

*Medical Progress*

## ATRIAL FIBRILLATION

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**E**LECTROCARDIOGRAPHICALLY, atrial fibrillation is characterized by the presence of rapid, irregular, fibrillatory waves that vary in size, shape, and timing. This set of findings is usually associated with an irregular ventricular response, although regularization may occur in patients with complete heart block, an accelerated junctional or idioventricular rhythm, or a ventricular paced rhythm. In the past decade, we have gained a greater understanding of atrial fibrillation. Experimental studies have explored the mechanisms of the onset and maintenance of the arrhythmia; drugs have been tailored to specific cardiac ion channels; nonpharmacologic therapies have been introduced that are designed to control or prevent atrial fibrillation; and data have emerged that demonstrate a genetic predisposition in some patients.<sup>1</sup>

## EPIDEMIOLOGY

The incidence of atrial fibrillation approximately doubles with each decade of adult life and ranges from 2 or 3 new cases per 1000 population per year between the ages of 55 and 64 years to 35 new cases per 1000 population per year between the ages of 85 and 94 years. The arrhythmia may be an independent risk factor for death, with a relative risk of about 1.5 for men and 1.9 for women after adjustment for known risk factors.<sup>2</sup> It has been suggested that, in patients with underlying ventricular dysfunction, this increased risk of death is due primarily to heart failure.<sup>3</sup>

The term "lone atrial fibrillation" describes atrial fibrillation in the absence of demonstrable underlying cardiac disease or a history of hypertension. It may be due to fibrotic areas in the atrium that predispose patients to arrhythmia, to increased susceptibility to autonomic neural stimuli to the heart,<sup>4</sup> or to localized atrial myocarditis.<sup>5</sup> Although the Framingham Heart Study suggested that patients with lone atrial fibrillation had a risk of stroke that was four times that of age-matched controls in sinus rhythm,<sup>6</sup> the absence of structural heart disease was determined in that study without the use of echocardiography, and hypertension was not a criterion for exclusion. It has been estimated that lone atrial fibrillation occurs in approximately 3 percent of pa-

tients with atrial fibrillation.<sup>7</sup> In patients younger than 60 years old, lone atrial fibrillation, although uncommon, has a benign prognosis. However, patients older than 61 years of age who have lone atrial fibrillation have an increased risk of stroke and death.<sup>7,8</sup>

Whether the treatment of atrial fibrillation reduces mortality can be evaluated only by prospective, randomized trials. One such study, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, is currently being conducted in the United States.<sup>9</sup> Its primary aim is to determine whether allowing atrial fibrillation to persist while controlling the heart rate and administering antithrombotic therapy is associated with the same rate of mortality as restoring sinus rhythm with antiarrhythmic drugs. Several secondary analyses will define the optimal therapy and the risks for specific subgroups of patients.

## HISTOLOGIC AND ELECTROPHYSIOLOGIC FEATURES

Atrial fibrillation is usually precipitated by underlying cardiac or noncardiac disease. The resultant atrial abnormality (frequently inflammation or fibrosis) acts as a substrate for the development of the arrhythmia.<sup>10</sup> In addition, the onset of atrial fibrillation usually requires a trigger. Triggers that may initiate the arrhythmia include alterations in autonomic tone,<sup>11</sup> acute or chronic changes in atrial wall tension,<sup>12</sup> atrial ectopic foci, and local factors. Cardiothoracic surgery, a potent trigger of atrial fibrillation, has been discussed by Ommen et al.<sup>13</sup>

In most cases of atrial fibrillation, multiple, small reentrant circuits are constantly arising in the atria, colliding, being extinguished, and arising again.<sup>14-16</sup> A critical mass of atrial tissue is required to sustain the minimal number of simultaneous circuits necessary for the perpetuation of the arrhythmia. Drugs can prevent atrial fibrillation by increasing the circuit wavelength,<sup>17</sup> and invasive techniques can prevent it by decreasing the size of the atrial segments.<sup>18</sup>

A second distinct mechanism causing atrial fibrillation has recently been recognized — a rapidly firing focus (or foci), usually located in or near the pulmonary veins. Such foci may mimic the appearance of atrial fibrillation on the surface electrocardiogram<sup>19</sup> or, more commonly, may degenerate into or trigger classic atrial fibrillation after a brief burst of ectopic activity.<sup>20</sup> In animals, repeated episodes of induced atrial fibrillation result in the development of sustained arrhythmia.<sup>21</sup> The electrophysiologic effect of these repeated episodes is a marked shortening of the atrial refractory period and the loss of the normal lengthening of atrial refractoriness at slower heart rates. This phenomenon, which may be reversible with the maintenance of sinus rhythm,<sup>22</sup> has been termed atrial electrical remodeling.<sup>23</sup> Pretreatment with verapamil may markedly reduce the extent of remodeling,<sup>24</sup> suggesting that cytosolic calcium overload is a contributory

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factor. This observation may have clinical applications, and the use of verapamil in conjunction with antiarrhythmic drugs before cardioversion from atrial fibrillation may reduce the risk of recurrence of arrhythmia.<sup>25,26</sup>

Prolonged episodes of atrial fibrillation frequently cause mechanical dysfunction of the atrium.<sup>27</sup> Restoration of sinus rhythm is generally associated with the normalization of function over a period of two to four weeks.<sup>28</sup> Possibly because of the delayed recovery of atrial mechanical function, the risk of thromboembolism posed by atrial fibrillation seems to persist for a few weeks after cardioversion.

