



# Current clinical issues in atrial fibrillation

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**B**ecause atrial fibrillation (AF) affects a heterogeneous clinical population, applying evidence-based approaches to individual patients with AF remains a challenge. The mainstays of therapy include pharmacologic rate control and antiarrhythmic therapy, cardioversion, and antithromboembolic management. Nonpharmacologic therapies, including ablation, devices, and surgical approaches, are now increasingly used and, in some cases, potentially curative. This article surveys the clinical challenges posed by AF and broadly assesses current and evolving treatment strategies to manage them.

## ■ MAGNITUDE OF THE PROBLEM

AF is the most common sustained arrhythmia seen in clinical practice. **Table 1** presents a basic classification of the common types of AF.

The prevalence of AF is estimated at 0.4% of the general population; an estimated 2.2 million Americans have paroxysmal or persistent AF.<sup>1,2</sup> The Framingham Heart Study reported a 0.1% annual incidence of AF, which translates to more than 160,000 new US cases per year.<sup>3</sup>

The prevalence of AF increases with age;<sup>1</sup> age-specific prevalence rates are as follows:<sup>1,2,4-6</sup>

- 0.2% in the population aged 25 to 34 years
- less than 1% in the population under age 60
- 2% to 5% in the population over age 60
- 6% to 10% in the population over age 80.

In light of these findings, AF will be a growing clin-

ical challenge as the US population ages (**Figure 1**).<sup>7</sup>

AF is often associated with other cardiovascular diseases, most commonly hypertension and ischemic heart disease. Other predisposing conditions and factors are listed in **Table 2**. Factors that can predispose to AF in a normal heart include high adrenergic states, alcohol, stress, certain drugs (especially sympathomimetics), excessive caffeine, hypoxia, hypokalemia, hypoglycemia, and systemic infection. The incidence of AF is particularly high, 20% to 40%, after cardiac surgery.<sup>8</sup>

## ■ CLINICAL CONSEQUENCES OF ATRIAL FIBRILLATION

**Mortality.** Though not usually considered a life-threatening arrhythmia, AF is associated with a 1.5-fold to twofold increase in total and cardiovascular mortality, based on Framingham Heart Study data.<sup>9,10</sup> Factors that may increase mortality in patients with AF include advanced age, mitral stenosis, aortic valve disease, coronary artery disease, hypertension, and congestive heart failure. Acute myocardial infarction and congestive heart failure are each associated with higher mortality if AF is present.

**Stroke and thromboembolic events** are both associated with AF and are among its most clinically important consequences.<sup>11</sup> AF is one of the most potent risk factors for stroke in the elderly<sup>3</sup> and is the most common cause of cardiogenic stroke. It also carries a significant risk for silent cerebral infarction.<sup>12</sup> The risk of stroke in patients with nonvalvular AF increases with age, concomitant cardiovascular disease, and other risk factors for stroke.<sup>13</sup> Patients with nonvalvular AF show an approximately twofold to sixfold increase in the risk of stroke, with an incidence of 3% to 5% per year.<sup>2,11,14</sup> In the presence of rheumatic heart disease, chronic AF is associated with a 17-fold increase in the risk of stroke.<sup>15</sup> The Framingham Heart Study reported an annual stroke rate of 4.2%<sup>15</sup> and showed that the relative risk of stroke was significantly increased in the

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**TABLE 1**

Basic classification of the types of atrial fibrillation (AF)

**Lone AF** occurs in the absence of cardiac or other conditions predisposing to AF

**Acute AF** generally refers to AF lasting less than 48 hours

**Paroxysmal AF** generally is characterized by recurrent, transient episodes that revert to sinus rhythm spontaneously or with treatment

**Persistent AF** does not convert to sinus rhythm without intervention or cardioversion

**Permanent AF** is persistent despite cardioversion

presence of AF, congestive heart failure, coronary artery disease, and hypertension; the increase in the presence of AF was nearly fivefold.<sup>11</sup>

