

# GETTING TO THE HEART of ATRIAL FIBRILLATION



An update for **NURSE PRACTITIONERS**  
and **PHYSICIAN ASSISTANTS**

## FACULTY

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## Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in the practice of cardiology and primary care

## Goal

To provide clinicians with the most timely scientific information and evidence-based clinical practice recommendations for the detection and management of atrial fibrillation (AF).

## Learning Objectives

After completing this activity, participants should be better able to:

- Develop protocols for the risk stratification and evaluation of patients with AF.
- List the various medical, noninvasive, and invasive AF management strategies.
- Compare strategies for managing patients with AF based on the latest evidence.
- Evaluate the benefits and limitations of antiarrhythmic and anticoagulation therapies.
- Educate patients about AF and its management.

## Accreditation Information

 The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.



This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel.

**ATRIAL FIBRILLATION** (AF) is the most common sustained cardiac arrhythmia affecting 2.2 million Americans. Management of patients with AF will become increasingly important as the prevalence of AF is expected to increase to 5.6 million by 2050 due to the increase in the elderly population. AF is chronic, progressive, and often permanent; it doubles the risk for death independently of coexisting illness. For patients with AF, the primary treatment goal is stroke prevention. Strategies to reduce morbidity and mortality have been debated for decades, but only proper use of warfarin anticoagulation in patients at increased risk for stroke has been shown to improve survival or prevent stroke. With the recent introduction of a new class III antiarrhythmic agent and the potential for new anticoagulation agents that are less management intensive, efforts continue to improve treatments and quality of life (QoL) for patients with AF.

Approval is valid for 1 year from the issue date of February 17, 2010. Participants may submit the self-assessment at any time during that period. This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

This program was supported by an educational grant from sanofi-aventis.

## How to Receive Credit

Participants wishing to earn CME/CE credit must:

1. Read the newsletter.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and evaluation form online at [www.practicingclinicians.com/afibnews](http://www.practicingclinicians.com/afibnews).

Successful completion of the self-assessment is required to earn CME/CE credit. Successful completion is defined as a cumulative score of at least 70%.

The estimated time to complete this activity is 1 hour.

**Release date:** February 17, 2010

**Expiration:** Required materials must be submitted before February 17, 2011

## Disclaimer

The opinions or views expressed in this continuing education activity are those of the faculty and do not necessarily reflect the opinions or recommendations of Practicing Clinicians Exchange; University of Nebraska Medical Center College of Nursing Continuing Nursing Education; or sanofi-aventis.

## Disclosures

**Dr Calkins:** consultant: Biosense Webster, sanofi-aventis; scientific advisory board: Ablation Frontiers.

**Mr McGinnity:** honorarium: Forest Pharmaceuticals, Inc., Pfizer Inc; speakers bureau: Novartis.

The Planning Committee for this activity included Catherine A. Bevil, RN, EdD, and Lisa Anzai, RN, MA, of the University of Nebraska Medical Center College of Nursing Continuing Nursing Education; and Ruth Cohen and Grace Halsey of Continuing Education Alliance.

The members of the Planning Committee have no significant relationships to disclose.

Please contact Practicing Clinicians Exchange at [pce@cealliance.org](mailto:pce@cealliance.org) for questions regarding this activity.

## AF: Who Is at Risk?

AF is primarily a disease of the elderly, affecting 3% to 5% of those aged ≥65 years and 9% of those aged >80 years.<sup>1</sup> As America continues to age, the incidence and prevalence of AF among the elderly will rise. In 2000, 82% of Americans with AF were aged ≥65 years and 37% were ≥80 years; by 2050, 88% will be aged ≥65 and 53% will be ≥80 years.<sup>1</sup> A recent analysis of Framingham data<sup>2</sup> found that the lifetime risk of developing AF at ≥40 years of age is approximately 25%.<sup>2</sup> AF can occur in the absence of other cardiac or cardiovascular diseases (CVDs), but aside from advanced age, hypertension is the cause of more AF (14%) than any other risk factor.<sup>3,4</sup> Patients with AF often have CVD such as ischemic heart disease or heart failure (HF) or risk factors for CVD such as diabetes.<sup>5</sup> A number of non-cardiac causes have been implicated in AF, including overt hyperthyroidism, autonomic dysfunction, and systemic or cardiometabolic inflammation.<sup>6</sup> Sleep apnea is strongly associated with AF and smoking is an important—and modifiable—risk factor.<sup>5</sup> In up to 30% of patients, however, AF is not related to disease or known risk factors and is referred to as “lone AF” (Table 1).<sup>7</sup>

According to findings from the Framingham Heart Study, AF doubles the risk for all-cause and cardiovascular mortality in men and women across ages<sup>3</sup> independent of comorbidities.<sup>4</sup> Stroke is the most frequently observed cardiovascular event in patients with AF.<sup>5,8</sup> Although the level of risk for stroke varies from patient to patient, developing AF raises the risk for stroke approximately 2- to 3-fold.<sup>3</sup> AF is an independent risk factor for primary and secondary ischemic stroke<sup>9</sup> and is responsible for 15% to 20% of all ischemic strokes.<sup>1</sup> Hospitalization for AF has increased 66% in the past 20 years due primarily to an aging population, an increase in chronic heart disease, and better diagnosis.<sup>5</sup> Preventing thromboembolic complications, particularly stroke, is the primary goal of AF treatment.