#### HEMODYNAMIC EFFECTS

Atrial fibrillation is associated with the loss of the atrial contribution to ventricular filling. This may result in a decrease in ventricular stroke volume of up to 20 percent.<sup>29</sup> The irregularity of the ventricular response may also contribute to hemodynamic impairment.<sup>30</sup> The ventricular rate in patients with atrial fibrillation frequently has wide swings, with peaks that exceed those that occur during sinus rhythm.<sup>31</sup> In some patients with a poorly controlled ventricular rate (generally, a mean of more than 100 beats per minute), persistent tachycardia results in ultrastructural changes that cause ventricular dysfunction.<sup>24</sup> This tachycardia-mediated cardiomyopathy is often reversible after sinus rhythm has been restored or when the heart rate during atrial fibrillation is controlled.<sup>32</sup>

#### SYMPTOMS

Some patients with atrial fibrillation have minimal symptoms or none, whereas others may have severe symptoms, particularly at the onset of the arrhythmia. Symptoms may range from palpitations to acute pulmonary edema, but fatigue and other nonspecific symptoms are probably the most common.<sup>33</sup> The cognitive function of elderly patients with persistent arrhythmia may be impaired, as compared with that of age-matched controls in sinus rhythm.<sup>34</sup> Whether this impairment is due to recurrent cerebral embolism or cerebral hypoperfusion is unclear.

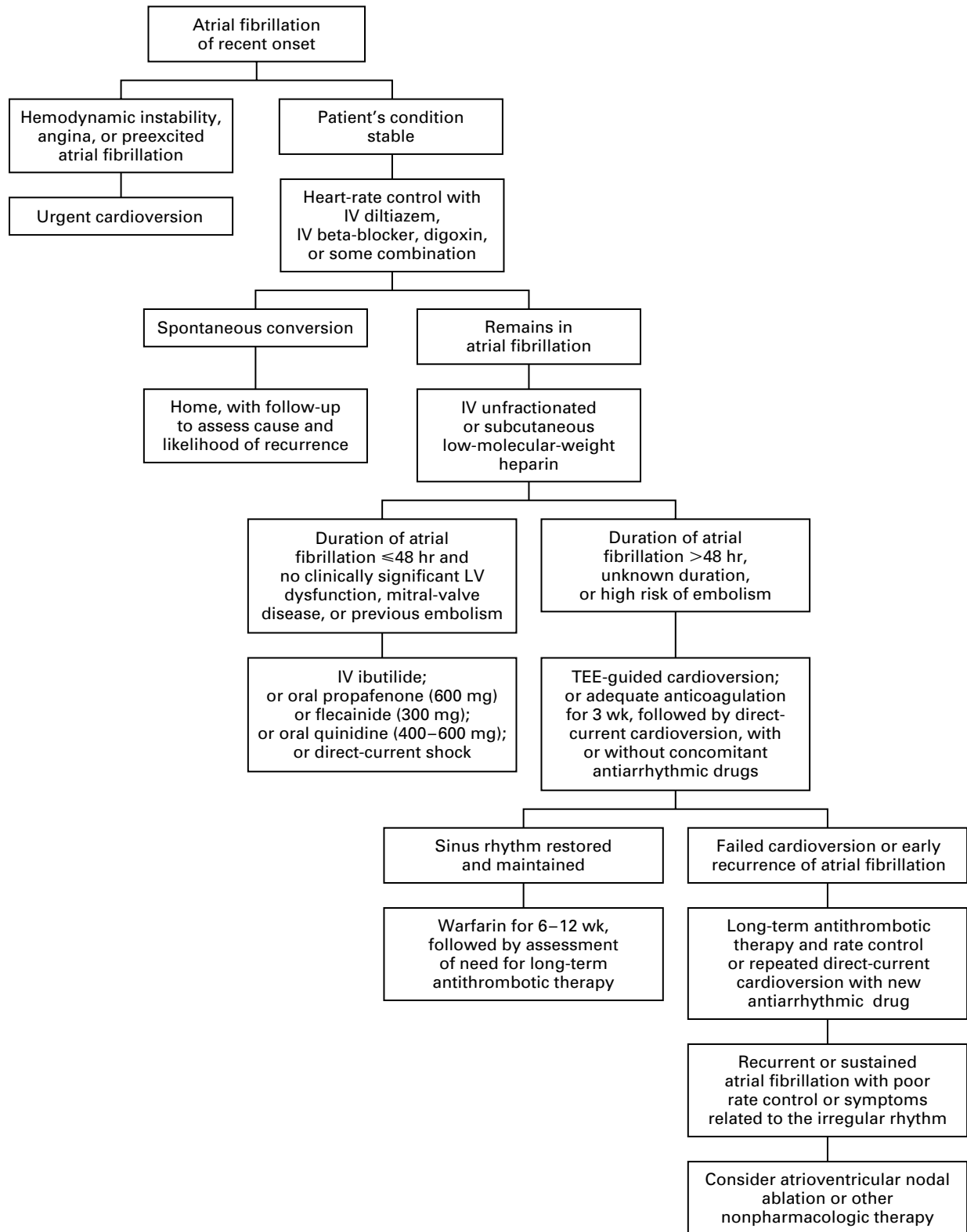
Not all episodes of arrhythmia are symptomatic, and monitoring studies in patients with paroxysmal atrial fibrillation demonstrate that asymptomatic episodes occur more frequently than do symptomatic ones.<sup>35</sup> Preliminary data suggest that the quality of life is significantly impaired during atrial fibrillation, as compared with the quality of life after the restoration of sinus rhythm.<sup>36</sup> However, in a recent small trial, control of the heart rate with the use of diltiazem during atrial fibrillation produced as much relief of symptoms as did attempts at the maintenance of sinus rhythm with amiodarone.<sup>37</sup> The impairment in the quality of life in patients with paroxysmal atrial fibrillation is equivalent to that seen in patients with more severe cardiac disease, such as those who have undergone angioplasty.<sup>38</sup> The ablation of the atrioventricular node along with the implantation of a pacemaker significantly improves quality-of-life scores.<sup>39</sup>