At the same time, the risk of stroke is low in patients with AF who are younger than age 60 and do not have hypertension or cardiovascular disease. A meta-analysis of five major primary prevention trials for stroke in patients with AF<sup>13</sup> estimated the incidence of stroke to be approximately 1% per year in those younger than age 65 without hypertension, diabetes, or prior stroke or transient ischemic attack. The incidence of stroke in patients who are older, have risk factors for stroke, or have concomitant cardiovascular disease is approximately 3% to 5% per year. Patients older than age 75 who have risk factors for stroke are at particularly high risk (8% incidence per year). Furthermore, stroke development tends to cluster at the onset of AF.<sup>16,17</sup>

**Tachycardia-induced cardiomyopathy.** Persistent rapid rates in patients with AF can lead to tachycardia-mediated cardiomyopathy with left ventricular dysfunction and congestive heart failure.<sup>18,19</sup> The cardiomyopathy may be reversible with ventricular rate control or regularization of the rhythm.<sup>18,19</sup> This may be achievable with medical rate control, atrioventricular node ablation, or restoration of sinus rhythm. An atrial cardiomyopathy can also result from structural remodeling during AF, leading to an increase in atrial size.<sup>20</sup>

**Symptoms and hemodynamics.** AF may cause symptoms as a result of rapid ventricular rates, irregularity of ventricular rhythm, or loss of atrioventricular synchrony. Symptoms may include functional capacity limitations, palpitations, fatigue, dyspnea, angina, and congestive heart failure.

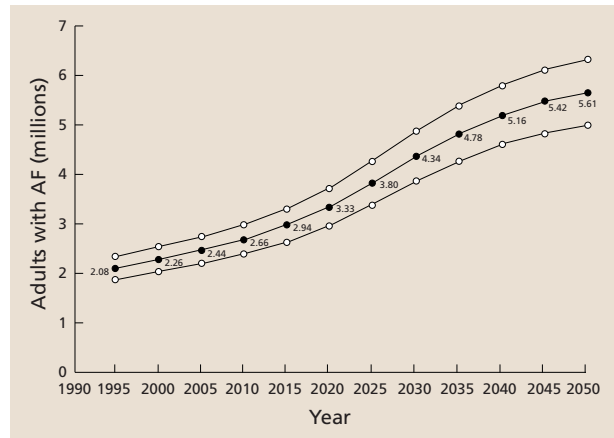


Figure 1. Projected number of adults with atrial fibrillation in the United States, 1995 to 2050. Upper and lower curves represent the upper and lower projections based on sensitivity analysis. Reprinted from reference 7 with permission.

## ■ RHYTHM VS RATE CONTROL AFTER AFFIRM

The concept of substrates supporting reentry and their susceptibility to structural and electrical remodeling (see the review by Van Wagoner earlier in this supplement) provides a theoretical rationale for a rhythm-control approach to restoring and maintaining sinus rhythm in AF. Class IA and III antiarrhythmic drugs have been used to prolong atrial refractory periods with the goal of limiting atrial reentrant circuits. Class IC agents, which are sodium channel blockers, slow conduction and may promote blocking of reentrant circuits. Verapamil has been studied as a calcium channel blocker that may abrogate the shortening of atrial refractory periods, potentially by preventing the calcium overload that may underlie early atrial electrical remodeling. Earlier conversion of AF to sinus rhythm may be more successful in avoiding the electrical and structural remodeling of the atria that may predispose to recurrent and persistent AF. In addition, maintenance of sinus rhythm may help to reverse electrical and structural remodeling.

