

## Epidemiology and Management of New-Onset Atrial Fibrillation

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### **Abstract**

Atrial fibrillation (AF) is a common acute or chronic cardiac disorder that can result in significant morbidity and mortality. Its incidence in the United States is increasing. Projections suggest that more than 5.6 million Americans (50% of whom will be  $\geq 80$  years of age) will have AF by 2050. The American College of Cardiology, American Heart Association, and the European Society of Cardiology define AF as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On an electrocardiogram, AF is characterized by the replacement of P waves by rapid oscillations or fibrillatory waves that vary in size, shape, and timing. Evidence suggests that histological changes exist in the atria of patients with AF, however, it is not known if these changes are a cause or a consequence of AF. Although the fundamental mechanism underlying the disorder is not known, clinical identifying factors are associated with the condition. These may be divided into noncardiac (thyrotoxicosis, alcohol use, electrolyte imbalance, certain pharmacologic and recreational drugs) and cardiac causes (any cause of enlarged left atrium, poor ventricular function, heart surgery). The principles of treatment for this condition are to stabilize the patient hemodynamically, simultaneously determine whether a reversible cause of the AF exists, control the patient's heart rate, determine whether the patient should be cardioverted or maintained in AF, and then develop strategies to prevent the most important complications of stroke. This article will describe in detail the acute management of AF as well as its epidemiology.

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### **Epidemiology**

The American College of Cardiology (ACC), American Heart Association, and the European Society of Cardiology define atrial fibrillation (AF) as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On an electrocardiogram, AF is character-

ized by the replacement of P waves by rapid oscillations or fibrillatory waves that vary in size, shape, and timing.<sup>1</sup> Evidence suggests that histological changes exist in the atria of patients with AF, but it is not known if these changes are a cause or a consequence of AF.<sup>2</sup>

The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study was a cross-sectional evaluation of 1.89 million US adults ( $\geq 20$  years of age) whose AF was diagnosed between July 1, 1996, and December 31, 1997.<sup>3</sup> The goal of the study was to determine the prevalence of AF in that population and to project the number of people in the United States who would exhibit AF between 1995 and 2050. At the time of the study conclusion, about 2.3 million US adults had AF, and 10.5% of those patients were  $\geq 80$  years of age. Projections indicated that  $>5.6$  million Americans would be afflicted by 2050, and more than 50% of those would be  $\geq 80$  years of age. The study also showed that AF occurred more often in men than in women and indicated age-related increases in incidence from 0.1% in people  $<55$  years of age to 3.8% in those  $\geq 60$  years of age to 9% in people  $\geq 80$  years of age.

AF is associated with significant mortality and morbidity because it increases the risk of stroke and thromboembolism.<sup>4</sup> The overall risk for thromboembolic events in patients with nonrheumatic AF increases 5-fold. For those  $>65$  years of age, there is a 5% to 7% yearly risk for the disorder.<sup>5</sup> The attributable risk of AF-related stroke increases with age, from 1.5% in people 50 to 59 years to 23.5% in those 80 to 89 years.<sup>6</sup> Adverse hemodynamic effects produced by the disorder include heart failure and decreased exercise tolerance.<sup>7</sup> In addition to overt stroke, silent cerebral infarction, which also may impair

cognitive function, occurs frequently in asymptomatic patients with AF.<sup>8</sup>

### Etiologic Factors

Many cardiac conditions and noncardiac disorders, some of which are listed below, are associated with AF (Table 1). Lone AF, which belongs to a special category, is defined as AF without underlying structural heart disease or precipitating illness. This disorder accounts for approximately 2.7% of AF in patients <60 years.<sup>9</sup> Higher rates of lone AF have been reported in the Framingham study, which included older patients and patients with a history of hypertension.<sup>10</sup> Familial transmission of AF is rare and may be associated with abnormalities in chromosome 10.<sup>11</sup>

In the West Birmingham Atrial Fibrillation Project, the disorders most often associated with AF were hypertension, which occurred in 37% of the subjects, and ischemic heart disease, which is found in 29% of patients with AF.<sup>12</sup> Those percentages are different in developing countries where rheumatic heart disease is more common and the aging population is smaller than that in developed countries.<sup>12</sup> The following factors are associated with the development of AF:

**Hypertension.** High blood pressure is the most common underlying disorder in patients with AF. Atrial dilatation caused by decreased left ventricular compliance may explain the increased incidence of AF in hypertensive patients.