#### APPROACH TO THE PATIENT WITH ATRIAL FIBRILLATION

In the assessment of a patient with atrial fibrillation, it is important to determine the clinical significance of the arrhythmia and to identify any associated conditions. The physician must be aware of any potentially negative effect that the therapy for the arrhythmia may have on the underlying heart disease (for example, the negative inotropic effects of some antiarrhythmic drugs). A careful history taking and physical examination are mandatory. In particular, physicians should seek evidence of a new onset or exacerbation of angina or congestive heart failure, since such evidence may suggest a need for early cardioversion. Echocardiography is invaluable for evaluating cardiac abnormalities, and thyroid-function tests occasionally reveal unexpected hyperthyroidism.

A three-part approach to treatment should be considered: physicians should assess the need for, the proper timing of, and the appropriate method for the restoration of sinus rhythm; they should evaluate the need for anticoagulation to prevent embolic stroke; and they should ensure appropriate control of the ventricular rate while the patient is in atrial fibrillation.

**Figure 1 (facing page).** An Approach to the Management of Newly Diagnosed Atrial Fibrillation or Atrial Fibrillation of Recent Onset. The pharmacologic therapies suggested for the termination of atrial fibrillation of less than 48 hours' duration are not presented in order of preference; to avoid drug interactions, no more than one should be used. Direct-current cardioversion can be attempted as the initial strategy or used if drug therapy fails. This figure does not detail the investigation into the cause of atrial fibrillation. Strong consideration should be given to the performance of echocardiography and thyroid-function tests, at minimum, for the evaluation of the cause and evaluation of ventricular function. Although low-molecular-weight heparin has not been compared in a clinical trial with unfractionated heparin in patients with atrial fibrillation of recent onset, it has been found to be at least as effective as unfractionated heparin in other situations when used for the prevention of arterial thromboembolism. It should also be noted that intravenous unfractionated heparin has never been formally evaluated as a therapy for atrial fibrillation of recent onset. Although the Food and Drug Administration has not approved low-molecular-weight heparin for use in atrial fibrillation, it is a logical alternative to intravenous unfractionated heparin. Both intravenous ibutilide and oral quinidine may provoke torsade de pointes. Although oral quinidine is quite effective for the termination of an episode of acute atrial fibrillation, long-term oral quinidine is not recommended for the maintenance of sinus rhythm (see Fig. 2). IV denotes intravenous, LV left ventricular, and TEE transesophageal echocardiography.



## NEWLY DIAGNOSED ATRIAL FIBRILLATION

An approach to newly diagnosed atrial fibrillation is outlined in Figure 1. Hospitalization is not required for all patients and can be limited to those with hemodynamic compromise or severely symptomatic arrhythmia, those at high risk for embolism (such as patients with heart failure), and patients in whom early cardioversion is considered. In the absence of angina, electrocardiographic evidence of myocardial ischemia, or a recent infarction, there is no need for admission to a coronary care unit in order to rule out myocardial infarction, since ischemic heart disease rarely presents as atrial fibrillation with no other signs or symptoms.<sup>40</sup>

In some patients, such as those with pulmonary edema, acute myocardial infarction, or unstable angina, urgent cardioversion may be necessary as the initial treatment. Even if their condition is clinically stable, patients with atrial fibrillation and a rapid, wide-complex ventricular response related to the preexcitation syndrome should also be considered for early electrical cardioversion, since the response to antiarrhythmic agents is unpredictable in such patients and most agents used for rate control are contraindicated.<sup>41</sup>

In the absence of an urgent need for cardioversion, consideration should be given to pharmacologic rate control. Although the atrial rate usually exceeds 350 beats per minute, the mean resting ventricular rate in a patient with atrial fibrillation of new onset is between 110 and 130 beats per minute.<sup>42</sup> In patients with the Wolff-Parkinson-White syndrome and a short refrac-

tory period of the accessory pathway, the ventricular response may exceed 250 beats per minute. In such cases, the electrocardiogram demonstrates a wide-complex tachycardia, due to predominant accessory-pathway conduction. A resting ventricular rate higher than 150 beats per minute in the absence of preexcitation should raise the suspicion of a hyperadrenergic state, such as occurs in thyrotoxicosis, fever, or acute gastrointestinal bleeding. A slow ventricular response in the absence of medication may occur with high vagal tone in young athletes<sup>43</sup> or in patients with conduction-system disease.

Digoxin is somewhat effective for slowing the ventricular rate in a patient at rest, but its maximal action is achieved only after several hours,<sup>42,44</sup> and it is of little value in patients who are in a hyperadrenergic state. Intravenous beta-blocking or calcium-channel-blocking drugs produce more rapid rate control, regardless of the level of sympathetic tone. The appropriate doses of these drugs are given in Table 1.

Spontaneous conversion to sinus rhythm within 24 hours after the onset of atrial fibrillation is common, occurring in up to two thirds of patients.<sup>45</sup> Once the duration of atrial fibrillation exceeds 24 hours, the likelihood of conversion decreases. After one week of persistent arrhythmia, spontaneous conversion is rare.<sup>45,46</sup>

Self-terminating episodes of atrial fibrillation often recur. However, the arrhythmia-free period is unpredictable, and it may not be necessary to prescribe either long-term antiarrhythmic therapy or anticoagulation for all patients after the first documented episode.