It remains controversial, however, whether a rhythm-control approach to maintain sinus rhythm is clinically superior to a strategy of ventricular rate control. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM),<sup>21</sup> the largest of several randomized trials comparing these two approaches, no survival benefit or improvement in quality of life was achieved with a rhythm-control approach. Whether the theoretical advan-

**TABLE 2**

Conditions and factors that can predispose to atrial fibrillation

|                                                                   |                                |
|-------------------------------------------------------------------|--------------------------------|
| Hypertension                                                      | Wolff-Parkinson-White syndrome |
| Ischemic heart disease                                            | Pericarditis                   |
| Advanced age                                                      | Pulmonary embolism             |
| Rheumatic heart disease*                                          | Thyrotoxicosis                 |
| Nonrheumatic valve disease                                        | Chronic lung disease           |
| Cardiomyopathies                                                  | Neoplastic disease             |
| Congestive heart failure                                          | Diabetes                       |
| Congenital heart disease                                          | Postoperative state            |
| Sick sinus syndrome/<br>degenerative conduction<br>system disease |                                |

\*Especially mitral valve disease

tages of avoiding or reversing structural or electrical remodeling justifies a rhythm-control strategy in some patients remains to be established, given the higher risk of adverse drug effects with this approach.

The results of AFFIRM and other recent randomized trials comparing rate control with rhythm control have prompted a redefinition of the types of patients who are appropriate candidates for these respective approaches. It is worth noting that patients who were highly symptomatic with rate-control therapy may not have been enrolled in AFFIRM. Patients with persistently symptomatic, new, or first-onset AF may be good candidates for rhythm control, as may younger patients, in whom avoiding remodeling might be advantageous over the long term. These patients might also be current or future candidates for newer curative procedures.

### ■ RATE CONTROL: DRUGS VS ATRIOVENTRICULAR JUNCTION ABLATION

The mainstays of a rate-control strategy for AF have been anticoagulation and pharmacologic treatment with beta-adrenergic blockers, calcium channel blockers, and digoxin. For patients with rapid rates refractory to these agents, atrioventricular junction ablation or modification with implantation of a permanent pacemaker has successfully improved symptoms, quality of life, and left ventricular dysfunction caused by tachycardia-mediated cardiomyopathy.<sup>22,23</sup> The disadvantage is that patients become pacemaker-dependent.

Early reports of an increased risk of late sudden death, primarily after early procedures using direct-current ablation, have not been confirmed in recent studies with radiofrequency ablation.<sup>24</sup> Nevertheless, recent studies have suggested a possible increase in heart failure and mortality in patients with implantable cardioverter defibrillators receiving right ventricular pacing.<sup>25</sup> Long-term follow-up studies of patients undergoing atrioventricular junction ablation are warranted to determine outcomes and whether left or biventricular pacing may be preferable or superior in these patients.

### ■ SELECTING DRUGS FOR RHYTHM CONTROL

When treating an individual patient, the decision between rhythm control and rate control often involves complex analyses of the risks and benefits of maintaining sinus rhythm. The safe and effective maintenance of sinus rhythm is an ongoing challenge in patients electing a rhythm-control approach. Patients may remain symptomatic in AF despite rate control and therefore may try a rhythm-control approach with its potential for more complete symptom relief and hemodynamic improvement. However, even with antiarrhythmic therapy, approximately one half of patients develop recurrent AF after cardioversion to sinus rhythm, and recent studies raise concern over the potential for increased mortality and proarrhythmic potential when antiarrhythmic drugs are used.

The decision to use an antiarrhythmic drug should be influenced by the frequency and duration of the AF, the symptoms involved, the reversibility of the arrhythmia, and the presence or absence of structural heart disease.<sup>2,26</sup> The risk of side effects, including organ toxicity and proarrhythmia, also should be weighed against the benefit and efficacy rates of the drugs.<sup>2,26</sup>

For example, amiodarone is an effective antiarrhythmic drug for AF and has a low proarrhythmic potential. However, long-term use may not be suitable for some patients, particularly younger patients, because of its risk of long-term organ toxicity. Nevertheless, amiodarone may be the first-line choice in patients with severe structural heart disease, regardless of patient age.

Inpatient initiation of some antiarrhythmic drugs may be advisable, particularly those that predispose to QT prolongation, proarrhythmia, or bradycardia, or for patients with risk factors for these effects.

