

CLINICAL PRACTICE

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Atrial Fibrillation

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 63-year-old otherwise healthy man is discovered to have atrial fibrillation during an evaluation for a viral respiratory infection. He reports that 3 months earlier he began noticing occasional dyspnea on climbing stairs, and this symptom has been persistent for the past month. On physical examination, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is 29, the blood pressure is 142/88 mm Hg, the pulse is irregular at 120 beats per minute, and there are irregular first and second heart sounds. Electrocardiographic (ECG) evaluation shows atrial fibrillation, normal QRS complexes, and a ventricular rate of 110 beats per minute. How would you evaluate and treat this patient?

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THE CLINICAL PROBLEM

IN CLINICAL PRACTICE, ATRIAL FIBRILLATION IS THE MOST COMMON SUSTAINED arrhythmia encountered in adults. Among patients in the Framingham Heart Study population, atrial fibrillation developed in 37% after the age of 55 years in those who reached that age.^{1,3} Risk factors include older age, coronary artery disease, male sex, European ancestry, hypertension, obesity, smoking, diabetes mellitus, obstructive sleep apnea, and a family history of atrial fibrillation in a first-degree relative.⁴ In a large multi-institutional study, 19% of the patients with newly diagnosed atrial fibrillation had an acute precipitant such as pneumonia or surgery (the two most common precipitants), myocardial infarction, pulmonary embolism, thyrotoxicosis, or alcohol intoxication.⁵

Atrial fibrillation is associated with an increased incidence of stroke (by a factor of approximately 4.0 in men and 5.7 in women), heart failure (by a factor of 3.0 in men and 11.0 in women), and dementia that is probably related to strokes and cerebral hypoperfusion (by a factor of 1.4 in a mixed population).^{3,4,6,7} Atrial fibrillation increases the risk of death by a factor of 2.4 among men and by a factor of 3.5 among women.⁸ In part, this increase reflects the fact that atrial fibrillation is often a marker for underlying heart and vascular disease. However, atrial fibrillation itself probably contributes to adverse outcomes by increasing the risk of stroke, diminishing cardiac performance, and exposing symptomatic patients to therapies that also have risks.

Although the mechanisms are debated and presumably vary among patients, abnormalities of electrophysiological atrial myocytes as well as atrial structural changes, including fibrosis, probably create the electrical substrate that causes atrial fibrillation. The extent and severity of abnormalities increase with age and vary according to the type of atrial fibrillation (Fig. 1).^{4,9} Paroxysmal atrial fibrillation occurs in episodes that terminate spontaneously, usually within hours to days. It is often initiated by rapid firing of myocardial triggers in the pulmonary-vein sleeves (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Persistent atrial fibrillation continues unless it is interrupted by electrical or pharmacologic cardioversion, and it is associated with greater atrial fibrosis than paroxysmal atrial fibrillation.^{10,11} Pulmonary-vein triggers may still initiate the arrhyth-



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KEY CLINICAL POINTS

ATRIAL FIBRILLATION

- Atrial fibrillation is associated with underlying heart disease and with increased risks of death, stroke, heart failure, and dementia.
- Therapy for conditions that are associated with a risk of atrial fibrillation, including hypertension, hyperlipidemia, diabetes mellitus, sleep apnea, obesity, and excessive alcohol consumption, may reduce the risk of recurrence of atrial fibrillation.
- The presence or absence of risk factors for stroke is used to estimate the risk of stroke in order to determine whether anticoagulation is indicated for paroxysmal or persistent atrial fibrillation.
- When atrial fibrillation has been present for 48 hours or longer or for an unknown duration and elective cardioversion is planned, a period of anticoagulation before and after cardioversion is warranted, even when risk factors for stroke are absent.
- Uncontrolled tachycardia can lead to deterioration of left ventricular function. Attempts to maintain sinus rhythm should be considered when atrial fibrillation has not been persistent for more than 1 year or is paroxysmal and symptomatic. Catheter ablation is more effective than antiarrhythmic drug therapy, particularly for paroxysmal atrial fibrillation.