TABLE 1. PHARMACOLOGIC HEART-RATE CONTROL IN ATRIAL FIBRILLATION.\*

DRUG	CONTROL OF ACUTE EPISODE	CONTROL OF SUSTAINED ATRIAL FIBRILLATION	COMMENTS
Calcium-channel blockers			
Diltiazem	20-mg bolus followed, if necessary, by 25 mg given 15 min later. Maintenance infusion of 5–15 mg/hr.	Oral controlled-release formulation, 180–300 mg daily.	Long-term control may be better with the addition of digoxin.
Verapamil	5–10 mg IV over 2–3 min, repeated once, 30 min later. Maintenance infusion rate is not reliably documented.	Slow-release formulation, 120–240 mg once or twice daily.	Causes elevation in digoxin level. May be more negatively inotropic than diltiazem.
Beta-blockers†			
Esmolol	0.5 mg/kg of body weight IV, repeated if necessary. Follow with infusion at 0.05 mg/kg/min, increasing as needed to 0.2 mg/kg/min.	Not available in oral forms.	Hypotension may be troublesome but responds to drug discontinuation.
Metoprolol	5-mg bolus IV, repeated twice at intervals of 2 min. No data on maintenance infusion.	50–400 mg daily in divided doses.	Useful if there is concomitant coronary disease.
Propranolol	1–5 mg IV, given over 10 min.	30–360 mg in divided doses or in long-acting form.	Noncardioselective: use cautiously in patients with a history of bronchospasm.
Digoxin	1.0–1.5 mg IV or orally over 24 hr in doses of 0.25 to 0.5 mg.	0.125–0.5 mg daily.	Renally excreted. Slow onset even if given IV, with less effective control than other agents, although may be synergistic with them. Poor efficacy for exertional heart-rate control.

\*IV denotes intravenously.

†The beta-blockers listed are representative of agents in this category. Other intravenous or oral beta-blockers may be equally acceptable.

Exceptions include highly symptomatic patients, patients who have had an embolic event, and those who are at high risk for thromboembolism. In such patients, it is prudent to administer antiarrhythmic therapy, anticoagulant therapy, or both after the initial episode.

**Antiarrhythmic-Drug Therapy**

Early drug therapy to restore sinus rhythm can be considered in patients in whom the arrhythmia has lasted less than 48 hours or who are receiving long-term warfarin therapy. Digoxin is not effective in converting atrial fibrillation to sinus rhythm,<sup>42,47</sup> but antiarrhythmic therapy increases the likelihood of conversion to as much as 90 percent, if the drugs are administered early and in adequate doses.<sup>48</sup> If pharmacologic therapy is contemplated, continuous electrocardiographic monitoring during the first 48 to 72 hours after the initiation of antiarrhythmic therapy should be considered. It is not necessary during the administration of amiodarone, unless sinus-node dysfunction is suspected. Although a limited number of drugs are approved by the Food and Drug Administration for the treatment of atrial fibrillation, there is considerable information about the use of oral and intravenous antiarrhythmic drugs for the conversion of recent-onset atrial fibrillation to sinus

rhythm. The drugs whose efficacy has been demonstrated are listed in Table 2.

**Anticoagulation**

In many patients, the precise time of onset of atrial fibrillation cannot be determined accurately. Under these circumstances, it is highly advisable to administer anticoagulant therapy to the patient before attempting cardioversion. There are two alternative approaches: outpatient systemic anticoagulation with warfarin to achieve an international normalized ratio of 2.0 to 3.0 for at least three weeks, followed by cardioversion; and cardioversion guided by transesophageal echocardiography. In the latter approach, multiplane transesophageal echocardiography that indicates the absence of thrombus is associated with an extremely low rate of thromboembolism after cardioversion,<sup>49</sup> provided that short-term anticoagulant therapy is used before and during the procedure and that warfarin is prescribed after the procedure. Regardless of which of these approaches is taken, anticoagulant therapy is mandatory for a minimum of three to four weeks after cardioversion. Since the greatest likelihood of reversion to atrial fibrillation occurs in the first three months after the restoration of sinus rhythm,<sup>50</sup> it is prudent to continue anticoagulation for this period unless there is a contraindication.

**TABLE 2. DOSES OF MEDICATIONS USED FOR CONVERSION OF RECENT-ONSET ATRIAL FIBRILLATION AND MAINTENANCE OF SINUS RHYTHM.\***

DRUG	DOSE FOR CONVERSION	DOSE FOR MAINTENANCE	COMMENTS
Flecainide	300 mg orally (2 mg/kg of body weight IV)	50–150 mg twice daily	IV formulation not available in U.S. Approved only for paroxysmal AF with structurally normal heart.
Propafenone	600 mg orally (2 mg/kg IV)	150–300 mg twice daily	Same limitations as flecainide.
Procainamide	100 mg IV every 5 min to maximum of 1000 mg	Slow-release formulation, 1000–2000 mg twice daily	Long-term use associated with lupus. Not FDA-approved for AF.
Quinidine	200 mg sulfate orally, followed 1–2 hr later by 400 mg	200–400 mg sulfate 4 times daily, or 324–648 mg gluconate 3 times daily	Approved for AF but risk of death increased during long-term therapy.
Disopyramide	200 mg orally every 4 hr to maximum of 800 mg	100–150 mg 4 times daily or 200–300 mg controlled-release formulation twice daily	Not FDA-approved for AF. Strong negative inotropic effect.
Sotalol	Not recommended (conversion rate is low)	120–160 mg twice daily	Poor conversion efficacy. Approved for maintenance of sinus rhythm. Hospitalization for initiation is mandatory.
Dofetilide	0.5 mg twice daily orally (adjust dose downward for patients with renal disease)	0.5 mg twice daily (adjust dose downward for patients with renal disease)	FDA-approved for conversion and maintenance. Hospitalization for initiation is mandatory.
Amiodarone	1200 mg IV in 24 hr	600 mg/day for 2 wk, then 200–400 mg daily (lower dose is preferable)	IV amiodarone moderately effective for conversion, but onset is slow. Good rate slowing in AF. Not FDA-approved for this indication.
Ibutilide	1 mg IV over 10 min in patients weighing ≥60 kg, or 0.01 mg/kg over 10 min in patients weighing <60 kg; may be repeated once if arrhythmia does not end within 10 min after end of initial infusion	Not available for maintenance (IV formulation only)	Do not use in patients with hypokalemia, a prolonged QT interval, or torsade de pointes.