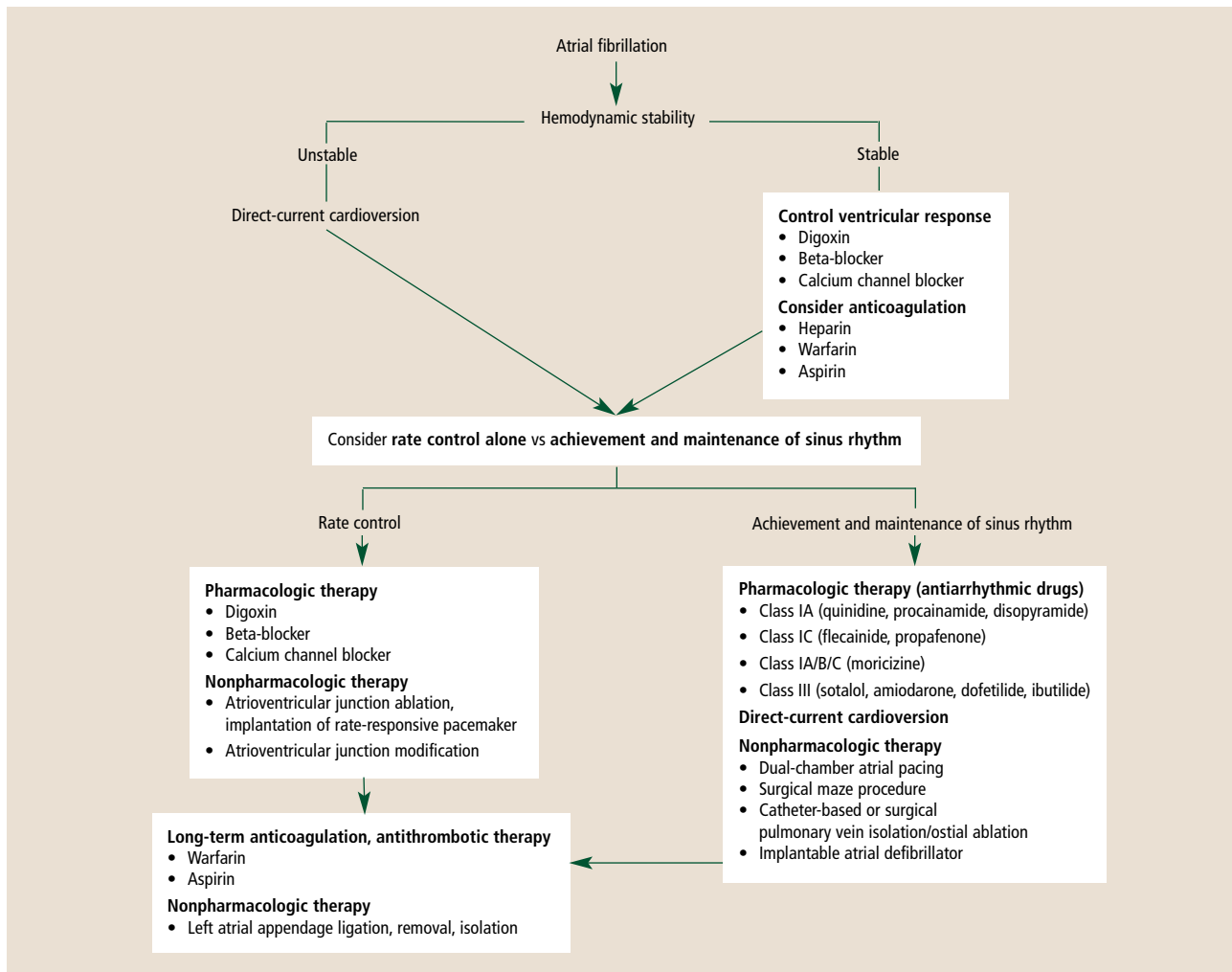


Figure 2. General algorithm for the management of atrial fibrillation.

When AF is treated medically, recurrences are expected (50% at 6 to 36 months) but are generally not life-threatening. Because total suppression of AF episodes may risk drug toxicity, quality-of-life improvement may be a reasonable goal for guiding therapy.