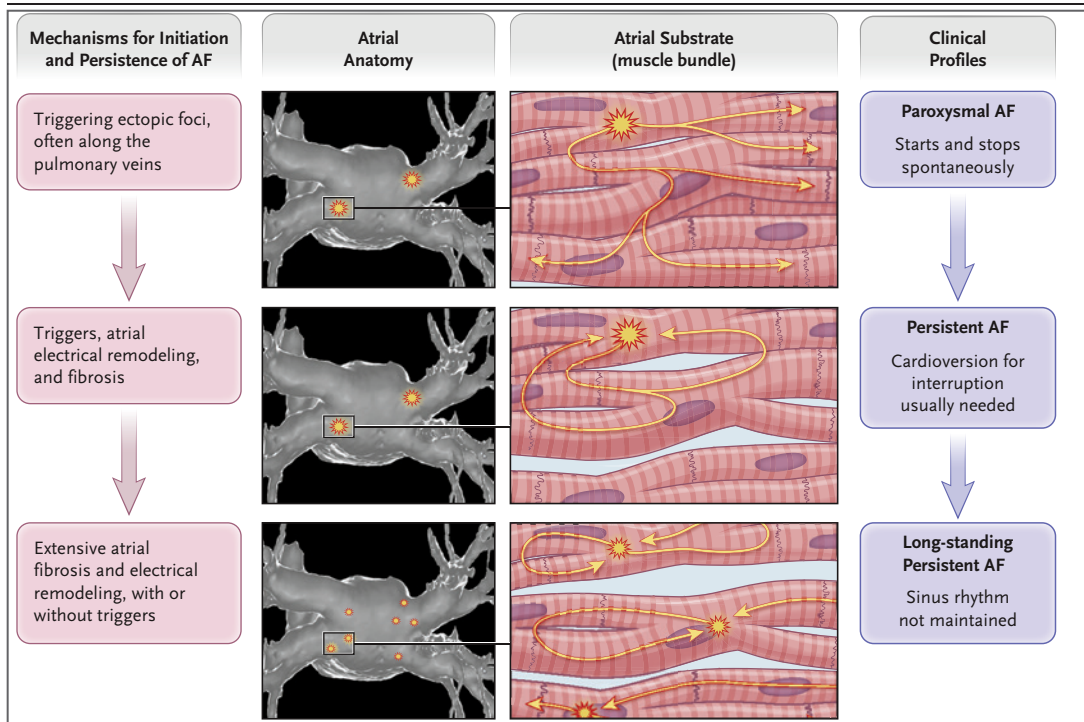


Figure 1. Types and Triggers of Atrial Fibrillation (AF).

Mechanisms for the initiation and persistence of AF and the left atrial anatomy are shown on the left. Clinical profiles of AF related to the underlying atrial substrate at the muscle-bundle level are shown on the right. Paroxysmal AF is associated with triggering foci that are most commonly located in sleeves of muscle along the pulmonary veins. Persistent AF is often characterized by some evidence of atrial remodeling with electrophysiological changes in the atrial myocytes, as well as fibrosis. Triggering foci are also present. In long-standing persistent AF, the atrial remodeling, including fibrosis, is more extensive and severe than in persistent AF.

nia, but additional structural and electrophysiological changes allow atrial fibrillation to persist once it is initiated. Electrical isolation of pulmonary veins alone is less likely to prevent the recurrence of persistent atrial fibrillation than to

prevent the recurrence of paroxysmal atrial fibrillation.

More than two thirds of patients with recently discovered atrial fibrillation have a paroxysmal pattern, but 5 to 10% per year have progression to

persistent atrial fibrillation. Among patients who present with persistent atrial fibrillation and successfully undergo cardioversion, up to 20% have recurrent atrial fibrillation such that it becomes difficult to maintain sinus rhythm.^{4,12,13}