\*Intravenous (IV) flecainide and propafenone (the doses of which are given in parentheses) are not available in the United States. AF denotes atrial fibrillation, and FDA Food and Drug Administration.

## RECURRENT PAROXYSMAL ATRIAL FIBRILLATION

In trials of anticoagulant therapy, patients with paroxysmal atrial fibrillation had the same risk of stroke as subjects with persistent atrial fibrillation.<sup>51,52</sup> Thus, unless a patient with paroxysmal arrhythmia is younger than 65 years old and has no hypertension or underlying heart disease, long-term warfarin therapy should be instituted.

### Antiarrhythmic-Drug Therapy

Several drugs have been shown to be effective in the treatment of paroxysmal atrial fibrillation. These include propafenone,<sup>53</sup> flecainide,<sup>54</sup> and sotalol.<sup>55</sup> These agents often do not totally abolish the arrhythmia, but they increase the length of the interval between the paroxysms. Although this decrease in the frequency of paroxysm is often satisfactory for a reduction of symptoms, there are no data supporting the possibility that having fewer episodes of atrial fibrillation decreases the risk of thromboembolism. Furthermore, patients who have symptomatic episodes of paroxysmal arrhythmia may also have multiple episodes of asymptomatic atrial fibrillation.<sup>35</sup> Although asymptomatic episodes tend to be shorter than the symptomatic episodes, they may still pose a risk of thromboembolism.

The treatment of paroxysmal atrial fibrillation with antiarrhythmic drugs that also slow the heart rate (such as sotalol) may convert symptomatic episodes to asymptomatic ones.<sup>56</sup> Decisions regarding the discontinuation of anticoagulation in such patients remain clinically challenging, requiring physicians to weigh the risk of bleeding against the risk of a stroke from asymptomatic arrhythmia. Holter monitoring may be valuable for assessing the presence of brief, asymptomatic runs of atrial fibrillation in such cases.

## PERSISTENT ATRIAL FIBRILLATION

Once an episode of atrial fibrillation has lasted more than seven days, spontaneous conversion is rare and the condition can be defined as persistent. The decision to attempt to restore sinus rhythm in a patient with persistent atrial fibrillation is not always clear-cut. Restoration of sinus rhythm will generally improve the patient's symptoms, but not all patients have symptoms. There is thus a need to strike a balance between the need for antiarrhythmic therapy and the likelihood of side effects, particularly proarrhythmia.<sup>41</sup>

### Cardioversion

Unless it is deemed urgent, the restoration of sinus rhythm should be attempted only after adequate anticoagulant therapy, as described above. Synchronized, direct-current cardioversion is usually required in order to restore sinus rhythm, although pharmacologic conversion is successful in 10 to 30 percent of cases, depending on the drug used and on the duration of

the arrhythmia.<sup>46,48,57</sup> Restoration of sinus rhythm in patients with atrial fibrillation frequently requires at least 300 J of energy with most defibrillators currently in use. However, the recent introduction of defibrillators with a biphasic wave form, rather than the traditional monophasic damped-sine wave form, is associated with a marked decrease in the energy required for atrial defibrillation and with fewer failures.<sup>58</sup>

Failure to terminate an arrhythmia with a specific antiarrhythmic agent does not mean that the same drug will be ineffective in maintaining sinus rhythm after electrical cardioversion. For the patient with minimal symptoms, it may be sufficient to perform direct-current cardioversion without the administration of an antiarrhythmic drug. If the arrhythmia recurs, the cardioversion can be repeated in combination with the use of an antiarrhythmic agent.

In some cases, sinus rhythm is not restored or is restored only very briefly by electrical cardioversion. In such a case, the use of intravenous ibutilide followed by another shock increases the likelihood of restoration and the maintenance of sinus rhythm.<sup>59</sup> However, ibutilide should be used with caution in patients with impaired ventricular function, since it may cause torsade de pointes,<sup>60</sup> and the safety of this approach in patients already receiving another antiarrhythmic drug has not been established. If a patient fails to return to sinus rhythm even for one or two beats despite these measures, transvenous internal cardioversion may be successful.<sup>61</sup>

The decision regarding which antiarrhythmic agent to use for the maintenance of sinus rhythm should be based on the known properties of the drugs, their side effects, and their safety in the presence of structural heart disease. There are few studies of comparative efficacy, but amiodarone has been shown to be superior to both sotalol and propafenone for the maintenance of sinus rhythm.<sup>62</sup> To date, only dofetilide and amiodarone have been shown not to increase mortality when prescribed to patients with heart failure.<sup>63,64</sup> A proposed outline for drug therapy is given in Figure 2.

