or a stepwise algorithm of cardioversion, followed by antiarrhythmic medications to maintain NSR. All subjects undergoing cardioversion received anticoagulant therapy for four weeks before and after the procedure. Those achieving NSR one month following cardioversion could stop anticoagulation or could change to aspirin therapy. Rate-control participants received anticoagulation therapy unless they were younger than 65 years of age without cardiac disease. The composite primary endpoint was cardiovascular death, hospitalization for heart failure, thromboembolic complications, severe bleeding, pacemaker implantation, or severe drug side effects from the antiarrhythmic drugs.

Patients in the rate-control group reached the primary endpoint less often than the rhythm-control group (17.2% vs. 22.6%, respectively; 90% CI, –1 to 0.4). This difference in the event rate did not reach the prespecified criteria for determining superiority between the two treatments; however, it did meet the prespecified criteria for demonstrating non-inferiority with rate control.

Adverse events, including thromboembolic complications (7.9% vs. 5.5%, respectively; 90% CI, –6.2 to 1.2); heart failure, 4.5% vs. 3.5%; 90% CI, –3.8 to 1.8); and serious AEs (4.5% vs. 0.8%; 90% CI, –6.3 to –1.4), were more common in the rhythm-control patients than in the rate-control patients. As seen in AFFIRM, most thromboembolic events occurred when anticoagulation was stopped following cardioversion and in patients with an inadequate INR.

Overall, the RACE investigators concluded that rate control was not inferior to rhythm control.\(^4\) In summary, both RACE and AFFIRM demonstrated that neither strategy was more beneficial in preventing death and stroke; however, the rate of AEs was higher in the rhythm-control group.

Based on the results of these trials, a rate-control strategy should be used initially in most patients when the ventricular rate can be controlled and symptoms are not bothersome. In addition to the lack of an efficacy benefit of one strategy over the other and the increase in AEs with antiarrhythmic drugs, rhythm-controlling agents are generally more expensive.

For all patients, attention should be directed toward controlling the ventricular rate to allow for increased ventricular filling time, to minimize the risk of demand ischemia from elevated heart rates, and to prevent hemodynamic alterations.\(^4\) Recent evidence suggests that strict rate control (achieving a resting heart rate of less than 80 beats/minute and a heart rate during moderate exercise of less than 110 beats/minute) offers no benefit over lenient rate control (achieving a resting heart rate of below 110 beats/minute) in people who do not have symptoms caused by AF with a left ventricular ejection fraction (LVEF) exceeding 40%.\(^9\) Uncontrolled tachycardia can lead to a reversible decline in ventricular performance over time.\(^4\)

In the RACE II trial (Rate Control Efficacy in Permanent Atrial Fibrillation), 614 patients with permanent AF were randomly assigned to receive strict rate control or lenient rate control. Patients were observed for at least two years with a maximum follow-up period of three years. The primary endpoint was a composite of cardiovascular death, hospitalization for heart failure and stroke, systemic embolism, major bleeding, and arrhythmic events. Kaplan–Meier estimates for the three-year incidence for the primary endpoint were 12.9% in the lenient control group and 14.9% in the strict control group (HR, 0.84; 90% CI, 0.58–1.21). Based on predetermined criteria, lenient control was considered non-inferior to strict control. The rate of AEs was also similar in the two groups.\(^9\) It is now recommended that there is no benefit of strict rate control, compared with lenient rate control, when symptoms are tolerable.\(^4\)

Rhythm control is used in an attempt to restore or maintain NSR. Pharmacological cardioversion has been efficacious with amiodarone (Cordarone, Wyeth/Pfizer), dofetilide (Tikosyn, Pfizer), flecainide (e.g., Tambocor, 3M), intravenous (IV) ibutilide (Corvert, Pfizer), and propafenone (Rythmol, Reliant/Abbott). This strategy is preferred in patients with symptoms of AF despite rate control. Rhythm control is also necessary if hypotension or heart failure secondary to AF develops. Rhythm control may be selected as the initial treatment strategy for younger patients.\(^10\)

Pharmacological cardioversion appears to be the most effective approach when therapy is initiated within seven days of the onset of AF. Electrical cardioversion or ablation, which is associated with higher success rates of restoring NSR compared with pharmacological therapy, may be offered to selected patients for initial management. The most commonly used nonpharmacological strategies include cardioversion and catheter ablation. Patients with AF or atrial flutter with myocardial ischemia, heart failure, symptomatic hypotension, angina, or hemodynamic instability often require immediate direct current cardioversion.\(^4\)

Currently, catheter ablation is considered a second-line therapy in most patients with symptomatic AF, and it can be considered for patients experiencing AEs resulting from antiarrhythmic therapy. In younger patients with symptomatic AF, catheter ablation may be considered a first-line strategy and may help to minimize long-term exposure to antiarrhythmic medications.\(^4\)

After rate control or rhythm control is selected, many patient factors must be considered before the appropriate agent (or agents) is chosen. The decision for selecting pharmacological therapies is based on the patient’s comorbid conditions, most notably the LVEF, because some drugs have deleterious effects in those with an LVEF below 40%. Clinicians must also consider previous treatments, concomitant medications, and drug costs.

**New Agents for Rhythm Control**

Numerous antiarrhythmic medications can be used to manage AF, but only a handful of these, such as amiodarone, dofetilide, and sotalol (Betapace AF, Berlex), are routinely used in practice today. The availability of current antiarrhythmic agents is limited because of their less than optimal efficacy, their adverse-event profile or tolerability, and drug inter-
Dronedarone

A non-iodinated analogue of amiodarone, dronedarone is less lipophilic and has a lower volume of distribution than amiodarone. This molecule has been developed with hopes of achieving efficacy rates similar to those of amiodarone but with fewer AEs. The half-life of dronedarone is 24 hours, and elimination is via the fecal route. Dronedarone is metabolized through the cytochrome P450 (CYP) 3A4 system and inhibits CYP2D6.

Dronedarone 400 mg is administered twice daily with morning and evening meals. It is contraindicated in combination with agents that prolong the QT interval or with drugs that are potent inhibitors of the CYP3A4. Its use with CYP3A4 inducers should be avoided, and clinicians should monitor the concentrations of agents that are CYP3A4 substrates and that have narrow therapeutic indexes such as tacrolimus (Prograf, Astellas/Fujisawa) and sirolimus (Rapamune, Wyeth/Pfizer) when used in conjunction with dronedarone. It is recommended that when dronedarone is combined with digoxin, the dose of digoxin should be reduced by 50% or discontinued.