**Thyroid Disease.** AF occurs in 10% to 30% of older patients with thyrotoxicosis, and it is more common in the elderly.<sup>13</sup> The risk of AF increases up to 5-fold in patients with subclinical hyperthyroidism.<sup>14</sup> That disorder is often not obvious in the elderly, in whom AF may be the only manifestation of thyroid dysfunction. The identification of hyperthyroidism as a precipitating factor for AF is important. In one study, 60% of patients who received treatment for hyperthyroidism exhibited spontaneous reversal of AF with maintenance of sinus rhythm.<sup>15</sup>

**Alcohol Consumption.** AF occurs in up to 60% of binge drinkers of alcohol.<sup>16</sup> Heavy

**Table 1.** Causes of Atrial Fibrillation

Cardiac Causes	Noncardiac Causes
Hypertension	Alcohol
Cardiomyopathy	Fever
Ischemic heart disease	Hyperthyroidism
Cardiac surgery	Electrolyte abnormalities
Valvular heart disease	Drugs (norepinephrine and other sympathomimetic medications)
Pericarditis	
Congenital heart disease	Hypothermia
Tumor	Hypovolemia
Ventricular hypertrophy	Sudden emotional changes
Ventricular pacing	Chronic pulmonary disease
Lipomatous hypertrophy	Cerebrovascular accident
Preexcitation syndrome	Pregnancy
Tachycardia-bradycardia syndrome	Trauma

alcohol consumption on holidays or weekends may predispose an individual to an episode of AF ("holiday heart syndrome"), which can occur in otherwise healthy people with normal cardiac function.

**Cardiac Surgery.** AF occurs in 15% to 33% of patients who have undergone coronary bypass surgery and in 38% to 64% of those who have had cardiac valvular surgery.<sup>17,18</sup> Episodes of AF increase the duration and cost of hospitalization in those patients and may be associated with stroke or hemodynamic adverse effects. The risk for postcardiac surgery AF is highest in the elderly, in those with a history of previous AF, in patients with significant stenosis of the right coronary artery, and in patients who have discontinued treatment with a beta blocker before surgery.<sup>19</sup>

**Cardiac Valvular Disease.** Valvular heart disease increases the risk of thromboembolism. Thromboembolic events occur in up to 17% of patients with both AF and rheumatic heart disease.<sup>20</sup> This risk of stroke and thromboembolism is several times greater

than the risk seen in patients with normal sinus rhythm.<sup>21</sup> Rheumatic heart disease, which contributes to AF, is less common in developed countries. In a study of approximately 1100 patients with rheumatic heart disease, the highest incidence (70%) of AF was found in those with combined mitral stenosis, mitral regurgitation, and tricuspid regurgitation. AF occurred in 29% of the subjects with isolated mitral stenosis, in 16% of those with isolated mitral regurgitation, and in 52% of those with both conditions. AF occurs in only 1% of patients with isolated aortic stenosis (unless heart failure is present).<sup>21</sup>

**Heart Failure.** In patients with mild-to-moderate heart failure, AF is not associated with an increase in morbidity or mortality.<sup>22</sup> Total morbidity and mortality rates from sudden cardiac death are increased in patients with both advanced heart failure and AF.<sup>23</sup>

**Treatment**

The first step in evaluating a patient with AF is to determine whether the patient's symptoms warrant immediate cardioversion. The patient who is hemodynamically unstable or ischemic in spite of attempts to control the heart rate should be immediately cardioverted under general anesthesia. Full-dose heparin should be used to prevent stroke. Warfarin can be initiated and continued in addition to treatment with heparin until the international normalized ratio (INR) is in the range of 2.0 to 3.0, at which time heparin therapy can be terminated. Anticoagulation should be continued for at least 4 weeks after restoration of normal sinus rhythm.

The immediate evaluation and treatment of patients with AF also should include a thorough investigation of any underlying and reversible cause, controlling the heart rate, and starting anticoagulation therapy. Thereafter, a decision should be made regarding the long-term management of the patient. Either control the rate with life-long anticoagulation or restore rhythm control and normal sinus rhythm, which requires life-long anticoagulation in most patients as well.

**Identifying the Cause.** Management of the hemodynamically stable or unstable patient

consists of identifying any underlying reversible causes of AF, which requires obtaining a comprehensive medical history and performing a physical examination, basic laboratory tests, and echocardiography.