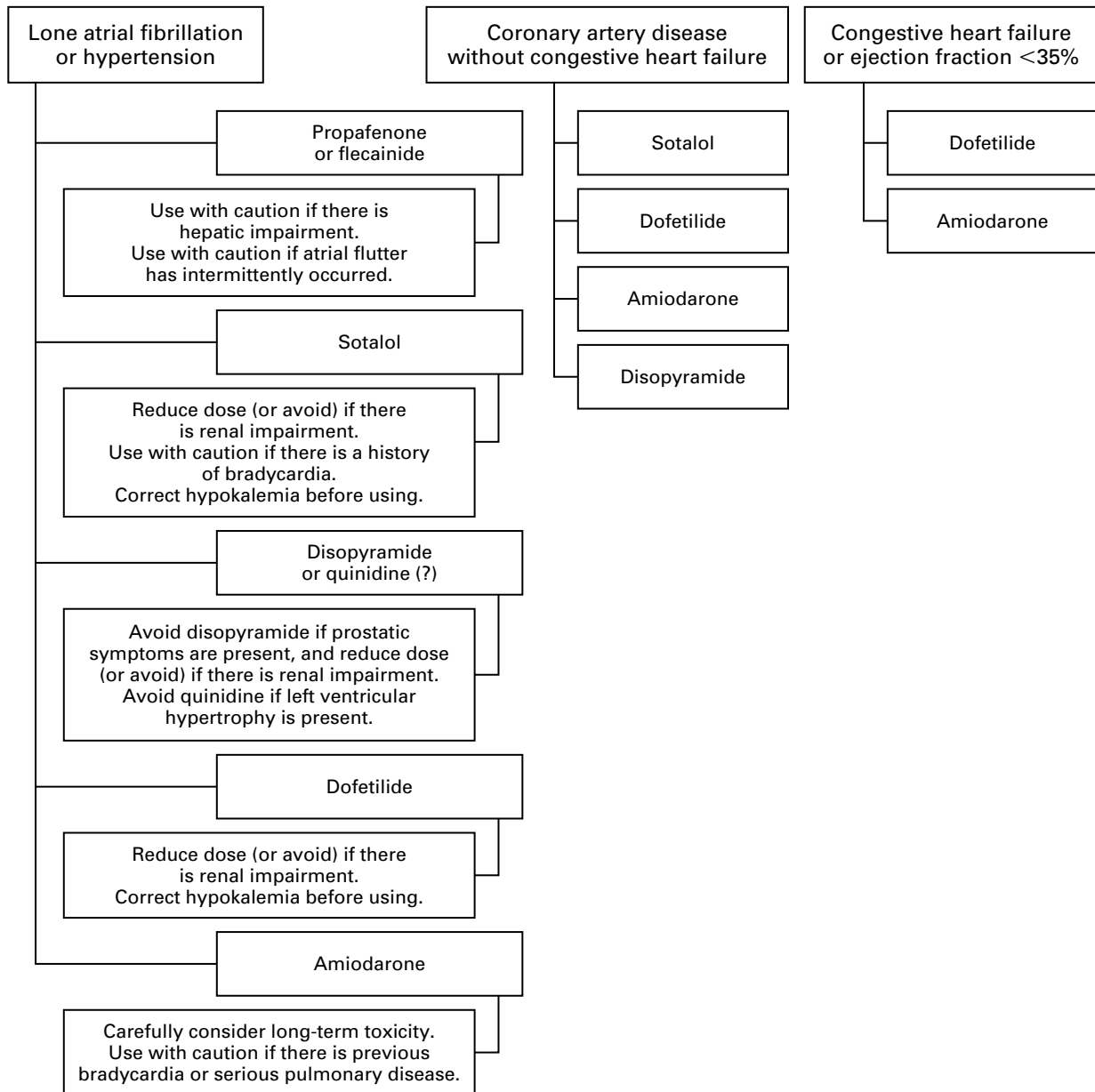
Most recurrences of atrial fibrillation occur within three months after cardioversion of a first episode of atrial fibrillation, regardless of the antiarrhythmic agent used.<sup>50</sup> Recurrence during this three-month period usually indicates a failure or an inadequate dose of the drug and suggests the need to change the drug or increase the dose if repeated cardioversion is contemplated. If the period after cardioversion during which the patient is free of atrial fibrillation is longer than three months, and particularly if it is longer than six months, it may be reasonable to repeat direct-current cardioversion with the use of the same regimen (after readministration of anticoagulant therapy if necessary), particularly if there was evidence of clinical improvement when the patient was in sinus rhythm. Acceptance of the atrial fibrillation along with the institution of rate control and adequate anticoagulation

is an alternative, especially if symptoms related to arrhythmia are minimal.

**Long-Term Anticoagulation**

Several large trials have demonstrated the efficacy of warfarin for the prevention of stroke in patients with atrial fibrillation. Both the risk of stroke and the

efficacy of warfarin among patients with persistent arrhythmia were equivalent to those among patients with paroxysmal arrhythmia. A high rate of intracranial hemorrhage complicated the use of warfarin in elderly patients in one trial (the Stroke Prevention in Atrial Fibrillation II study),<sup>65</sup> but analysis of the degree of anticoagulation at the time of bleeding indicat-



**Figure 2.** A Suggested Approach for the Selection of Antiarrhythmic Therapy to Maintain Sinus Rhythm after Cardioversion. The order of the listed drugs is merely a guideline. Which drug to use first in each group will depend, to some extent, on the preference of the physician as well as the clinical characteristics of the specific patient. In patients with coronary disease, especially active ischemia, it is prudent to avoid the class IC agents flecainide and propafenone, even though propafenone was not evaluated in the Cardiac Arrhythmia Suppression Trial. Quinidine is included in this figure despite concern about increased mortality with its use, since it is still used widely in some countries and no comparative mortality studies have been performed.