The combined use of dronedarone with beta blockers and calcium-channel blockers (which depress sinus and atrioventricular node conduction) can potentiate dronedarone’s effect on the heart rate. Care should also be taken when combining dronedarone with simvastatin (Zocor, Merck), because dronedarone can result in significant elevations in simvastatin levels. Recommendations on the label for statins should be followed for use with CYP3A4 and P-glycoprotein inhibitors. For example, the maximum dose of simvastatin should be 20 mg.

Dronedarone has not been shown to increase the risk of bleeding when used in combination with warfarin, but care should still be taken in monitoring the INR when therapy is initiated. Dronedarone is a Pregnancy Category X drug. Whether it is excreted in human milk is unknown.

Dronedarone Versus Placebo

Identical in design, the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American–Australian Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) evaluated the effect of dronedarone in maintaining normal sinus rhythm (NSR) after electrical, pharmacological, or spontaneous cardioversion. The rate of AF at 12 months was significantly reduced with dronedarone. Patients with New York Heart Association (NYHA) Class III and IV symptoms were excluded from the studies. Combined data from the two trials revealed the recurrence rate of AF to be 64.1% in the treatment group and 75.2% in the placebo group (HR, 0.75; 95% CI, 0.65–0.87; P < 0.0001). There was no difference in the rate of hypothyroidism, pulmonary events, photosensitivity, or elevated liver function enzymes between the two groups. However, hyperthyroidism was more common in the placebo group.

The QT interval was prolonged by 23.4 msec with dronedarone and by 9 msec with placebo (P < 0.001); no episodes of torsades de pointes were reported. Serum creatinine levels were increased in 2.4% of the dronedarone patients and in 0.2% of the placebo group. This difference is considered to be a result of dronedarone’s inhibition of serum creatinine excretion at the renal tubular level. A reduction in the glomerular filtration rate was not observed.

A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA) compared dronedarone and placebo in 4,628 high-risk elderly patients with AF or atrial flutter. Dronedarone was associated with a significant reduction in the rate of cardiovascular hospitalization or all-cause death compared with placebo (31.9% vs. 39.4% respectively; HR, 0.76; 95% CI, 0.69–0.84; P < 0.001). Patients with NYHA Class IV symptoms were not included in this trial.

The most commonly observed AEs noted with dronedarone were GI sequelae. There was no difference in rates of thyroid and pulmonary events or in rates of elevated liver enzymes between groups. Serum creatinine levels were increased in the dronedarone patients (4.7% vs. 1.3%, respectively; P < 0.001). The Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) evaluated dronedarone in patients with an LVEF of less than 35% and with NYHA II–IV symptoms to determine whether treatment would reduce the rate of hospitalization or death from heart failure. This trial was stopped early because of an increased rate of death in patients receiving dronedarone at a median of two months of follow-up. Even though ANDROMEDA did not evaluate the effect of dronedarone in patients with AF, the results suggest that this drug should not be used in patients with heart failure and a depressed LVEF regardless of the indication.

Dronedarone Versus Amiodarone

The Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation (DIONYSOS) trial compared the safety and efficacy of these two drugs in maintaining NSR in patients with persistent AF (n = 504). Subjects were followed for a mean duration of seven months. The primary endpoint was AF recurrence or premature drug discontinuation resulting from intolerance or lack of efficacy. The incidence of the primary endpoint was 75.1% with dronedarone and 58.8% with amiodarone (HR, 1.59; 95% CI, 1.28–1.98; P < 0.0001). Dronedarone was not as effective as amiodarone in maintaining NSR following electrical cardioversion.

Atrial fibrillation recurred in 63.5% of subjects in the dronedarone group and in 42% of those receiving amiodarone. There was a nonsignificant reduction in the primary safety endpoint (the first occurrence of the following treatment-emergent events: thyroid, pulmonary, neurological, skin, ocular, or GI
events) in those receiving dronedarone (83 subjects, or 33.3% vs. 107, or 42%; \( P = 0.1291 \)). The rate of GI events was increased in the dronedarone group. Dronedarone patients tended to be less likely (10.9%) to have a QT interval of 500 msec or more (based on the Bazett equation) than the amiodarone patients (20.5%) (\( P = 0.0033 \)). No cases of torsades de pointes were reported in either group.\(^{18}\)

At present, dronedarone may be considered an alternative therapy for maintaining NSR. The risk of AEs appears favorable when compared with amiodarone. In January 2011, the FDA advised health care professionals detailing the rare cases of hepatotoxicity observed with dronedarone. Two liver transplants had been required because of dronedarone toxicity. It is recommended that hepatic serum enzymes be assessed periodically during the first six months of dronedarone therapy.\(^{19}\)

In July 2011, the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial was stopped prematurely because of an increased risk of cardiovascular events in those receiving dronedarone. This was a phase 3 trial comparing dronedarone to placebo in patients with permanent AF (for at least six months) who were older than 65 years of age and who had comorbid conditions. Patients with NYHA class III and IV heart failure were excluded.\(^{20}\)

Dronedarone is approved only for use in individuals with non-permanent AF. However, the drug’s efficacy cannot be considered to be more beneficial in maintaining NSR when compared with other antiarrhythmic medications, because the only head-to-head trial that has been conducted compared this agent with amiodarone.

As seen in DIONYSOS, dronedarone was not as efficacious as amiodarone. Data from dronedarone trials cannot be compared directly with other agents in published studies, because patient populations were different in these other trials. The ACCF/AHA/HRS 2011 Management of AF guidelines indicate that dronedarone is a viable option for decreasing the need for hospitalization or referral to a specialized heart failure clinic, based on the results of the ANDROMEDA trial.\(^{14}\) Because symptoms of heart failure are not predictable, clinicians should consider refraining from prescribing this medication in patients with a depressed LVEF.