**Controlling the Heart Rate.** Control of heart rate is a central component to the management of AF, although the definition of adequate control remains controversial. Keeping the heart rate under 90 bpm at rest and under 120 to 140 bpm during exercise is usually considered sufficient. In most patients, calcium channel blockers and beta blockers (with or without the addition of digoxin) are the drugs of choice for achieving adequate heart rate control. Those 2 classes of drugs are equally effective, and the choice of medication should be dictated by the patient's tolerance of therapy and his or her other medical conditions. For example, AF is better managed with beta blockers in people with thyrotoxicosis and those with previous myocardial infarction. If beta blockers are contraindicated because of bronchospastic pulmonary disease, then verapamil or diltiazem can be used as alternative medications. In patients with hypertrophic cardiomyopathy, beta blockers and verapamil are useful, exerting a beneficial effect on outflow tract obstruction. In this situation, digoxin may be detrimental. In contrast, digoxin or beta blockers can benefit patients with heart failure or dilated cardiomyopathy, but calcium channel blockers are not recommended.

Experimental data suggest that verapamil may prevent or delay atrial remodeling when given early after the onset of AF.<sup>24</sup> The implication of this finding on the choice of treatment (a calcium channel blocker or a beta blocker) still requires additional study.

**Controlling the Heart Rhythm.** Approximately 72% of new-onset AF terminates spontaneously.<sup>25</sup> In the remaining patients with AF, the heart rhythm can be treated by medication or electrical cardioversion.

- **Pharmacologic Cardioversion (Table 2).** Several antiarrhythmic drugs have been used for the rapid conversion of AF to normal sinus rhythm. Class Ia drugs such as quinidine (conversion rate within 2 days, up

**Table 2.** Pharmacologic Treatment for Rapid Cardioversion and Long-Term Atrial Fibrillation Management

Drug Class and Name	IV or Oral Therapy for Rapid Cardioversion	Prophylactic Long-Term Oral Therapy	Adverse Effects
<b>Class Ia</b>			
■ Procainamide	500-1200 mg IV over 30-60 min	2000-4000 mg/d	Torsades de pointes, lupus-like syndrome, hypersensitivity, vasodilation and hypotension (with large doses), potentiates digoxin toxicity, may aggravate myasthenia gravis, exacerbates congestive heart failure
■ Quinidine	16 mg/min until arrhythmia subsists or adverse effects adhere	600-1200 mg/d	AV conduction delay, may exacerbate myasthenia gravis, potentiates digitalis toxicity
■ Disopyramide	Multiple IV and PO regimens were effective in clinical trials	450-600 mg/d	Negative inotropic effect, AV block, QT prolongation
<b>Class Ic</b>			
■ Flecainide	2 mg/kg IV over 10 min	150-300 mg/d	Dizziness, visual disturbances, LV function depression, proarrhythmic adverse effects in patients with structural heart disease
■ Propafenone	2 mg/kg IV over 10 min, or 450-600 mg PO	450-900 mg/d	Nausea, vomiting, bitter metallic taste, rash, AV nodal block, negative inotropic activity, potentiates digoxin toxicity, increases plasma warfarin level
<b>Class III</b>			
■ Ibutilide	1 mg IV repeat once after 10 min	Not available	QT prolongation, torsades de pointes
■ Sotalol	Not recommended	160-480 mg/d	QT prolongation, torsades de pointes, negative inotropic activity
■ Amiodarone	Not recommended	400-1200 mg/d for 7 d, then taper to 100-300 mg/d	Corneal microdeposition, transitional elevation of liver enzymes, hypothyroidism, hyperthyroidism, photosensitivity, interstitial lung disease, peripheral neuropathy, myopathy, bradycardia, potentiates digoxin toxicity
■ Dofetilide	8 mcg/kg IV over 15 min	250-500 mg/d	QT prolongation, torsades de pointes

IV indicates intravenous; LV, left ventricular; PO, by mouth; AV, atrioventricular.

to 80%) and procainamide (conversion rate within 2 days, 40%-60%) have been used for decades.<sup>26-28</sup> Because of the risk of proarrhythmia, these drugs have been supplanted by the use of the class Ic drugs flecainide and propafenone or class III drugs, such as ibutilide. All of these drugs have been approved by the US Food and Drug Administration for rapid cardioversion of AF.

Flecainide and propafenone produce fewer adverse effects than class III drugs, which increase the risk for QT prolongation and ventricular arrhythmia.<sup>28</sup> The rate of

conversion produced by flecainide and propafenone is reported to be as high as 80%.<sup>28,29</sup> However, their use should be limited to patients without structural heart disease or coronary disease.