AF presents with a range of symptoms and each can have a substantial negative impact on patients' QoL. Clinical presentation of AF can include

<b>Cardiovascular Disease</b>	<b>Extracardiac Disease</b>	<b>Lone AF</b>
Hypertension	Infections	Unrelated to disease; no known risk factors
Cardiomyopathy	Pulmonary diseases	
Rheumatic heart disease	Electrolyte disturbance	
Coronary artery disease	Alcohol abuse	
Congenital heart disease	Thyrotoxicosis	
Pericarditis	Noncardiac surgery	
Previous stroke or TIA	Cerebrovascular event	
Cardiac surgery		

Adapted from Grönefeld GC, et al.<sup>7</sup>

palpitations, angina, dyspnea, impaired exercise tolerance, and fatigue. However, some patients may be asymptomatic, even those with severe AF and at high risk for stroke.<sup>5,10</sup> If left untreated, AF that results in a rapid ventricular response may induce a rate-related cardiomyopathy.<sup>10</sup>

## Medical Management of AF: In Search of Balanced Treatment

The medical management of AF is a challenge, primarily due to the range of clinical presentations and the inherently erratic nature of the disease. Available medical therapy for AF is also heterogeneous, whether for controlling heart rate, converting AF to normal sinus rhythm (NSR), or maintaining NSR. Drug development continues at a rapid pace, particularly the pursuit of antiarrhythmic drugs (AADs) with more favorable safety and efficacy profiles and anticoagulants that are easier for patients and clinicians to manage. This shifting environment requires a careful review of the literature and the clinical acumen and flexibility to reassess and revise therapy in appropriate patients.

The primary and overarching treatment goal in patients with AF is to minimize the risk of stroke—a goal that requires awareness of the relative risk for stroke in individual patients and the proper assessment for anticoagulation with warfarin. The specific strategies used to reduce AF-related morbidity and mortality—restoration and maintenance of

NSR or control of ventricular rate—have been the impetus for a number of high-profile clinical trials to prove superiority or disprove inferiority of one over the other.

Conventional wisdom was based on the idea that restoring and maintaining NSR produced better clinical outcomes than controlling ventricular rate and allowing AF to continue.<sup>11</sup> For many patients, restoring sinus rhythm (SR) can improve symptoms (palpitations, dyspnea, and fatigue) and subjective distress and thus enhance QoL.<sup>11</sup> Consistent SR also has been shown to help prevent tachycardia-stimulated heart remodeling and improve hemodynamics.<sup>6</sup> It was once thought restoring and preserving NSR would eliminate the need for long-term anticoagulation by preventing (or reducing the risk of) thromboembolism—a notion now disproved.<sup>11</sup> Whether ventricular rate control is chosen as a long-term approach to AF management, it is one of the first steps in managing acute or recurrent AF and seeks to achieve a rate <100 bpm (60–80 at rest; 90–115 during moderate exercise).<sup>5</sup> In appropriate patients, AF management through rate control also has benefits—it generally is easier to achieve, costs less to maintain, and relies on medications (ie, calcium channel blockers, beta blockers, digoxin) with more favorable adverse event profiles than current AADs.<sup>5</sup>

Five large randomized clinical trials: RAte Control versus Electrical Cardioversion for Persistent Atrial

Fibrillation (RACE)<sup>12</sup>; Pharmacological Intervention in Atrial Fibrillation (PIAF)<sup>13</sup>; Strategies of Treatment of Atrial Fibrillation (STAF)<sup>14</sup>; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)<sup>15</sup>; and How to Treat Chronic Atrial Fibrillation (HOT CAFE)<sup>16</sup> have demonstrated equivalence between the 2 strategies or shown noninferiority of one over the other. Overall, no significant differences in mortality or other cardiac and noncardiac end points were found between rhythm- or rate-controlled groups.<sup>12-16</sup> The American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines state that the 2 strategies are basically equivalent in terms of risk/benefit ratio for most patients. It is important to recognize that patients enrolled in the largest of the trials (AFFIRM) had to be candidates for rhythm or rate control. As a result, patients selected generally were minimally symptomatic or asymptomatic. Thus, it cannot be extrapolated from these studies that rate and rhythm control strategies are equivalent for patients with highly symptomatic AF. Many highly symptomatic patients with AF prefer a rhythm-control strategy because of improvement in QoL.

Long-term rate control plus antithrombotic therapy may be preferred in some populations, including patients who are asymptomatic, have a low chance of maintaining SR, and are not suffering from AF-induced hemodynamic deterioration.<sup>5,10</sup> For patients with symptomatic AF of several weeks duration, anticoagulation and rate control may serve as an initial strategy while restoration of SR is the long-term goal. If at any point, rate control fails to provide adequate symptom relief, restoration of SR becomes the long-term goal.<sup>5</sup> For any patient at any specific point in time and disease progression, the choice of how to manage AF will be dictated by presenting factors including stroke risk, history, and comorbidities (Figure 1).

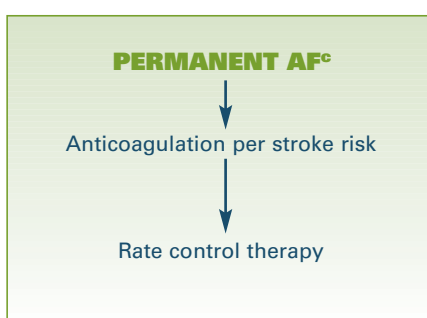
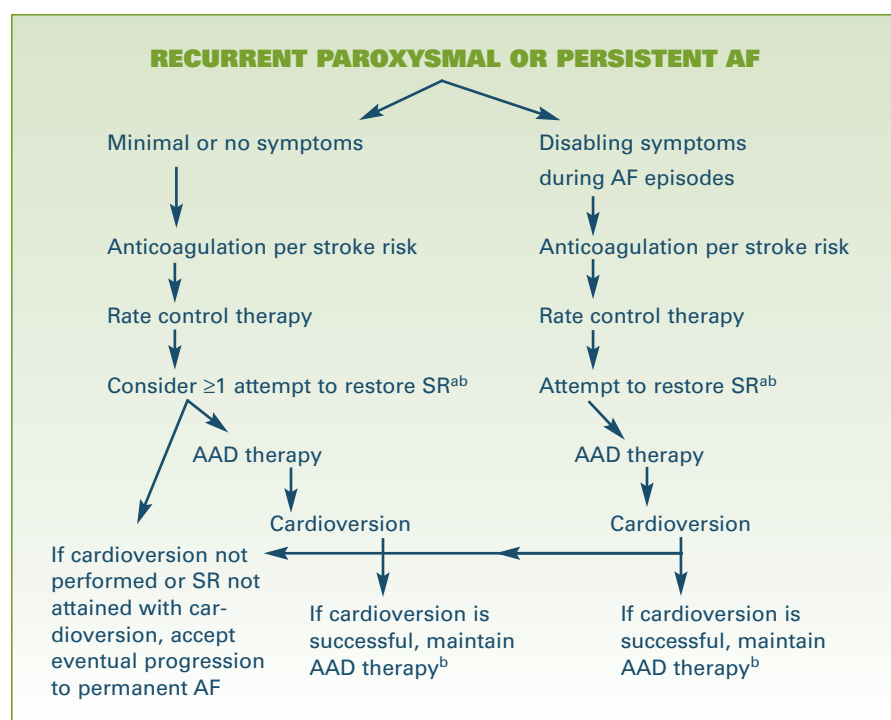
### Rhythm Versus Rate: Truly Equal?