**Vernakalant**

Vernakalant HCl (Merck/Cardiome/Astellas US), an IV sodium and potassium-channel blocker, is currently under review for approval by the FDA. Vernakalant was developed to promote rapid conversion of AF to NSR while minimizing the AEs associated with other antiarrhythmic agents.\(^{21}\) Vernakalant’s primary effect is the blockage of the ultra-rapid potassium channels involved in atrial repolarization. As a result of this unique feature, previous trials have shown that the QT interval and ventricular refractory period were not significantly prolonged. A secondary effect is the drug’s inhibition of sodium channels.\(^{22}\)

Vernakalant possesses a quick onset of action, and its half-life is two hours. It is 25% to 50% protein-bound. This drug is metabolized by CYP2D6 to its major active metabolite, RSD1385, which is then conjugated to its inactive form. Vernakalant has not been shown to induce or inhibit the CYP2D6 isoenzyme.\(^{23}\)

The dose being studied is 3 mg/kg in an IV formulation (Kynapid), given over a period of 10 minutes. An additional dose of 2 mg/kg, given over 10 minutes, may be prescribed 15 minutes later if conversion to NSR has not occurred. Dose adjustments are not required in relation to the patient’s age, sex, or degree of renal impairment.

It has not been determined whether adjustments must be made for patients with hepatic impairment. Formal studies involving drug interactions of vernakalant have not been conducted. Because vernakalant is not highly protein-bound, it is thought that it does not interact with other highly protein-bound drugs, including amiodarone, warfarin, phenytoin (Dilantin, Pfizer), diltiazem, and verapamil.\(^{24}\)

**Vernakalant Versus Placebo**

Vernakalant has been evaluated in multiple trials as a novel agent for conversion to NSR. Four phase 3 studies, conducted by Atrial Arrhythmia Conversion Trial (ACT) investigators, evaluated the drug’s safety and efficacy. The first three trials were similar in design. The exclusion criteria for these trials included (but were not limited to) pregnant or nursing women and patients with sick sinus syndrome, a QRS greater than 0.14 seconds without a pacemaker, a ventricular rate of less than 50 beats per minute, an uncorrected QT interval greater than 440 msec, NYHA Class IV heart failure, a reversible cause of AF, and end-stage disease.

The primary outcome was used in all of the trials as well and was defined as the number of patients experiencing NSR for at least one minute within 90 minutes of starting vernakalant. The dose used was 3 mg/kg IV, followed by 2 mg/kg if the participant did not experience conversion to NSR. The most common AEs in these trials were AF, nausea, dysgeusia, sneezing, and paraesthesia.\(^{24,26}\)

In ACT I, the first of these studies,\(^{25}\) patients were stratified based on the duration of AF. Seventy-five patients (51.7%) with AF lasting from three hours to seven days (the short-duration group) achieved the primary endpoint, compared with 4% of those in the placebo group (\( P < 0.0001 \)).

In ACT II, a study of postoperative AF patients, 45% of vernakalant patients experienced conversion to NSR in the first 90 minutes, with a median time to conversion of 12 minutes, compared with 15% of placebo patients (\( P < 0.001 \)).\(^{26}\)

In ACT III, 51% of patients receiving vernakalant (n = 44) experienced conversion to NSR in eight minutes on average, compared with 4% of placebo patients (\( P < 0.0001 \)).\(^{27}\)

ACT IV,\(^{28}\) an open-label study, was conducted to gain additional insight into the safety of using 3 mg/kg plus 2 mg/kg of the drug if required. The primary efficacy measure was the proportion of patients with recent-onset AF who experienced conversion to NSR for at least one minute within 90 min-
utes after the start of the initial infusion. In this trial, 51% of those receiving vernakalant (n = 85) experienced conversion to NSR in 14 minutes on average. There were no deaths within the first 24 hours of vernakalant administration; one patient with breast cancer died during the 30-day follow-up period from an upper GI hemorrhage. The most common serious AEs were bradycardia (1.7%) and hypotension (1.3%). The most common treatment-emergent AEs were dysgeusia (18.6%), sneezing (16.1%), paresthesia (7.6%), and cough (5.5%).

**Vernakalant Versus Amiodarone**

In the Active-Controlled, Multicenter Study of Vernakalant Injection versus Amiodarone in Subjects with Recent Onset Atrial Fibrillation (AVRO), 116 subjects with AF lasting for three to 48 hours were randomly assigned to receive either vernakalant or amiodarone. Amiodarone was given as a loading dose of 5 mg/kg, followed by a one-hour maintenance infusion of 50 mg.

The primary endpoint in AVRO was the same used in ACT and was reached by 51.7% of the vernakalant patients and by 5.2% of the amiodarone group (P < 0.001). Side effects were similar to the results found in other studies as well.25

Following the submission of an NDA to the FDA in December 2007, vernakalant was recommended for approval by the FDA Cardiovascular and Renal Drugs Advisory Committee for conversion of recent-onset AF. In August 2008, the FDA requested additional safety data.28,30 In October 2010, ACT V, a phase 3b randomized clinical trial that evaluated the safety and efficacy of vernakalant, was suspended after a subject receiving the study drug developed cardiogenic shock. ACT V evaluated patients with recent-onset, symptomatic AF (three hours to seven days) with no history of heart failure. Specific information about the patient who developed cardiogenic shock is unknown.

Because of this event, the European Medicines Agency updated the contraindications of vernakalant to warn against the use of Class I and III antiarrhythmic medications within four hours of administration of vernakalant.31 Currently, the FDA is continuing to review all available data. Vernakalant was approved for use in September 2010 in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF.32

Vernakalant appears to be effective for patients with recent-onset AF (seven days or less) who require rapid conversion to NSR. As discussed in the trials, the drug’s efficacy ranges from 51% to 79% for recent-onset AF.22 Vernakalant does not appear to cause torsades de pointes.25,33 Therefore, although this medication appears to be effective, it cannot be considered more effective than other antiarrhythmic agents because of a lack of data. More safety data are warranted before vernakalant can be recommended for use. In addition, more data in patients with heart failure are necessary, because many antiarrhythmic agents have resulted in worse outcomes in this population.