The class III drug ibutilide is specifically indicated for the rapid conversion of AF to sinus rhythm. A single intravenous dose or repeated doses given 10 minutes apart has been shown to rapidly restore sinus rhythm in 30% to 50% of patients with AF and 60% to 80% of patients with atrial flutter.<sup>30-32</sup> Ibutilide exerts only a short-term effect and is associated with a 1% to 2% risk of sus-

tained ventricular tachycardia and torsades de pointes that requires countershock.<sup>33</sup> In the absence of left atrium enlargement and mitral valve disease, ibutilide is 85% effective.<sup>34</sup> The effectiveness of ibutilide has not been compared with that of class Ic drugs.

Intravenously administered amiodarone is also effective (80% conversion rate) for converting AF to sinus rhythm.<sup>35</sup> The efficacy of sotalol, which may be used in patients with ischemic heart disease, is similar to that of class Ia and Ic agents.<sup>36,37</sup>

Dofetilide, another class III agent, has been shown to convert 31% of patients with sustained AF to sinus rhythm. Dofetilide is probably most effective in converting atrial flutter to normal sinus rhythm.<sup>38,39</sup>

- **External Electric Cardioversion.** Electric cardioversion restores sinus rhythm in patients with AF by repolarizing the atrial myocardium and thereby restoring organized conduction. This enables the sinoatrial node to resume its role as cardiac pacemaker. The underlying cause of the patient's AF, the size of the left atrium, and the duration of AF influence its success rate. The electric shock should be R-wave synchronized, and their recommended initial energy for transthoracic cardioversion of AF is 200 J. More than 75% of cases are successfully converted with that energy. Higher energies (300-360 J) may be required if shocks at 200 J do not restore the sinus rhythm.

Nonembolic complications of electric external cardioversion (eg, ventricular arrhythmias, sinus bradycardia, hypotension, pulmonary edema, skin burns, transient sinus tachycardia, ST segment, and T wave abnormalities) are rare.

- **Internal Electric Cardioversion.** Internal cardioversion can be used in patients for whom external or pharmacologic cardioversion is ineffective. It is also particularly effective in obese patients and those with lung disease. In one study, the immediate efficacy of internal cardioversion was significantly greater than that of external cardioversion (91% vs 67%).<sup>40,41</sup> During high-energy internal cardioversion, a shock of 200 to 300 J is delivered from an electrode catheter placed in the right atrial cavity to a dispersive electrode affixed to the patient's back. For low-energy cardioversion, electrode catheters in the right atrium and either the coronary sinus or the left pulmonary artery are used.

### Factors in Long-Term Management

There are 2 approaches to the long-term management of a patient with AF. The first is heart rhythm control with cardioversion followed by treatment with antiarrhythmic drugs. The other approach is to allow the abnormal rhythm to persist but with a controlled rate. Both treatments require that the patient undergo adequate anticoagulation therapy (the INR should be maintained between 2 and 3) unless contraindications for that treatment exist. Table 2 outlines pharmacologic therapy for the long-term maintenance of sinus rhythm. Patients in whom sinus rhythm is maintained would theoretically exhibit symptomatic improvement, better exercise tolerance, a lower risk of stroke, and longer survival, with the hope to discontinue anticoagulation therapy. However, this has been refuted in 2 recent trials.<sup>42,43</sup>

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study compared the efficacy of cardioversion and treatment with antiarrhythmic drugs with that of heart rate control in the long-term management of AF.<sup>42,43</sup> The AFFIRM trial studied 4060 US patients with AF who were at high risk for stroke or death because of their age (>65 years), a dilated left atrium, hypertension, coronary heart disease, or depressed left ventricular function.<sup>42</sup> The study showed that the rhythm control strategy offered no advantage over control of heart rate alone. Additionally, the latter therapy had a lower risk of adverse effects. The results indicated that anticoagulation therapy should be continued in patients at high risk for stroke even if their sinus rhythm is restored and maintained.

The RACE study, which was conducted in the Netherlands, compared heart rate control with heart rhythm control in patients who had recurrent persistent AF.<sup>43</sup> The study subjects consisted of 522 patients whose AF persisted even after they had undergone electrical cardioversion. The study showed that heart rate control is not inferior to rhythm control for the prevention of death and morbidity in patients with recurrent persistent AF. Notably, only 39% of patients in

the heart rhythm control group exhibited sinus rhythm, despite a careful treatment protocol. Those results indicate the need for more effective methods of maintaining sinus rhythm. Interestingly, the cardiovascular risk did not decrease in patients whose sinus rhythm was maintained.