Results of the AFFIRM trial, when first reported, supported findings from similar previous studies. The study's size and population complexity, however, opened doors to follow-up analysis. Post hoc analysis of mortality according to baseline patient characteristics in AFFIRM revealed several factors associated with an elevated risk of death among patients in the rhythm-control group compared

with the rate-control group: older age ( $\geq 65$  years), presence of coronary artery disease, and absence of HF.<sup>15</sup> Consistent with results of other rhythm- vs rate-control studies,<sup>12,14,16</sup> there were more adverse events in the AFFIRM rhythm-control group, and more patients in this group required hospitalization than in the rate-control group (80% vs 73%;  $P < .001$ ).<sup>20</sup>

Additional retrospective analysis of outcomes for AFFIRM patients who received AADs and those who achieved SR revealed that the presence of SR was associated with a 46% lower risk for death ( $P < .0001$ ).<sup>20</sup> However, the risk for death was increased by 89% for those taking rhythm-control drugs ( $P = .0005$ ).<sup>20</sup> Additional subanalysis of AFFIRM results found that patients in SR not taking AADs did significantly better than those whose rate was controlled but who were not in SR, suggesting that the presence of SR may offer survival benefits.<sup>20</sup> It looked as though any survival benefits conferred by SR were negated by the toxic effect of AAD therapy.<sup>20</sup>

The association of increased mortality with AADs is documented<sup>21-25</sup> and is consistent with knowledge of their toxicity. Conversely, a series of clinical trials found that patients in SR with or without AAD



**Figure 1. ACC/AHA/ESC algorithms for individualizing AF therapy for patients with paroxysmal or persistent AF and patients with permanent AF.** <sup>a</sup>Burden of symptoms occurring with AF episodes should be included in the risk/benefit analysis; <sup>b</sup>specific antiarrhythmic agent(s) determined according to patient's coexisting CVD and other disease history; <sup>c</sup>patients for whom SR could not be sustained after cardioversion or the physician and patient agreed to allow AF to continue without further attempts to restore SR. Adapted from Fuster V, et al.<sup>5</sup>

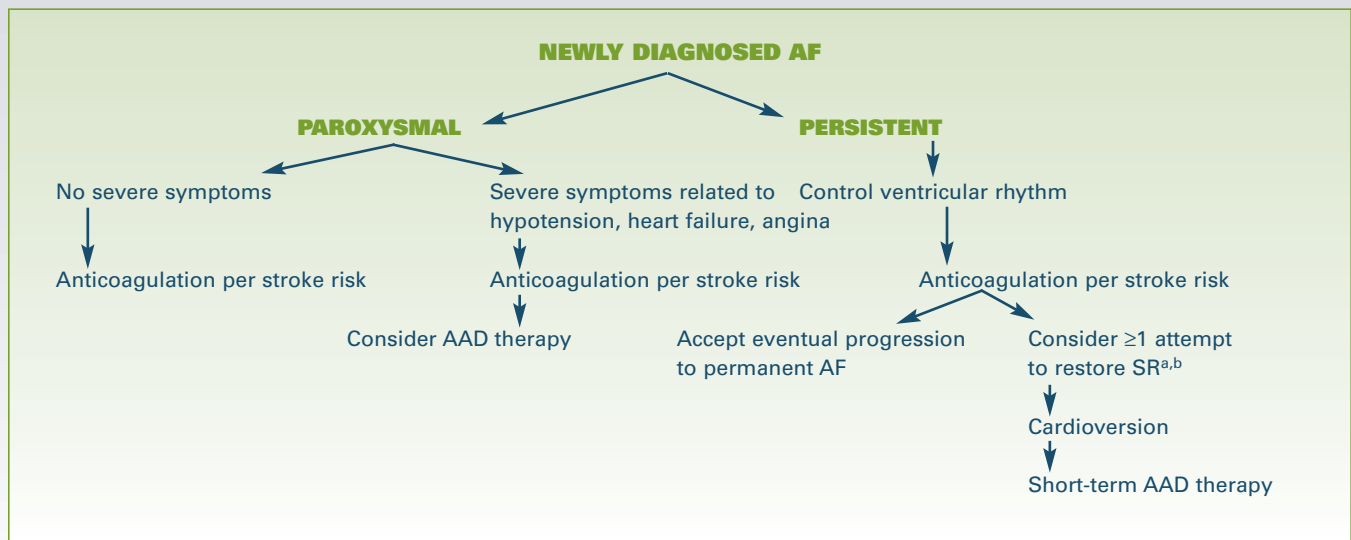
## Diagnosing AF

AF is chronic and progressive. In the early stages, episodes of AF may be paroxysmal—self-terminating with spontaneous conversion to NSR. AF can also be persistent, lasting >7 days and necessitating medical intervention for termination (Figure 2).<sup>5</sup> In its most severe form, AF becomes permanent.<sup>5</sup> As many as 25% of patients with paroxysmal AF will progress to chronic or permanent AF within 5 years.<sup>17,18</sup> Persistence of AF episodes and permanent AF result from aging of the atria and the progressive nature of this condition.