### ■ THROMBOEMBOLIC RISK: LIFELONG MANAGEMENT NEEDED

Several studies have established warfarin's efficacy in reducing the risk of stroke and thromboembolism in patients with AF and risk factors for stroke. Although treatment with warfarin before cardioversion and for about 4 weeks afterward has been a common practice, AFFIRM and other recent trials have shown that thromboembolic risk is not reduced by a rhythm-con-

trol strategy with apparent maintenance of sinus rhythm. AFFIRM showed no reduction in thromboembolism with rhythm control over rate control,<sup>21</sup> and the Rate Control vs Electrical Cardioversion (RACE) for Persistent Atrial Fibrillation study<sup>27</sup> found a higher incidence of thromboembolism with rhythm control than with rate control. In both studies most events occurred after anticoagulation had been stopped or when it was subtherapeutic.

These findings underscore the importance of continued anticoagulation, even in the context of a rhythm-control strategy with apparent achievement and maintenance of sinus rhythm. Moreover, the only intervention or therapy that has been shown to improve survival in patients with AF has been the use of warfarin. The Atrial Fibrillation Investigators reported a 33% relative reduction in mortality with

warfarin compared with control therapy in a combined analysis of five randomized trials.<sup>13</sup> New antithrombotic agents that might be effective substitutes for warfarin are being studied (eg, in the Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation [SPORTIF] trial and others).

## ■ ASSESSING THE VALUE OF ABLATIVE APPROACHES

The recognition of triggering foci that initiate AF has led to surgical and catheter-based ablative approaches that allow AF to be cured in some patients. These two types of procedures are the most promising and exciting approaches to AF management to emerge over the past several years.

**The surgical maze procedure** has been used with a high degree of success, and newer related approaches are now employing cryoablation or innovative methods to deliver radiofrequency or microwave energy to isolate the pulmonary vein ostia. Surgical approaches also may be combined with left atrial appendage removal or ligation.

**Catheter-based ablation** has been directed toward isolating pulmonary vein ostial or superior vena cava sources and has been associated with long-term success rates of 49% to 86%.<sup>28–31</sup> Limitations of current methods include a high rate of recurrence, leading to a need for repeat procedures, and the risk of symptomatic pulmonary vein stenosis from ablation within the pulmonary vein (~2% to 5% risk).<sup>32</sup> The latter has led to the use of intracardiac ultrasound and ring-type electrode catheters to isolate pulmonary vein ostia by applying ablation energy to the left atrial side rather than inside the pulmonary vein ostia. Circumferential ablation methods using alternative delivery techniques or energy sources (eg, ultrasound, microwave, or laser energy; cryoablation) are under investigation, as are novel imaging and navigation methods.

The success of applying catheter-based ablation to the spectrum of AF patients is not yet defined, but the procedure has been used with success even in patients with chronic persistent AF.

The favorable efficacy and improving complication rates of surgical and catheter-based ablative procedures have made these potentially curative strategies a hopeful treatment option for many patients with refractory symptomatic AF. Whether and when the benefits of these procedures outweigh the risks are questions that arise more and more often in the management of individual patients. Whether to proceed with current ablative methods or await future advances, albeit at an older age, is a decision that faces many patients today. As technological advances further improve efficacy and safety, both the surgical and catheter-based procedures will likely become viable options for more patients.

## ■ SUMMARY AND IMPLICATIONS

Treatment of patients with AF should aim to reduce the risk of AF-related mortality and morbidity, including thromboembolic events, symptoms, and hemodynamic effects, and to ameliorate the effects of structural and electrical remodeling induced by the arrhythmia. Both rate-control and rhythm-control strategies are reasonable primary approaches. For some patients, cure of AF may be possible via catheter-based or surgical ablation techniques. Evidence-based selection of a strategy from the palette of treatment choices (**Figure 2**) requires an understanding of each patient's presentation and individual needs and of the risks and benefits of each option. Broadly applicable interventions to reduce the mortality associated with AF remain elusive, but reduction in thromboembolic risk with warfarin may contribute to improved prognosis.

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