The AFFIRM and RACE studies suggest that heart rate control should be considered a primary approach to therapy for AF and that heart rhythm control may be abandoned early if the results are not completely satisfactory. Additional studies are needed to determine whether that treatment strategy should be used in individuals with new-onset AF and in AF patients at low risk for cardiovascular events.

The incidence of thromboembolic events in patients with AF that persisted for less than 48 hours before converting to sinus rhythm is 0.8%.<sup>44</sup> Although the incidence is small when compared to the 5% to 7% risk of stroke in patients with prolonged AF, it is still significant. These studies recommend the use of anticoagulation therapy in all patients with new-onset AF, regardless of its duration. It should be mentioned that the 2 strategies of cardioversion can be used. The conventional treatment strategy calls for 3 to 4 weeks of anticoagulation before cardioversion.<sup>45</sup> At the very least, patients require 4 weeks of anticoagulation therapy after having undergone cardioversion, because a significant lag can occur between the restoration of sinus rhythm and the resumption of normal atrial mechanical function. In most patients long-term indications for anticoagulation exist because of the high incidence of recurrent fibrillation, especially in a patient with risk factors for stroke.

The daily dose of warfarin correlates poorly with the INR, and the correct dosage varies among patients. Fixed-dose warfarin trials have uniformly failed to show the benefit seen in adjusted-dose warfarin therapy.<sup>46</sup> However, new orally active thrombin inhibitors, when available, should simplify treatment.

Anticoagulation treatment with heparin and warfarin is required before transesophageal echocardiography (TEE) is performed. TEE is highly accurate in detecting

thrombi in the left atrial appendage. If thrombi are not detected, the patient can then undergo cardioversion before anticoagulation. Anticoagulation therapy should be continued unless there is a contraindication or unless the patient is at very low risk for thromboembolism, in which case the anticoagulation can be stopped at 1 month. Preliminary studies indicate that the TEE guided approach has a safety profile similar to that of the conventional approach to treating AF.<sup>47,48</sup>

### Stroke Prevention

Anticoagulation therapy is also used to prevent stroke, which is an essential part of the long-term management of patients with AF. The patient's risk for stroke must first be determined. Several stroke risk factors (previous stroke or transient ischemic attack, age >75 years of age, hypertension, diabetes, impaired left ventricular function) have been identified.<sup>49,50</sup> The risk of stroke is high (3.5%-8.1% per year) in patients with these risk factors.<sup>50</sup> In these patients, treatment with warfarin is recommended unless it is contraindicated, with the goal of anticoagulation therapy an INR level between 2 and 3. Anticoagulation therapy should be continued indefinitely unless it is contraindicated.

In patients who are 65 to 75 years old and who have no stroke risk factors, the risk of stroke is 4% per year without antiplatelet and anticoagulation therapy. Those patients could be treated with either anticoagulation or antiplatelet therapy (aspirin 325 mg/day). In patients who have no stroke risk factors and are younger than 65 years of age, the annual risk of stroke is 1% (which is equal to the risk in the general US population). For those individuals, the recommended prevention therapy is aspirin 325 mg/day.<sup>49,50</sup>

### Conclusion

AF remains the most common cardiac disorder in the United States, and during the next several decades its incidence will likely increase. It occurs more frequently in the elderly and more often in men than women. The onset of the disorder is associated with a host of contributing factors: cardiac conditions (coronary heart and valvular disease, heart failure), thyroid disorders, cardiac sur-

gery, hypertension, and heavy alcohol consumption. AF may require emergent treatment and long-term management to prevent recurrence. The need for immediate cardioversion must be determined quickly. This therapy is clearly indicated in patients hemodynamically unstable because of ischemia, hypotension, or pulmonary edema. These patients should be cardioverted under general anesthesia. All patients should be heparinized. Long-term management of a patient with AF involves 2 approaches, either heart rhythm control with antiarrhythmic drugs or rate control that allows the abnormal rhythm to persist under a controlled heart rate. Unless contraindicated, both approaches require that the patient be anticoagulated, and heart rate control should be a primary goal of therapy for AF. Because of the high incidence of cerebrovascular events in patients with AF, the risk of stroke should always be assessed and appropriate therapy administered to prevent thromboembolic events.

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