Trials involving an oral formulation of vernakalant are under way. This agent is being evaluated to determine its role in conversion to NSR as well as in maintenance of NSR following electrical cardioversion.34

### Therapy for Stroke Prevention

The management of AF must also include therapy to minimize the risk of stroke. Current treatment options include warfarin and aspirin therapy. Guidelines issued by the American College of Chest Physicians (ACCP) and ACCF/AHA/HRS and by the American Academy of Family Physicians and the American College of Physicians (AAFP/ACP) recommend antithrombotic therapy based on various risk-stratification algorithms. The ACCP guidelines use a risk-stratification scheme and recommend either aspirin 81 to 325 mg or warfarin, depending on the presence of additional risk factors.4

The CHADS-2 score (Congestive heart failure, Hypertension, Age, Diabetes, Stroke [Doubled]) is one method that can be used to determine a patient’s risk for stroke. Table 1 presents a review of this scoring system, which is used to determine appropriate antithrombotic therapy based on an individual’s risk.35,36

The ACCF/AHA/HRS guidelines recommend anticoagulation therapy with warfarin for patients with persistent or paroxysmal AF with high risk factors, namely, prior ischemic stroke, transient ischemic attack, or systemic embolism; mitral stenosis; a prosthetic heart valve; or more than one moderate risk factor (age older than 75 years, heart failure, an LVEF below 35%, hypertension, or diabetes mellitus). Warfarin should be given to achieve an INR between 2.0 and 3.0, with a target of 2.5. Patients with one moderate risk factor

<table>
<thead>
<tr>
<th>Table 1: Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke (CHADS-2) Risk-Stratification Scheme*</th>
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<tr>
<td><strong>Risk Factor Score</strong></td>
</tr>
<tr>
<td>C = Congestive heart failure</td>
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<tr>
<td>H = Hypertension</td>
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<tr>
<td>A = Age &gt; 75 years</td>
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<tr>
<td>D = Diabetes</td>
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<tr>
<td>S = History of stroke or transient ischemic attack</td>
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The American College of Chest Physicians recommends:

- Score ≥ 2: long-term anticoagulation with warfarin (INR range 2 to 3; goal 2.5);†
- Score = 1: long-term anticoagulation with warfarin (INR range 2 to 3; goal 2.5); or aspirin 75 to 325 mg/day; warfarin is suggested rather than aspirin.
- Score = 0: long-term therapy with aspirin 75 to 325 mg/day

This scheme allocates points based on existing risk factors to determine an individual’s risk of embolic events secondary to atrial fibrillation or atrial flutter. The scheme can be used to determine the most appropriate therapy to reduce the risk of an embolic event. INR = International Normalized Ratio.

*This scheme does not apply to patients with valvular heart disease.
†The goal may be higher for selected patients such as those with valvular heart disease.

should receive warfarin (INR 2.0 to 3.0, target 2.5) or aspirin 81 to 325 mg. The INR goal may be higher in selected patients, including those with mechanical mitral valves. In patients with persistent or paroxysmal AF who are younger than 65 years of age with no other risk factors, aspirin 81 to 325 mg is recommended.4

Despite the known benefits of warfarin, only 25% to 50% of patients with AF are receiving it. This may be the result of the various challenges that warfarin poses for both prescribers and patients, such as bleeding, the need for frequent monitoring, dosing variability, and drug–food interactions.35,37,38

Because of these factors, therapies including clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-aventis), oral direct thrombin inhibitors (ximelagatran and dabigatran [Pradaxa]), as well as oral factor Xa inhibitors—rivaroxaban (Xarelto), apixaban, betrixaban (PRT-054021, Merck), YM150 (Astelas), and edoxaban (DU-176b, Merck)—have been or are being studied to minimize the risk of stroke in patients with AF. Table 2 summarizes completed and ongoing phase 3 trials evaluating these new agents.39–43

**Clopidogrel (Plavix)**

The combination of clopidogrel and aspirin (3,335 patients) was compared with vitamin K antagonists (INR goal, 2.0–3.0; n = 3,371) in patients with AF and with one or more risk factors for stroke.44 This trial was terminated early, owing to the significant benefit of vitamin K antagonists in reducing the combined endpoint of the first occurrence of stroke, non–central nervous system (CNS) systemic embolus, myocardial infarction (MI), or vascular death.

The combination of clopidogrel and aspirin was compared with aspirin alone in patients with AF with one or more risk factors for stroke who were unable to take vitamin K antagonists. The same endpoint was used in this trial; the rate of the combined endpoint was 6.8% in the combination therapy arm and 7.6% in the aspirin arm; the relative risk (RR) was 0.89 (95% CI, 0.81–0.98; P = 0.01). This benefit must be weighed against the increased risk of major bleeding with combination therapy (2% vs. 1.3%, respectively; RR, 1.57; 95% CI, 1.29–1.92; P < 0.001). Rates of overall bleeding were 9.7% with clopidogrel/aspirin and 5.7% with aspirin (RR, 1.68; 95% CI, 1.52–1.85; P < 0.001).45

It is recommended that this combination of therapies be considered to reduce the risk of stroke in those with AF who are not candidates for warfarin therapy based on the physician’s assessment. This strategy can also be considered in patients who do not wish to receive warfarin.4

**Ximelagatran**

Ximelagatran (AstraZeneca), an oral direct thrombin inhibitor, was denied approval by the FDA because of angina and coronary ischemia. The risk of hepatotoxicity was increased in subjects receiving ximelagatran; alanine aminotransferase (ALT) levels were also three times the upper limit of normal (ULN).

**Dabigatran Eteoxilate (Pradaxa)**

Dabigatran (Pradaxa, Boehringer Ingelheim), another oral direct thrombin inhibitor, was approved by the FDA to decrease the risk of stroke in patients with AF.46 Unlike warfarin, dabigatran has a quick onset of action with anticoagulant effects within two hours, which can eliminate the use of “bridging” with a low-molecular-weight heparin or unfractionated heparin. The half-life is 14 to 17 hours with multiple doses. Dabigatran undergoes conjugation with glucuronic acid; 80% of the drug is eliminated renally.