ed that virtually all episodes occurred at an international normalized ratio greater than 3.0.<sup>66</sup> Subsequent analyses suggest that the optimal international normalized ratio for the prevention of stroke in patients with atrial fibrillation lies between 2.0 and 3.0.<sup>67,68</sup> Pooled data from the anticoagulation trials offer insights into risk stratification with respect to stroke. Clinical risk factors included a previous stroke or transient ischemic attack, hypertension (current or past), an age of more than 70 years, diabetes, and congestive heart failure.<sup>51,69</sup>

The role of aspirin in the prevention of stroke in patients with atrial fibrillation remains controversial. In one trial, aspirin, in a prescribed dose of 325 mg daily, reduced the annual rate of stroke by 42 percent, as compared with placebo (absolute reduction, from 6.3 percent to 3.6 percent).<sup>70</sup> A statistically insignificant reduction was found in two other trials, one of which included only high-risk patients who had had a previous stroke or transient ischemic attack.<sup>71</sup> The other trial used a lower dose of aspirin (82 mg).<sup>72</sup> Aspirin (325 mg) prescribed in conjunction with "mini-dose" warfarin (1 to 3 mg daily) was also found to be ineffective for the prevention of stroke in patients with clinical risk factors.<sup>69</sup> The Stroke Prevention in Atrial Fibrillation III investigators studied the effects of 325 mg of aspirin alone in a group of patients initially believed to be at low risk for stroke.<sup>69,73</sup> The stroke rate was 2.2 percent per year among the patients for whom aspirin was prescribed but was higher in the subgroup with a history of hypertension (3.6 percent per year, as compared with 1.1 percent among the patients who had never had hypertension).<sup>73</sup> Although this study demonstrated that it is possible to identify a cohort of patients with atrial fibrillation and a low risk of stroke, it did not have a placebo group and thus did not prove that aspirin is superior to no therapy.

Recommendations for antithrombotic therapy in patients with atrial fibrillation are summarized in Table 3. As a rule of thumb, all patients with atrial fibrillation should receive long-term anticoagulant therapy with warfarin unless they are young (younger than 65 years old) and have none of the risk factors described above, or unless there is a major contraindication to the use of warfarin. In the absence of risk factors, aspirin alone (or no antithrombotic therapy) may be adequate.<sup>74</sup> Advanced age is a risk factor for both stroke and bleeding in patients receiving anticoagulation therapy. However, the relative risk of stroke exceeds that of bleeding, and whenever possible, elderly patients with atrial fibrillation should receive warfarin therapy.<sup>67</sup>

#### Heart-Rate Control

The aims of pharmacologic control of the heart rate in patients with persistent atrial fibrillation are to minimize symptoms related to swings in heart rate and

**TABLE 3. ANTITHROMBOTIC THERAPY IN PATIENTS WITH PERSISTENT OR PAROXYSMAL ATRIAL FIBRILLATION.**

AGE	RISK FACTORS FOR STROKE*	THERAPY
≤65 yr	None	Aspirin or none (no proof that aspirin is superior in this group)
>65–75 yr	None	Aspirin or warfarin (assess risk of warfarin as compared with the small risk of stroke)
Any	One or more (including age >75 yr)	Warfarin (strongly advised unless very clear contraindications are present)

\*Risk factors for stroke in patients with atrial fibrillation include mitral stenosis, hypertension (including treated hypertension), previous transient ischemic attack or stroke, congestive heart failure or left ventricular dysfunction, and an age of more than 75 years.

prevent excessive tachycardia during normal daily activities. Digoxin may be acceptable as the sole therapy in an elderly, sedentary patient, but it is not very effective for preventing excessive tachycardia during moderate exertion. Beta-blocking drugs, verapamil, and diltiazem are much more effective, and there is synergism between these drugs and digoxin.<sup>31,75</sup> Beta-blocking agents are probably the drugs of choice in patients with both atrial fibrillation and coronary artery disease, and they may also be valuable when systolic dysfunction is present. Verapamil may elevate serum digoxin levels into the toxic range, so the dose of digoxin should be reduced if it is used with verapamil.<sup>76</sup>

#### DRUG-REFRACTORY ATRIAL FIBRILLATION

##### Ablation of the Atrioventricular Node and Implantation of a Pacemaker

The combination of persistent atrial fibrillation and systolic dysfunction poses a challenge for ventricular rate control, since digoxin is often ineffective and other agents may have a negative inotropic effect. Radio-frequency energy applied to the atrioventricular junction is highly effective in treating patients with these conditions. It produces complete heart block, usually with a slow junctional escape rhythm. Implantation of a permanent pacemaker (either single- or dual-chamber, depending on whether the patient has paroxysmal or persistent atrial fibrillation) is required in order to maintain an adequate heart rate after ablation. Patients with paroxysmal atrial fibrillation often have symptoms caused by a rapid, irregular ventricular response. After ablation of the atrioventricular node and initiation of permanent pacing, there is usually a marked improvement in the patient's sense of well-being.<sup>77</sup>

Both paroxysmal atrial fibrillation and persistent atrial fibrillation with an uncontrolled and rapid ventricular response have been associated with the development of tachycardia-mediated cardiomyopathy.<sup>78</sup>

Uncontrolled studies have demonstrated that ablation of the atrioventricular node and implantation of a pacemaker are associated with improvement in ventricular function in a substantial proportion of selected patients.<sup>78,79</sup>

#### Focal Ablation

Recently, a group of patients has been described in whom atrial fibrillation is triggered by a rapidly firing atrial focus located in the pulmonary veins or (far less commonly) in the right atrium. In a substantial number of patients, the application of radio-frequency energy in the pulmonary veins at the site of the ectopic foci or the electrical isolation of the pulmonary veins from the atrium results in a marked reduction in spontaneous atrial ectopy and the abolition of atrial fibrillation.<sup>20,80,81</sup> The prevalence of this mechanism of arrhythmia is unknown, but it may be relatively common in young patients who have paroxysmal atrial fibrillation associated with a structurally normal heart and frequent atrial ectopic beats.