In some patients, the initial presentation of AF may be an embolic event or exacerbation of HF.<sup>5</sup> More commonly, a patient will describe palpitations, chest pain, dyspnea, fatigue, lightheadedness, and, rarely, syncope. Polyuria may occur as an episode begins or

terminates.<sup>5</sup> The ACC/AHA/ESC guidelines provide recommendations for diagnostic workup for the patient with suspected or proven AF.<sup>5</sup> It is recommended that investigations verify AF and collect the necessary information to develop a clinical management strategy.

A diagnosis of AF is based on a clinical examination and thorough history and confirmed by electrocardiographic documentation. The arrhythmia may be suspected during physical examination based on irregular pulse, irregular jugular venous pulsations, and variation in intensity of first heart sound or absence of a fourth sound heard previously during SR. The physical examination may also detect underlying valvular heart disease, myocardial abnormalities, or HF.<sup>5</sup> A full medical history from the patient is necessary, including presence and burden of symptoms, whether the patient is



**Figure 2. Newly diagnosed AF.** <sup>a</sup>Weight potential benefit of preventing permanent AF with the potential toxicity of antiarrhythmic drug therapy. <sup>b</sup>Burden of symptoms occurring with AF episodes should be included in the risk/benefit analysis. Adapted from Fuster V, et al.<sup>5</sup>

therapy had a better prognosis than those who were rate controlled but had continued AF.<sup>26</sup> A study that examined atrial and ventricular remodeling in patients with and without SR found a significant increase in atrial size in the AF group compared with patients in SR, again suggesting that consistent SR may provide an advantage. Because these evaluations were retrospective, it is not clear whether SR is a determinant of survival or a marker for other survival factors not determined.

Another important finding from AFFIRM was that while rates of ischemic stroke were similar between the rhythm- and rate-control groups (~1%/y), most occurred in patients who had stopped warfarin (44%) or who had an INR in the subtherapeutic range (28% [ $<2.0$ ]).<sup>20</sup> This confirmed stroke

outcome data in other rhythm versus rate trials<sup>12,13</sup> and made it clear that in patients with AF, there is an ongoing risk of recurrence—a risk that increases with age, disease duration, and number and severity of episodes.<sup>5</sup> Whether a rhythm or rate control strategy is selected, the need for anticoagulation is standard of care.<sup>5</sup> (See *AF, Stroke, and Anticoagulation: Evidence and Practice*, page 6). In a proportion of patients, AF can be asymptomatic, elevating the risk of thromboembolism without prophylactic anticoagulation.<sup>5</sup>

### Rhythm Control: Search for Safety and Efficacy Current AADs

For patients with AF who require rhythm control, the pharmacologic treatment landscape is daunting. The AADs that are

available to restore and maintain NSR differ in efficacy for sustaining postcardioversion SR. In addition, they are associated with a wide range of adverse events, including photosensitivity; torsades de pointes<sup>40</sup>; and extracardiac toxicities involving the lungs, thyroid, and other organ systems (Table 5, page 8). Many AADs are mediated by common drug-metabolizing pathways. As a result, drug-drug interactions are a significant concern.<sup>5</sup> The majority of available AADs are associated with risk of proarrhythmia. This requires that several AADs be initiated on an inpatient basis.<sup>40</sup>

Vaughan-Williams class I (a and c) and class III agents are the primary AADs. A recent systematic review of randomized controlled trials<sup>41</sup> to evaluate the effects of long-term treatment with these medications found that all significantly

aware of previous episodes, and the patient's cardiovascular health before the episode. Family history is important to assess possible genetic transmission and specific questioning about environmental triggers is recommended as patients may not spontaneously report such information (ie, excessive alcohol use, sleep deprivation, emotional stress).<sup>5</sup>

AF must be verified during an episode by electrocardiography (at least a single-lead recording), which can be conducted in a medical setting or via bedside telemetry or ambulatory Holter recordings. Long-term monitoring is needed to diagnose paroxysmal AF, and in patients with relatively frequent or daily episodes, a 24- to 48-hour Holter monitor is appropriate. For patients who have symptoms only rarely, 30-day event monitors or implantable recording devices are indicated.<sup>19</sup> ACC/AHA/ESC guidelines state that initial evaluation

should include transthoracic 2-dimensional echocardiography to assess left atrial (LA) and left ventricular (LV) dimensions and LV wall thickness and function and to exclude occult valvular or pericardial disease and hypertrophic cardiomyopathy.<sup>5</sup> LV systolic and diastolic performance will help guide decisions about antiarrhythmic and antithrombotic therapy and will provide additional information on cardiac function and pathology, which will be taken into account for deciding treatment. Hyperthyroidism is a common precipitant of AF and thyroid function tests should be routine practice. Minimal assessments recommended by the ACC/AHA/ESC are described in Table 2.

The ideal evaluation will characterize the pattern of the arrhythmia (paroxysmal or persistent); determine cause; and define cardiac and noncardiac factors relevant to etiology, tolerability, and history of prior management, where appropriate.<sup>5</sup> ◆

**Table 2.** Diagnosis of AF: Minimum Requirements From the ACC/AHA/ESC Guidelines

History and Physical Examination	Electrocardiogram	Transthoracic Echocardiogram
Presence and nature of AF symptoms Clinical type of AF Onset of first symptomatic attack  Frequency, duration, precipitating, and terminating factors Response to pharmacologic agents Underlying heart disease or reversible conditions associated with AF Blood tests for thyroid, renal, and hepatic function	Verify AF by rhythm LV hypertrophy P-wave excitation and morphology of fibrillatory waves Pre-excitation  Bundle-branch block Prior MI  Other atrial arrhythmias	Valvular heart disease LA and RA size LV size and function  Peak RV pressure  LV hypertrophy LA thrombus (low sensitivity)  Pericardial disease