The dose is 150 mg twice daily, reduced to 75 mg twice daily for patients with a creatinine clearance (CrCl) of below 30 mL/minute. It is not recommended for patients with a CrCl of less than 15 mL/minute or for hemodialysis patients because of a lack of sufficient evidence supporting its use in this population.46

Dabigatran does not inhibit or induce the CYP isoenzymes, and it is not metabolized by CYP isoenzymes.47 Dabigatran should be avoided with P-glycoprotein inducers (e.g., rifampin). Dose adjustments are not required for use with P-glycoprotein inhibitors such as amiodarone, clarithromycin (Biaxin, Abbott), diltiazem, ketoconazole (Nizoral, Janssen), quinidine, and verapamil.

Dabigatran is considered a Pregnancy Class C medication; it is unknown whether it is excreted in breast milk.46 Based on its pharmacokinetic/pharmacodynamic profile and its quick onset of action, this agent would be an ideal alternative to warfarin to reduce the risk of stroke in patients with AF or atrial flutter.

Data from a pilot trial—PETRO (Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation)—suggested that dabigatran might be a suitable substitute for warfarin to minimize the risk of thromboembolic events in those with AF.48 Based on these results, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial was conducted. In this trial 18,113 subjects with AF at risk for thromboembolism were randomly assigned to receive warfarin (target INR 2.0–3.0) or one of two doses of dabigatran 110 or 150 mg twice daily. Of note, patients with a CrCl of less than 30 mL/minute were excluded from the trial (see Table 2).

The primary endpoint of this non-inferiority trial (RE-LY) was stroke or systemic embolism. Major bleeding in this trial was defined as a drop in hemoglobin of 2 g/L, transfusion of 2 or more units of blood, or symptomatic bleeding in a critical area or organ.

Patients were evaluated for a median of two years. The primary endpoint occurred in 182 patients receiving dabigatran 110 mg (1.53% per year) and in 199 (1.69% per year) of those receiving warfarin (RR, 0.91; 95% CI, 0.74–1.11; P < 0.001 for non-inferiority and P = 0.34 for superiority). The rate of AEs in those receiving dabigatran 150 mg was 134 (1.11% per year) (RR, 0.66; 95% CI, 0.53–0.82; P < 0.001 for superiority).

The risk of hemorrhagic stroke was significantly reduced with dabigatran 110 mg (RR, 0.31; 95% CI, 0.17–0.56; P < 0.001) and 150 mg (RR, 0.26; 95% CI, 0.14–0.49; P < 0.001) when compared with warfarin. Major bleeding was significantly reduced with dabigatran 110 mg compared with warfarin (RR, 0.80; 95% CI, 0.69–0.93; P = 0.003) but not with 150 mg compared with warfarin (RR, 0.93; 95% CI, 0.81–1.07; P = 0.31).

The rate of GI bleeding, whether life-threatening or not, was higher in the 150-mg dabigatran group than in the warfarin group (RR, 1.5; 95% CI, 1.50 1.19–1.89; P < 0.001).
Table 2  Factor Xa and Direct Thrombin Inhibitors in Clinical Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Study Design</th>
<th>Patient Population</th>
<th>Primary Outcome</th>
<th>Major Safety Endpoints</th>
</tr>
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<tr>
<td><strong>Completed Phase 3 Trials</strong></td>
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<tr>
<td>RE-LY39</td>
<td>Dabigatran 110 or 150 mg twice daily vs. warfarin (INR goal 2.5, range 2.0–3.0)</td>
<td>Nonvalvular AF with risk factors for stroke</td>
<td>Stroke or systemic embolism: event rate 1.53%/year with dabigatran 110 mg vs. 1.69%/year with warfarin, (RR, 0.91; 95% CI, 0.74–1.11; P &lt; 0.001 for non-inferiority) and 1.11%/year with dabigatran 150 mg (RR, 0.66; 95% CI, 0.53–0.82; P &lt; 0.001 for superiority of dabigatran 150 mg vs. warfarin)</td>
<td>Major bleeding: event rate with dabigatran 110 mg, 2.71% vs. 3.36%/year with warfarin (RR, 0.80; 95% CI, 0.69–0.93; P = 0.003) and 3.11%/year with dabigatran 150 mg (RR, 0.93; 95% CI, 0.81–1.07; P = 0.31 for dabigatran 150 mg vs. warfarin)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Stroke or systemic embolism: event rate 1.53%/year with dabigatran 110 mg vs. 1.69%/year with warfarin, (RR, 0.91; 95% CI, 0.74–1.11; P &lt; 0.001 for non-inferiority) and 1.11%/year with dabigatran 150 mg (RR, 0.66; 95% CI, 0.53–0.82; P &lt; 0.001 for superiority of dabigatran 150 mg vs. warfarin)</td>
<td>Intracranial hemorrhage: event rate with warfarin, 0.74%/year vs. dabigatran 110 mg, 0.1%/year (RR, 0.31; 95% CI, 0.2–0.47; P &lt; 0.001) and 0.3%/year with dabigatran 150 mg (RR, 0.40; 95% CI, 0.27–0.60; P &lt; 0.001 for dabigatran 150 mg vs. warfarin)</td>
</tr>
<tr>
<td>ROCKET-AF39,40</td>
<td>Rivaroxaban 20 mg daily (15 mg daily for those with CrCl 30–49 mL/minute) vs. warfarin (INR goal 2.5, range 2.0–3.0)</td>
<td>Nonvalvular AF with risk factors for stroke</td>
<td>Composite of stroke and systemic embolism: event rate 1.71% with rivaroxaban vs. 2.16% with warfarin (HR, 0.79; 95% CI, 0.66–0.96; P &lt; 0.001 for non-inferiority)</td>
<td>Major and non-major bleeding: rivaroxaban (14.91%) and warfarin group (14.52%; P = 0.442)</td>
</tr>
<tr>
<td>AVERROES41</td>
<td>Apixaban 5 mg twice daily (2.5 mg twice daily in certain patients) vs. ASA 81–324 mg daily</td>
<td>Nonvalvular AF with risk factors for stroke unsuitable for VKA therapy</td>
<td>Occurrence of stroke or systemic embolism: event rate with apixaban, 1.6%/year vs. 3.7%/year with ASA (HR, 0.45; 95% CI, 0.32–0.62; P &lt; 0.001)</td>
<td>Major bleeding: apixaban, 1.4%/year vs. ASA, 1.2%/year (HR, 1.13; 95% CI, 0.74–1.75; P = 0.57)</td>
</tr>
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<td></td>
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<td>Minor bleeding: apixaban, 6.3%/year vs. ASA, 5%/year (HR, 1.24; 95% CI, 1.00–1.53; P = 0.05)</td>
<td>No difference in the rate of intracranial hemorrhage or GI bleeding</td>
</tr>
<tr>
<td><strong>Ongoing Phase 3 Trial</strong></td>
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<tr>
<td>ARISTOTLE42</td>
<td>Apixaban 5 mg twice daily vs. warfarin (INR goal 2.5, range 2–3)</td>
<td>Nonvalvular AF with risk factors for stroke</td>
<td>Time to stroke or systemic embolism</td>
<td>Ischemic/hemorrhagic stroke, systemic embolism, and all-cause death</td>
</tr>
<tr>
<td><strong>Completed Trial</strong></td>
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<tr>
<td>Efficacy and Safety of Rivaroxaban for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation43</td>
<td>Rivaroxaban 15 mg daily (10 mg daily for CrCl 30–49 mL/minute) vs. dose-adjusted warfarin</td>
<td>Japanese men and women with non-valvular AF at risk for stroke</td>
<td>Composite of stroke and systemic embolism</td>
<td>Stroke, systemic embolism, vascular death, bleeding, and adverse events</td>
</tr>
</tbody>
</table>