A novel approach to the treatment of drug-resistant atrial fibrillation is a hybrid of pharmacologic and nonpharmacologic therapy.<sup>82</sup> This approach is suitable for patients in whom atrial fibrillation is transformed to atrial flutter after the initiation of drug therapy, most commonly with a class IC antiarrhythmic agent or amiodarone. After it has been demonstrated that atrial flutter has become the sole rhythm, radio-frequency ablation of the flutter frequently results in the maintenance of sinus rhythm, although antiarrhythmic therapy must be continued in order to prevent reemergence of the fibrillation.

#### The Maze Procedure

In 1987, Cox and colleagues introduced a surgical procedure that they called the maze procedure,<sup>18</sup> in which the atrial appendages are excised and the pulmonary veins isolated. With the use of additional, carefully placed incisions, a narrow, tortuous path of atrial tissue is created that directs the sinus-node impulses across the atria to the atrioventricular node. The incisions are placed so that no area is wide enough to sustain multiple reentry circuits, and thus atrial fibrillation cannot occur. Several dead-end "alleyways" create a maze-like pathway and permit the depolarization of all the atrial tissue. As an isolated technique for the treatment of atrial fibrillation, the maze procedure has the limitation of requiring cardiopulmonary bypass. However, it has been used successfully in conjunction with other cardiac operations, particularly mitral-valve surgery.<sup>83</sup> The most recent modification of the maze procedure uses minimally invasive surgery and cryoablation, resulting in fewer atriotomy procedures,<sup>84</sup> and a preliminary report of an experimental study suggests the possibility that the procedure can be performed in the beating heart without the need for cardiopulmonary bypass.<sup>85</sup>

Attempts have been made to duplicate the effects of the surgical maze procedure with the creation by radio-frequency energy of lesions in the atria — the so-called "catheter maze."<sup>86</sup> This procedure is time consuming and is associated with a risk of serious complications.<sup>87</sup> Attempts to modify and shorten the procedure by limiting lesions to the right atrium have been reported. However, initial results suggest a high recurrence rate,<sup>88</sup> and it is unlikely that right-atrial lesions alone will prevent the recurrence of the arrhythmia. At present, the catheter maze procedure should be considered experimental.

#### Pacemaker Therapy

Several novel pacing techniques are being investigated for the prevention of paroxysmal atrial fibrillation. These are based on the concept that inhomogeneous or delayed interatrial or intraatrial conduction times predispose persons to the development of arrhythmia. Both dual-site atrial pacing (high in the right atrium and at the coronary-sinus ostium) and biatrial pacing (high in the right atrium and in the mid- or proximal coronary sinus) reduce the duration of the P wave and result in a more homogeneous atrial depolarization. Data from uncontrolled trials in patients with atrial fibrillation that is refractory to drugs suggest a benefit of dual-site pacing over single-site pacing for the prevention of paroxysmal atrial fibrillation.<sup>89,90</sup> Among such patients, pharmacologic therapy usually has to be combined with pacing for optimal results, and pacing at 80 to 90 beats per minute is usually required.

#### Implantable Atrial Defibrillators

The success of the implantable ventricular defibrillator led to the concept of a device that would terminate atrial fibrillation by means of an internal shock.<sup>91-93</sup> The first such devices were designed for atrial defibrillation only, but they are no longer being manufactured. A new model of implantable atrial defibrillator combines the option of atrial defibrillation with the capacity for ventricular defibrillation.<sup>94</sup> This device permits the termination of atrial arrhythmias in patients with coexisting paroxysmal atrial fibrillation and ventricular tachycardia, and it can act as a safety device in the very rare event that an atrial shock precipitates ventricular fibrillation. In addition to the capability of delivering an atrial shock, the new device offers the option of applying antitachycardia pacing and burst atrial pacing in a tiered fashion, as programmed by the physician. Since atrial fibrillation is rarely associated with sudden hemodynamic instability, the atrial defibrillator can be activated by the patient, rather than automatically delivering a shock to the patient. This feature allows the patient to avoid unexpected, painful shocks and permits patients who prefer to have sedation before a shock to seek medical help.<sup>95</sup>

Despite the vast number of patients with atrial fi-

brillation, there is still uncertainty about the appropriate role of implantable atrial defibrillators. Clinical experience remains limited, but the device appears to be safe,<sup>96,97</sup> and it is probable that the indications for its use will expand as experience with it grows. However, unless a ventricular defibrillator is also required for coexisting ventricular arrhythmias, it is unlikely that the atrial defibrillator will be used in more than a very small proportion of patients — those with highly symptomatic paroxysmal atrial fibrillation that has proved resistant to other therapies.

### CONCLUSIONS

The past decade has witnessed extraordinary growth in all fields of knowledge regarding atrial fibrillation. There is little doubt that pharmacologic therapy will remain a mainstay of treatment, although it is likely that the results of the AFFIRM trial,<sup>9</sup> when they become available, will modify practice in some fashion. There is also little doubt that nonpharmacologic therapy will have an increasing role in the treatment of highly symptomatic patients with atrial fibrillation that is refractory to drug therapy. The precise direction that these therapies will take is intimately connected to ongoing investigations of the electrophysiologic and molecular changes that cause, and are produced by, this arrhythmia.<sup>98</sup> The next decade promises to be an exciting one, in which we may finally overcome the challenge of atrial fibrillation — so aptly termed “the last big hurdle in treating supraventricular tachycardia.”<sup>99</sup>

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