RA = right atrial; RV = right ventricular. Adapted from Fuster V, et al.<sup>5</sup>

reduced recurrence of AF. Pooled recurrence rates at 1 year for controls were 71% to 84% and were reduced to 44% to 67% in treated patients.<sup>41</sup> When AADs were compared, the class III agent amiodarone reduced AF recurrence significantly more than combined class Ia and Ic drugs (odds ratio [OR], .31; 95% confidence interval [CI], .21-.45;  $P < .001$ ).<sup>41</sup> Selection of an appropriate agent is based first on safety related to underlying cardiac disease and the risk for triggering proarrhythmias.<sup>5</sup> For example, patients with HF are prone to the ventricular proarrhythmic effects of AADs. Randomized trials have demonstrated the safety of class III AADs amiodarone and dofetilide for patients with HF.<sup>42</sup> For patients with stable coronary artery disease, beta blockers are effective, but there are little data on their

efficacy to maintain NSR after cardioversion. The class III agent sotalol has excellent beta-blocking activity and may be the preferred initial AAD in patients with ischemic heart disease, whereas class Ic drugs (flecainide, propafenone) are contraindicated.<sup>5</sup> Class Ic AADs and class III amiodarone are the preferred treatment with left ventricular failure (LVF) due to an increased risk for torsades de pointes after ventricular afterdepolarizations.<sup>43</sup> Table 5 lists specific cardiac conditions for which there is evidence for safe use of AADs to maintain NSR.<sup>5</sup>

### The Trouble With Amiodarone

Class III amiodarone is FDA-approved only for ventricular rate control and is the most commonly used AAD based on its greater ability to maintain SR compared with other AADs and its low risk

of proarrhythmic effects. Amiodarone also has demonstrated safety in patients with HF requiring long-term management of NSR.<sup>45-48</sup> Dofetilide is the only other agent considered safe in HF patients.<sup>40</sup> Studies show amiodarone maintains NSR in >60% of patients at 1 year after cardioversion.<sup>49</sup> Comparative efficacy studies with amiodarone and the class Ic agent propafenone and class III AAD sotalol demonstrated a 60% recurrence rate in patients treated with sotalol versus 29% for patients treated with amiodarone ( $P = .008$ ).<sup>50</sup> In the Canadian Trial of Atrial Fibrillation (CTAF), patients in the amiodarone group had a lower recurrence rate of AF (35%) versus sotalol or propafenone (63%;  $P < .001$ ).<sup>51</sup>

Amiodarone is a bit of a wolf in sheep's clothing. Its ability to maintain

(continued on page 7)

## AF, Stroke, and Anticoagulation: Evidence and Practice

There are several classification schemes for determining stroke risk in patients with AF that are used to select the type and intensity of anticoagulation therapy for long-term prophylaxis. The most widely used classification is referred to as CHADS<sub>2</sub> – a mnemonic for the top 5 risk factors: C = congestive heart failure, H = hypertension, A = age >75 years, D = diabetes, and S = prior stroke or transient ischemic attack (TIA). Prior stroke or TIA is assigned 2 points in this system, and the other factors are assigned 1 point each (Table 3).<sup>6</sup>

### Warfarin: Gold Standard to Date

The superior efficacy of the vitamin K antagonist warfarin in reducing stroke risk in patients with nonvalvular AF is well documented<sup>27,28</sup> and associated with a 68% overall risk reduction. It is the standard of therapy for anticoagulation in moderate- to high-risk patients with AF. In a meta-analysis of <10,000 patients with nonvalvular AF, warfarin (compared to placebo) was associated with a risk reduction of 59% for primary prevention and 68% for secondary prevention. When the type of stroke was addressed, the analysis found the risk for ischemic stroke declined by 65% with warfarin. Although the risk for hemorrhagic stroke increased with warfarin compared with placebo, the incidence was low—.3%/year with warfarin and .1%/year with placebo.<sup>27</sup> This same analysis demonstrated the superiority of warfarin over aspirin therapy for stroke prevention in AF. Patients receiving warfarin had a 36% lower risk for any type of stroke and a 46% lower risk for ischemic stroke.<sup>27</sup> The ACC/AHA/ESC guidelines do, however, recommend aspirin for prevention of AF-related stroke according to a patient's category of risk (Table 4).<sup>5</sup> Comparison of stroke reduction with warfarin and antiplatelet therapy demonstrated the superiority of warfarin, with a difference of 37%.<sup>28</sup>

Hart and coworkers undertook another meta-analysis, adding to the data on the 10,000 patient results from randomized trials including another <18,000 patients.<sup>28</sup> The results confirmed the efficacy of warfarin versus placebo; warfarin was associated with a 64% reduction in all strokes and a similar reduction in disabling and nondisabling strokes (60% for both types). Ischemic stroke risk was lowered by 67%. Antiplatelet therapy reduced strokes by 22%. Comparison of stroke reduction with warfarin and antiplatelet therapy demonstrated the superiority of warfarin, with a difference of 37%.<sup>28</sup>

### Underuse of Warfarin: Why?

Despite its proven efficacy for reducing primary and secondary stroke risk in patients with AF, warfarin is widely underused. For example, a study of patients with AF in community, academic, and VA hospitals found that only about half of high-risk patients with AF received warfarin therapy.<sup>29</sup> In another study of almost 600 patients with documented AF who were hospitalized with a first ischemic stroke, only 40% had been using warfarin therapy, and among those patients, three-fourths had an International Normalized Ratio (INR) <2.0. In that same study, patients with AF admitted

for ischemic stroke who had a previous TIA or stroke, INR levels indicated subtherapeutic warfarin therapy in 39%.<sup>30</sup>

As ideal as it may be for the job of stroke prevention, in daily life, effective adherence to warfarin therapy is a challenge for patients, their families, and clinicians. Use of the drug requires a risk/benefit calculation where the benefit = reducing risk of stroke, and risk = potential to produce intracranial bleeding. Maintaining goal INR (between 2.0 and 3.0) minimizes the risk of ischemic and hemorrhagic stroke,<sup>5,31,32</sup> but staying within that therapeutic window can require frequent blood monitoring and sometimes frequent dose adjustments.<sup>33,34</sup> Other factors that prevent clinicians from prescribing anticoagulation therapy include the necessary dietary restrictions and contraindications as well as potential drug interactions and the risk of easy bruising and bleeding.<sup>34</sup>

### In the Pipeline

The quest to find alternatives to warfarin for anticoagulation in patients with AF has been the focus of much drug development and clinical research. The ideal antithrombotic agent would have high specificity for inhibiting thrombin, a favorable efficacy/safety balance, a fixed dose with no requirement for monitoring or dose adjustment, a rapid onset of action, fewer drug/drug interactions, and no interactions with food. Clinical trials now in progress of factor Xa inhibitors and oral direct thrombin inhibitors have shown mixed results, but an oral direct thrombin inhibitor in phase III trials offers good promise.