*The full results of these trials have not been published.
† Patients meeting two of the following criteria: age, 80 years or older; body weight, 60 kg or lower; or serum creatinine, 1.5 mg/dL or more.
AF = atrial fibrillation; ASA = acetylsalicylic acid; CI = confidence interval; CrCl = creatinine clearance; GI = gastrointestinal; HR = hazard ratio; RR = relative risk; VKA = vitamin K antagonist.

Trials: ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic events in Atrial Fibrillation; AVERROES = Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K Antagonist Treatment; RE-LY = Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation.
The rate of intracranial hemorrhage was significantly higher with warfarin. AE rates were 0.74% per year with warfarin and 0.3% per year with dabigatran 150 mg (RR, 0.31; 95% CI, 0.2–0.47; P < 0.001).  

The 150-mg dose was associated with a lower risk of stroke or systemic embolism than the 110-mg dose (RR, 0.73; 95% CI, 0.58–0.91; P = 0.005), but no statistical difference in major bleeding was seen (RR, 1.16; 95% CI, 1.00–1.34; P = 0.052). The difference in the primary endpoint between the doses was driven by a difference in the risk of stroke caused by ischemic or unspecified causes. The rate of MI was significantly increased with both dabigatran 110 mg (RR, 1.35; 95% CI, 0.98–1.87; P = 0.07) and dabigatran 150 mg (RR, 1.38; 95% CI, 1.00–1.91; P = 0.048) compared with warfarin. Unlike the risk of hepatotoxicity noted with ximelagatran, another direct thrombin inhibitor, dabigatran in this trial was not associated with hepatotoxicity or elevated levels in liver function tests. Dyspepsia was the only other AE seen more often in patients receiving dabigatran.  

Subsequently, the RE-LY investigators published revised data for the primary endpoint and the rate of MI that occurred during the trial based on newly identified events. Incorporation of these results did not change the primary efficacy or safety results. However, the difference in the rate of MI in the comparison of the 150-mg dose with placebo was no longer significant (RR, 1.27; 95% CI, 1.094–1.71; P = 0.12).  

The RE-LY findings suggested that dabigatran could be an alternative to warfarin for reducing the risk of stroke and systemic embolism in patients with AF and risk factors for stroke. The 150-mg dose offered better stroke and systemic embolism protection than warfarin, but there was no difference in the risk of bleeding. The FDA did not approve the 110-mg dose that was used in the RE-LY trial, probably because of the increased risk of ischemic strokes in this group. The 75-mg dose that the FDA did approve for patients with renal impairment has not been evaluated in clinical trials.  

Warfarin is available as a generic medication, but therapy comes with the added cost of office visits and laboratory monitoring. Although patients receiving dabigatran do not require specific monitoring, the cost of the medication is much higher than that of warfarin. Therefore, a cost-effectiveness analysis using data primarily from RE-LY was conducted. The cost of dabigatran used in this analysis ($13 per day for the 150-mg dose in 2008 U.S. dollars) was estimated based on pricing from the United Kingdom. Total costs (in 2008 U.S. dollars) associated with warfarin were $143,193 and $168,398 for dabigatran 150 mg twice daily (the FDA-approved standard dose). The incremental cost-effectiveness ratio was $45,372 per quality-adjusted life year (QALY) with dabigatran 150 mg compared with warfarin. In this analysis, the cost-effectiveness of this dose seemed to become less effective when the daily cost of the dabigatran 150-mg dose exceeded $13.70. The current average wholesale price (AWP) for the 150-mg dose is $8.10 per day. Of note, cost-effectiveness data are not available for the 75-mg twice-daily dose, which is approved for use and is recommended in patients with a CrCl of less than 30 mL/minute.  

Dabigatran is recommended in the ACCF/AHA/HRA guidelines as an alternative to warfarin to decrease the risk of stroke and systemic embolism in patients with AF at risk for stroke who do not have a mechanical valve, significant valvular disease, a CrCl below 15 mL/minute, or advanced liver disease. Clinicians who switch their patients from warfarin can initiate treatment with dabigatran when the INR is below 2.0. Specific recommendations to guide prescribers in converting a patient from warfarin therapy to dabigatran or from dabigatran to warfarin are available from Boehringer Ingelheim, the drug’s manufacturer. Dabigatran should be discontinued one or two days before invasive or surgical procedures in patients with a CrCl of 50 mL/minute or more or for three to five days in those with a CrCl below 50 mL/minute. Therapy should be stopped earlier for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.  

Further, the INR cannot be used to monitor the effects of dabigatran, and no reversal agent currently exists. Bleeding risk can be evaluated by assessing a patient’s Ecrin clotting time; the activated partial prothrombin time (aPTT) can be used if the Ecrin clotting time test is not available. The Ecrin test, however, is a better marker of the anticoagulation effect of dabigatran. This drug has not been evaluated in patients with mechanical heart valves.  