Factor Xa inhibitors offer more selective anticoagulation. The first large phase III trial of one of these agents (weekly subcutaneous idraparinux) compared the drug to dose-adjusted warfarin and found it noninferior for the prevention of stroke.<sup>35</sup> However, the study ended early because patients in the idraparinux arm had increased rates of major bleeding and intracranial hemorrhage.<sup>35</sup> A new formulation is now in phase III recruiting. Ximelagatran, an oral direct thrombin inhibitor, progressed as far as the FDA review panel but was withdrawn from further clinical development when it was found to cause clinically important hepatic toxicity.<sup>36</sup> Apixaban, an oral factor Xa inhibitor, is part of a large clinical program to evaluate antithrombotic efficacy. Phase III trials are underway to study stroke prevention in patients with AF. One study will compare apixaban with warfarin and a second will compare it with aspirin in patients who are ineligible for vitamin K agonist treatment or have not tolerated it in the past.<sup>37</sup> Another factor Xa inhibitor, rivaroxaban, compared favorably with enoxaparin in the prevention of venous thromboembolism (VTE) in

**Table 3.** Relative Risk and CHADS<sub>2</sub> Scoring for Stroke Risk

Risk Factor	CHADS <sub>2</sub> Point(s)
HF	1
Hypertension	1
Aged ≥75 years	1
Diabetes mellitus	1
Prior stroke, TIA, or systemic embolism	2

Adapted from Crandall MA, et al.<sup>6</sup>

the setting of major joint replacement and was recommended to the FDA for approval. A decision is on hold as the agency waits for additional information, primarily on the risks of bleeding and possible hepatotoxicity.<sup>38</sup>

**Table 4.** ACC/AHA/ESC Guidelines on Anticoagulation Therapy for Patients With AF

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81-325 mg daily
1 moderate risk factor	Aspirin, 81-325 mg daily OR warfarin (INR 2.0-3.0)
Any high-risk factor or >1 moderate risk factor	Warfarin (INR 2.0-3.0) <sup>a</sup>
<sup>a</sup> If mechanical valve, target >2.5. INR = international normalized ratio. Adapted from Fuster V, et al. <sup>5</sup>	

The good news is dabigatran, an oral direct thrombin inhibitor available in the European Union and Canada approved to prevent VTE during joint replacement therapy. In a noninferiority trial with warfarin in patients with ECG-confirmed AF that looked at stroke or systemic embolism (efficacy) and major bleeding (safety) the high-dose dabigatran was superior to warfarin for stroke prevention and systemic embolism.<sup>39</sup> The low-dose was noninferior for efficacy but associated with equivalent rates of major bleeding compared with warfarin. Both doses of dabigatran dramatically reduced (by approximately two-thirds) intracranial hemorrhage.<sup>39</sup> Liver function was extensively monitored with no evidence of hepatotoxicity. The drug has limitations including twice-daily dosing, which may affect adherence, and dependence on renal elimination, making it contraindicated in patients with stage IV or V chronic kidney disease. It is also associated with dyspepsia, a higher discontinuation rate than warfarin during 2-year follow-up, and a small but statistically significant increased risk for myocardial infarction (MI).<sup>39</sup> These issues, along with other questions, are the subject of ongoing preplanned substudies. ◆

(continued from page 5)

NSR is high relative to other AADs, but it is also among the most toxic drugs in this category, associated with a high incidence of potentially severe extracardiac effects: neuropathy, thyroid dysfunction, pulmonary fibrosis, hepatotoxicity, rash or photosensitivity, and ophthalmic effects.<sup>5</sup> Amiodarone is pharmacokinetically complex with a long half-life that can complicate loading dosing, side effect management, and switching among other AADs.<sup>52</sup> It also is absorbed into a wide variety of extracardiac tissue, and while adverse effects may not be observed early in therapy, risk increases after >6 months of treatment.<sup>5</sup> Although the drug's toxicity is dose-related, even low doses lead to increased frequency of subjective and end-organ toxic effects.<sup>53</sup>

### A New Class III AAD: Dronedaron

The early 2009 dronedarone release was the first AAD approval in the United States in 10 years. Dronedarone is structurally similar to amiodarone and, like the latter, has multiclass electrophysiologic activity.<sup>40</sup> With the addition of a methyl-sulfonamide group, which the amiodarone molecule lacks, dronedarone is less lipophilic and less likely to accumulate in tissue and thus poses less risk for extracardiac adverse events.<sup>54</sup> Without the iodine moieties found in amiodarone,

dronedarone is not associated with effects on thyroid function.<sup>55</sup> In addition, it has a half-life of 24 hours compared with amiodarone's elimination of several weeks.

Dronedarone was compared in 3 clinical trials with placebo: EURIDIS, ADONIS,<sup>56</sup> and ATHENA<sup>57</sup>; and in 1 head-to-head study with amiodarone: DIONYSOS<sup>58</sup> (see *Dronedarone Clinical Trials At-a-Glance*). EURIDIS and ADONIS enrolled 1237 patients (mean age, 63 years) with paroxysmal or persistent (>12 months) AF. Patients with New York Heart Association (NYHA) class III or IV HF were excluded. A substantial number of patients had structural heart disease. The time to recurrence of AF

(primary end point) after 12 months was 64% for dronedarone and 75.2% for placebo ( $P < .001$ ). The rate of hospitalization or death also was significantly lower for dronedarone (22.8%) than placebo (30.9%;  $P = .01$ ).<sup>56</sup> The primary side effects of dronedarone were gastrointestinal (GI), and no evidence was found of pulmonary, thyroid, hepatic, or neurologic toxic effects.<sup>56</sup> The subsequent ANDROMEDA,<sup>57</sup> designed to evaluate dronedarone in patients with severe disease (ie, NYHA class III or IV HF and depressed left ventricular ejection fraction [ $\leq 35\%$ ]), but not specifically with AF, was terminated early due to an excessive death rate in the dronedarone group.<sup>57</sup>

### Dronedarone Clinical Trials At-a-Glance

**EURIDIS**—European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm

**ADONIS**—American-Australian-African Trial With Dronedarone in Atrial Fibrillation Patients for the Maintenance of Sinus Rhythm

**ATHENA**—A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From any Cause in Patients With Atrial Fibrillation/Atrial Flutter

**DIONYSOS**—Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

**ANDROMEDA**—Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease

**Table 5.** Drugs Used to Maintain Sinus Rhythm in Patients With AF<sup>a</sup>

Drug	Potential Adverse Effects	Specific Cardiac Indications	Contraindications
<b>Class Ia</b> Disopyramide	Torsades de pointes, HF, glaucoma, urinary retention, dry mouth	None/minimal heart disease <sup>c</sup>	
<b>Class Ic</b> Flecainide	Ventricular arrhythmia, HF, enhanced AV nodal conduction, (conversion to atrial flutter)	None/minimal heart disease <sup>b</sup> Hypertrophy/hypertrophic myopathy <sup>b</sup>	Post-MI/ischemia Dilated cardiomyopathy
Propafenone	Ventricular tachycardia, HF, enhanced AV nodal conduction (conversion to atrial flutter)	None/minimal heart disease <sup>b</sup> Hypertrophy/hypertrophic myopathy <sup>b</sup>	
<b>Class III</b> Amiodarone	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction	None/minimal heart disease <sup>c</sup> Hypertension with LVH <sup>b</sup> ; CAD <sup>b</sup> Post-MI/ischemia <sup>c</sup> ; Hypertrophy/hypertrophic myopathy <sup>c</sup> Dilated cardiomyopathy <sup>c</sup> HF <sup>b</sup>	
Dofetilide	Torsades de pointes	None/minimal heart disease <sup>c</sup> CAD <sup>b</sup> ; post-MI/ischemia <sup>b</sup> ; Dilated cardiomyopathy; HF	
Dronedarone	GI upset, asthenia	Post-MI/ischemia <sup>c</sup>	Severe HF <sup>d</sup>
Sotalol	Torsades de pointes, HF, bradycardia, exacerbation of COPD or bronchospastic lung disease	None/minimal heart disease <sup>b</sup> ; CAD <sup>b</sup> Post-MI/ischemia <sup>b</sup>	

CAD = coronary artery disease; LVH = left ventricular hypertrophy.

<sup>a</sup>Drugs are listed alphabetically within class; <sup>b</sup>first choice; <sup>c</sup>second choice; <sup>d</sup>NYHA class IV HF, or NYHA Class II-III HF with a recent decompensation requiring hospitalization or referral to a specialized HF clinic.

Adapted from Fuster V, et al<sup>5</sup>; Crandall MA, et al.<sup>6</sup>

The excess mortality was attributed primarily to worsening HF.<sup>57</sup>

### Largest AAD Safety Trial

To address the concerns raised by ANDROMEDA, the ATHENA trial—the largest safety trial of an AAD to date, enrolling more than 4600 patients—was conducted.<sup>57</sup> The ATHENA population differed significantly from that of ANDROMEDA. All patients had a history of paroxysmal or persistent AF; 71% had no evidence of HF; 25% were NYHA class I or II, and only 4% were class III. Before randomization, all patients were receiving usual care—antithrombotic therapy and rate control. Unlike prior studies, ATHENA did not use AF

recurrence as the primary end point, but instead a composite of all-cause mortality and first hospitalization for a cardiovascular event. Mean follow-up was 21 months (range 1–2.5 years).<sup>57</sup> Compared with standard care only, dronedarone was associated with a significantly lower incidence of first hospitalization for a cardiovascular event (31.9% vs 39.4%;  $P < .001$ ), reflecting a 24% risk reduction in the dronedarone group versus the standard care group. All-cause mortality was reduced by 16% with dronedarone ( $P = .18$ ), and cardiovascular deaths were reduced by 29% ( $P = .03$ ); most of this difference was due to a lower rate of death from arrhythmia with dronedarone.<sup>57</sup> Similarly, the reduction in

cardiovascular hospitalizations was accounted for by fewer admissions for AF. Pulmonary and thyroid-related adverse events were similar for the 2 groups.<sup>57</sup>

Adverse events occurring at a higher rate in the dronedarone group compared with the standard care group included bradycardia, QT-interval prolongation, nausea, diarrhea, rash, and an increased serum creatinine level. Post-hoc analysis of data on stroke in ATHENA found that dronedarone compared to standard care reduced the risk of stroke from 1.8% to 1.2% per year (HR = .66; 95% CI = .46–.96;  $P = .027$ ).<sup>57</sup> The effect on stroke risk was independent of the use of anticoagulant therapy and appeared to increase with higher CHADS<sub>2</sub> score.<sup>57</sup>

## Amiodarone Versus Dronedaron

The head-to-head DIONYSOS trial evaluated the safety of and efficacy for maintaining SR of dronedarone versus amiodarone. The primary composite end point was AF recurrence or premature study discontinuation for intolerance or lack of drug efficacy.<sup>58</sup> At a mean follow-up of 7 months, significantly more patients in the dronedarone group (73.9%) than in the amiodarone group (55.3%;  $P < .001$ ) had reached the end point. AF occurred in 36.5% of patients in the dronedarone arm versus 24.3% in the amiodarone arm—but was associated with fewer side effects and less premature discontinuation than amiodarone.<sup>58</sup> The pre-defined main safety end point included thyroid, hepatic, pulmonary, neurologic, skin, ocular, and GI adverse events as well as premature study drug discontinuation due to any adverse event. There were fewer thyroid and neurologic events in the dronedarone group and less drug discontinuation than in the amiodarone group. GI events were more prevalent with dronedarone. After excluding GI effects, there was a statistically significant decrease of 39% in the main safety end point favoring dronedarone. Amiodarone was associated with more bradycardia and QT prolongation, but no torsades de pointes was reported in either group.