### Rivaroxaban (Xarelto)  

Rivaroxaban (Xarelto, Bayer), an oral factor Xa inhibitor, has also been investigated as an alternative for stroke prevention in patients with AF. Factor Xa is the rate-limiting step in thrombin production. Rivaroxaban has a quick onset of action, and no routine monitoring is needed. The half-life is four to nine hours, and the area-under-the-curve (AUC) concentration is increased in patients older than 75 years of age as well as in those with impaired renal function. Of note, 30% of the drug is excreted unchanged in the urine, and trials have excluded patients with a CrCl of less than 30 mL/minute. Rivaroxaban undergoes hepatic metabolism primarily through the CYP3A4 system.  

The Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K antagonism for the Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a non-inferiority trial evaluating the rate of all-cause stroke and non-CNS systemic embolism in subjects receiving rivaroxaban or warfarin. In this trial, more than 14,000 patients with AF were randomly assigned to receive rivaroxaban 20 mg or dose-adjusted warfarin (INR goal, 2.5). The rivaroxaban dose was reduced to 15 mg in those with moderate renal impairment. More than 90% of the subjects included in this trial had a CHADS-2 score of 3 or more (see Table 1).  

The primary endpoint was reached by 1.71% of subjects in the rivaroxaban group (n = 7,081) and by 2.16% of those in the warfarin group (n = 7,090) (HR, 0.79; 95% CI, 0.66–0.96; P < 0.001 for non-inferiority). Rates of major and non-major bleeding were comparable for rivaroxaban (14.9%) and warfarin (14.5%) (P = 0.442). The full results of this trial have not yet been published. A second trial evaluating the use of rivaroxaban has been completed, but the results have not yet been reported.  

Currently, rivaroxaban has been used in Europe for the prevention of venous thromboembolism (VTE) in patients under-
going total hip- or knee-replacement therapy. On July 1, 2011, the FDA approved the drug as prophylaxis for deep-vein thrombosis, which can lead to pulmonary embolism, following hip- and knee-replacement surgery. In January 2011, Bayer had submitted an NDA to the FDA for the use of rivaroxaban in the prevention of stroke in patients with AF.

Apixaban

Apixaban (BMS-562247, Bristol-Myers Squibb) is a direct and competitive factor Xa inhibitor. Its half-life is approximately 12 hours, and approximately 25% of the medication is excreted renally. There is a low potential for drug interactions except when it is combined with strong CYP3A4 inhibitors. Specific data regarding these interactions are not available.

The Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial compared aspirin 81–324 mg (n = 2,791) with apixaban 5 mg (n = 2,808) twice daily (see Table 2).

The primary endpoint was the rate of stroke or systemic embolism in subjects with AF and an increased risk of stroke. Apixaban subjects received 2.5 mg twice daily if they met two of the following criteria: age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL or higher. Patients were enrolled if they were 50 years of age or older with documented nonvalvular AF in the past six months with at least one risk factor for stroke. Participants also had to be deemed unsuitable (or expected to be unsuitable) candidates for vitamin K antagonist therapy. Subjects were excluded from the study if serum creatinine levels exceeded 2.5 mg/dL, if the CrCl was below 25 mL/minute, if transaminase levels were elevated more than two times the ULN, or if the bilirubin level was more than two times the ULN.

AVERROES was terminated after the first interim analysis because of the decreased risk of stroke or systemic embolism with apixaban—an AE rate of 1.6% per year with apixaban vs. 3.7% per year with aspirin (HR, 0.45; 95% CI, 0.32–0.62; P = 0.001). The mean duration of the follow-up period was 1.1 years. There were 51 AEs in the apixaban group, and six AEs were the result of a hemorrhagic stroke. There were 113 AEs in the aspirin group; nine of these were the result of a hemorrhagic stroke.

The most common reasons for subjects being considered unsuitable for vitamin K antagonist therapy were as follows:

- The INR was unlikely to be assessed at requested intervals (46%).
- Patients refused to take vitamin K antagonist therapy (38%).
- Patients had a CHADS-2 score of 1 (see Table 1).
- The physician did not recommend the therapy (22%).
- Other (43%).

There was no difference in the rate of major bleeding between groups; the rate of AEs was 1.4% per year with apixaban and 1.2% with aspirin (HR, 1.13; 95% CI, 0.74–1.73; P = 0.57). The rate of minor bleeding AEs was increased in the apixaban group by 6.3% per year and by 5% per year in the aspirin group (HR, 1.24; 95% CI, 1.00–1.53; P = 0.05). No difference in the rate of elevated transaminases or bilirubin was noted between the groups.

The NDA for apixaban has not been submitted to the FDA. As with rivaroxaban, a reversal agent is not available. Data from the ongoing Apixaban for Reduction in Stroke and Other Thromboembolic events in Atrial Fibrillation (ARISTOTLE) trial should allow providers to better define the role of apixaban in preventing stroke in patients with AF (see Table 2).

Data from the Apixaban for the Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial demonstrated that the risk of bleeding was significantly increased when apixaban was combined with aspirin and clopidogrel, compared with the use of aspirin and clopidogrel plus placebo. The use of anticoagulation and dual antiplatelet therapy is likely to pose a continued concern to prescribers, even if these drugs are alternatives to warfarin. Prescribers will need to continue to assess the risks and benefits of this triple therapy, such as in patients with an acute coronary syndrome and AF who also have risk factors for stroke. No ongoing clinical trials are currently comparing any of the new anticoagulation agents with one another.

Conclusion

The management of AF will continue to evolve over time with the increased use of nonpharmacological treatment strategies, new antiarrhythmic agents, and anticoagulants. The focus of therapy will always be to reduce symptoms and to minimize the risk of stroke. Treatment plans should be individualized based on the presence or lack of symptoms and comorbid conditions. Care should be taken to manage drug interactions, to minimize the risk of toxicity from antiarrhythmics by ensuring that doses are adjusted for renal impairment when necessary, and to counsel patients on the need for monitoring of adverse effects. Finally, attention must be paid to ensuring that patients at risk for stroke receive anticoagulation therapy unless a true contraindication is present.

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**TOPIC:** Medication Management of Atrial Fibrillation

Emerging Therapies for Rhythm Control and Stroke Prevention

ACPE Program # 0079-9999-11-013-H01-P

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**Multiple Choice**

**Select the one correct answer.**

1. The RACE II trial found that:
   a. The rate of adverse events in the strict rate control group was significantly greater than in the lenient rate control group.
   b. Lenient rate control is considered superior to strict rate control.
   c. Strict rate control is considered superior to lenient rate control, and the rate of adverse events in both groups is not statistically different.
   d. Lenient rate control is considered non-inferior to strict rate control.

2. The ANDROMEDA trial found that:
   a. Dronedarone was safe and effective in all patients, regardless of New York Heart Association (NYHA) classification.
   b. Dronedarone is contraindicated in those with heart failure and a depressed left ventricular ejection fraction (LVEF) with NYHA Class IV symptoms, but it can be used with caution in those with NYHA Class II and III symptoms who required recent hospitalization or referral to a specialized heart failure clinic.
   c. Dronedarone is contraindicated only in those with NYHA Class II and III symptoms who required recent hospitalization or referral to a specialized heart failure clinic.
   d. Dronedarone is contraindicated in those with heart failure and a depressed LVEF with NYHA Class IV symptoms or NYHA Class II and III symptoms who required recent hospitalization or referral to a specialized heart failure clinic.

3. The DIONYSOS trial found that:
   a. Dronedarone was more effective than amiodarone in maintaining normal sinus rhythm following electrical cardioversion in subjects with persistent atrial fibrillation.
   b. Dronedarone was non-inferior to amiodarone in maintaining normal sinus rhythm following electrical cardioversion in subjects with persistent atrial fibrillation.
   c. Dronedarone was less effective than amiodarone in maintaining normal sinus rhythm following electrical cardioversion in subjects with persistent atrial fibrillation.
   d. Neither dronedarone nor amiodarone was effective in maintaining normal sinus rhythm following electrical cardioversion in subjects with persistent atrial fibrillation.

4. In a phase 3b randomized clinical trial known as ACT V, vernakalant was evaluated for safety and efficacy. The trial was suspended owing to which of the following safety concerns?
   a. Patients receiving vernakalant had a statistically significant increased rate of all-cause mortality.
   b. A patient receiving vernakalant went into cardiogenic shock.
   c. Patients receiving vernakalant developed serious torsades de pointes.
   d. A patient receiving vernakalant developed non-inferior to strict rate control.

5. Hypertension and congestive heart failure were diagnosed in a 76-year-old male patient. According to the American College of Chest Physicians’ (ACCP) risk-stratification scheme, the CHADS-2 score, which of the following therapies is most appropriate for the patient?
   a. long-term anticoagulation with warfarin (INR range 2.0 to 3.0; goal 2.5)
   b. no therapy needed
   c. short-term anticoagulation with warfarin (INR range 2.0 to 3.0; goal 2.5)
   d. long-term therapy with aspirin 75 to 325 mg/day

6. The American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) guidelines recommend anticoagulant therapy with warfarin for patients with persistent or paroxysmal atrial fibrillation with high risk factors who have any of the following features except:
   a. systemic embolism.
   b. diabetes mellitus.
   c. mitral stenosis.
   d. a prosthetic heart valve.

7. The following therapies have been or are currently being investigated in phase 3 trials to treat stroke risk with atrial fibrillation and to minimize the downside of warfarin except:
   a. clopidogrel.
   b. dabigatran.
   c. rivaroxaban.
   d. amiodarone.

8. Which of the following medications is recommended in the ACCF/AHA/HRA guidelines as an alternative to warfarin therapy to decrease the risk of stroke and systemic embolism in patients with atrial fibrillation at risk for stroke who do not have a mechanical valve, significant valve disease, a creatinine clearance below 15 ml/minute, or advanced liver disease?
   a. clopidogrel
   b. dabigatran
   c. rivaroxaban
   d. apixaban

9. Which of the following factors is not considered a moderate risk factor for atrial fibrillation?
   a. age older than 75 years
   b. heart failure
   c. transient ischemic attack
   d. LVEF below 35%

10. A randomized controlled trial (AVERROES, 2010), which included 5,600 patients and compared aspirin 81–324 mg with apixaban 5 mg twice daily, was stopped early because:
   a. there was a significant benefit of aspirin in reducing stroke, non–central nervous system systemic embolus, myocardial infarction, or vascular death.
   b. women taking apixaban therapy began to experience adverse reactions.
   c. treatment with apixaban significantly reduced the risk of stroke or systemic embolism after the first interim analysis.
   d. the rate of intracranial hemorrhage was significantly higher with apixaban than with aspirin.
CE Registration and Evaluation Form

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Authors: Emily Knapp, PharmD, MBA; and Kristin Watson, PharmD, BCPS
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City: ___________________________ State: __________ Zip: __________ Telephone: ___________________________
E-mail address: ___________________________ Check one: □ Physician □ Pharmacist □ Other
Time needed to complete this CE activity in hours: □ 0.5 hr □ 1 hr □ 1.5 hr □ 2 hr □ Other ______________________________
NABP ID # (required for pharmacists only): ___________________________ Date of birth (MM/DD): ___________________________
Certification: I attest to having completed this CE activity. ___________________________
Signature (required) Date ______________

Answer Sheet
Please fill in the box next to the letter corresponding to the correct answer
1. a □ b □ c □ d □ 6. a □ b □ c □ d □
2. a □ b □ c □ d □ 7. a □ b □ c □ d □
3. a □ b □ c □ d □ 8. a □ b □ c □ d □
4. a □ b □ c □ d □ 9. a □ b □ c □ d □
5. a □ b □ c □ d □ 10. a □ b □ c □ d □

Evaluation
Rate the extent to which: ___________________________

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<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
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1. Objectives of this activity were met
2. You were satisfied with the overall quality of this activity
3. Content was relevant to your practice needs
4. Participation in this activity changed your knowledge/attitudes
5. You will make a change in your practice as a result of participation in this activity. Specify the changes you plan to make.
6. This activity presented scientifically rigorous, unbiased, and balanced information
7. Individual presentations were free of commercial bias
8. Adequate time was available for Q&A
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   □ Discuss new information with other professionals
   □ Consult the literature
   □ Discuss with industry representative(s)
   □ Participate in another educational activity
   □ Other ___________________________ □ None

Send the completed form and $15 payment (make checks payable to P&T) to: The Jefferson School of Population Health, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.