Dronedaron also has been shown to reduce ventricular rate in patients with permanent AF when added to standard rate-control therapy.<sup>59</sup> The primary end point in a trial to evaluate the safety and efficacy of dronedaron in ventricular rate control was change in mean 24-hour ventricular rate between baseline and day 14. The difference was 11.7 bpm ( $P < .001$ ). The clinical significance of the difference is unknown, however, as the decrease in heart rate was not accompanied by improved exercise tolerance.<sup>59</sup> There were no untoward interactions between dronedaron and on-board rate control agents or anticoagulants, but a 41% increase in serum digoxin was observed.<sup>59</sup>

## What Role for Dronedaron?

Clinical trial data for dronedaron suggest it has a role in the maintenance of NSR among a large group of patients with symptomatic AF. Appropriate candidates include young patients who need AAD therapy but who prefer not to take amiodarone because of its association with cumulative organ toxicity, and patients with compensated NYHA class I and class II HF. Additional evidence is required in NYHA class III HF before broad clinical use can be recommended. Amiodarone, on the other hand, is widely used in advanced HF based on demonstrated safety in that population.<sup>60</sup> As with all AADs, the key to dronedaron's successful utilization will be careful patient selection and monitoring both safety and efficacy.

## The Future

Getting to the heart of AF is an ongoing journey. Anti-AF agents in development are broadly divided into multiple channel blockers (like amiodarone) and atrial-selective compounds. Agents that modulate non-ionic current targets (ie, “upstream” therapies) may help modify the substrate for AF maintenance. This group includes angiotensin II type 1 receptor antagonists, immunosuppressive agents, and statins. Drugs that block atrial selective ion-channel targets, including the ultra-rapid delayed rectifier current and the acetylcholine-regulated K<sup>+</sup> current also are in development. As a start, though, there is one new molecule that answers the call for AF treatment that is safer among therapeutic options that seem to ask clinicians first to do *less* harm.

## Cardioversion to Normal Sinus Rhythm: When, Why, How?

Cardioversion is elective for most patients. Many patients with new or recent-onset AF will achieve spontaneous conversion to NSR within 24 to 48 hours after onset. The likelihood of AF terminating spontaneously decreases as the episode of AF continues. For patients aged <70 years, it is usual to attempt medical cardioversion at least once. Conversion to NSR may be recommended for patients whose symptoms persist after rate control is achieved, but the decision is often multifactorial. Cardioversion may be necessary immediately in patients with HF, hypotension, and those with coronary artery disease and worsening angina.<sup>5</sup>

Cardioversion can be accomplished medically or with electrical current.<sup>5</sup> Cardioversion using electric shocks is a standard procedure. Efficacy depends on several factors: (1) timing—it is best when performed within 7 days of the onset of the arrhythmia; (2) nature of the underlying cardiac disease; and (3) density of the current supplied to the atrial myocardium. The primary drawback of electrocardioversion is it requires conscious sedation or anesthesia.

Other non-drug-based interventions for preventing AF such as catheter ablation of AF, minimally invasive surgical AF ablation, or the Cox Maze procedure are appropriate for some patients; selection is critical. For patients attempting rhythm control, an expert consensus statement on catheter and surgical ablation now defines indications, techniques, and outcomes of ablation for AF.<sup>60</sup> Criteria for the intervention stipulates symptomatic AF in a patient who has failed at least 1 antiarrhythmic agent (class I or III) or select symptomatic patients with HF.<sup>5,61</sup>

Pharmacologic cardioversion has become popular because it is easier to perform, but it is less effective than electrocardioversion and carries the risk of drug-induced torsade de pointes and other serious arrhythmias. The risk for torsade de pointes depends on the agent used and patient factors. For example, a 2004 study found a 3.9% overall rate of this event after cardioversion with ibutilide, with the incidence approximately twice as great in women as in men.<sup>62</sup> Because of these risks, pharmacologic cardioversion almost always is performed in the hospital setting.

Electrocardioversion and pharmacologic cardioversion require anticoagulation therapy before and for at least 1 month after cardioversion if a patient has been in AF for 48 hours or longer or an unknown duration. No anticoagulation is needed at the time of cardioversion for episodes lasting less than 48 hours. With either method, ongoing antiarrhythmic drug treatment often is needed to prevent relapse/recurrence of the arrhythmia. ◆

## PCE Takeaways

- AF poses a significant and increasing risk, particularly in the elderly population, which is growing at an unprecedented rate.
- Long-term management of persistent AF is complicated by coexisting CV disease, AF resistance to treatment, poor risk/benefit ratio associated with current antiarrhythmic medications, and issues inherent with chronic anticoagulant therapy.
- Controversy surrounding the roles of rate versus rhythm control have spurred research and development of new antiarrhythmic agents with improved safety and adverse event profiles that offer clinicians and patients more choice regarding safety/efficacy and symptoms/control.
- Nonpharmacologic interventions increasingly are accepted as an option for treating refractory AF in patients who are or intolerant of specific antiarrhythmics and are the topic of recently released clinical guidelines on the use of ablation techniques; ablation procedures are included for the first time in the ACC/AHA/ESC clinical guidelines on AF.
- Treatment for AF must be individualized, weighing the suitability of any single or combination of strategies for each patient against known risk/benefit profiles at any specific point in the progression of disease.

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