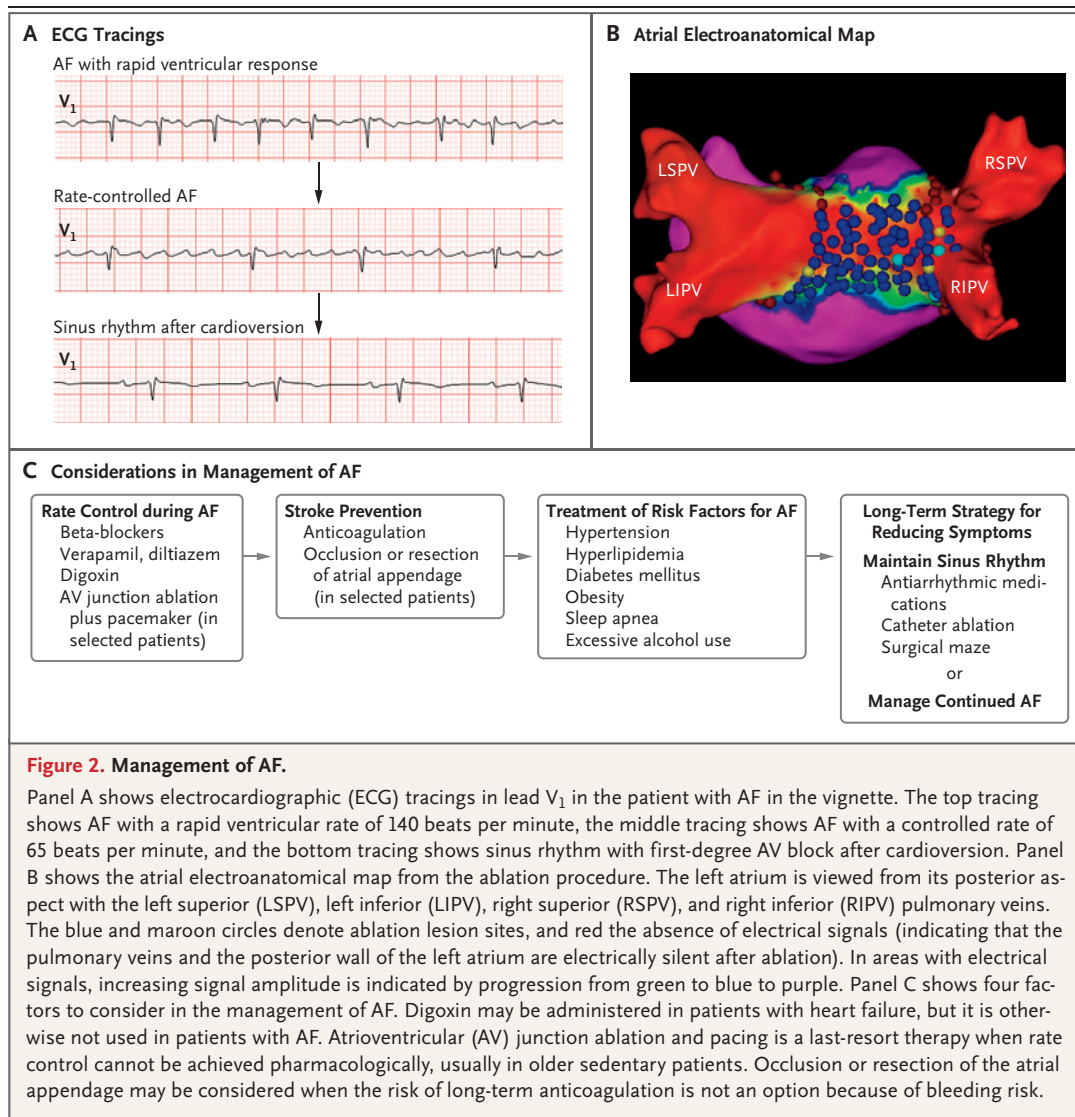
STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Symptoms of atrial fibrillation, when present, range from minimal to incapacitating. Atrial fibrillation may cause fatigue, decreased exercise tolerance, and palpitations. Rapid heart rates may cause hypotension, syncope, angina, or pulmonary edema, and emergency treatment may be warranted. Severe manifestations are often associ-

ated with acute illness or surgery that leads to increased sympathetic tone and a rapid ventricular rate.⁵ Atrial fibrillation can cause a depressed left ventricular ejection fraction that improves or completely reverses after adequate rate control or restoration of sinus rhythm.¹⁴ Although this atrial fibrillation–induced cardiomyopathy usually occurs when the ventricular rate is persistently faster than 110 beats per minute, it may occur at slower rates in some patients.¹⁵

An ECG recording that is required for diagnosis reveals QRS complexes that occur at irregular intervals, with variable oscillation of the baseline between beats and no discrete P waves (Fig. 1 and 2). Depending on the frequency of symptoms, ambulatory ECG recording may be



required for weeks to months in order to establish the diagnosis of paroxysmal atrial fibrillation. Personal ECG recording systems, including small handheld devices and watches, can reveal atrial fibrillation, but an artifact can mimic or obscure the diagnosis, and confirmatory ECG recordings should be obtained.¹⁶

The detection of atrial fibrillation warrants a careful history and physical examination, including measurement of blood pressure, to assess for evidence of predisposing diseases and risk factors and intercurrent illness. Long-term alcohol consumption of more than one drink per day in women and two drinks per day in men has been associated with atrial fibrillation, and binge drinking can precipitate atrial fibrillation.^{17,18} Caffeine consumption has not been shown to increase the incidence of atrial fibrillation.¹⁷ The patient's blood glucose and thyrotropin levels should be measured.

In addition to the ECG and other cardiac monitoring when needed, transthoracic echocardiography is routinely recommended. Screening for sleep-disordered breathing should be performed, and a sleep study should be conducted when the patient's history is suggestive of sleep apnea.¹⁷

TREATMENT

The management of atrial fibrillation has traditionally involved achieving adequate rate control, protection from thromboembolism and stroke, and reduction or elimination of symptoms, as well as the treatment of reversible risk factors (Fig. 2). Symptoms may be controlled either by preventing episodes of atrial fibrillation or by slowing the ventricular rate during recurrent atrial fibrillation. In patients in whom atrial fibrillation has developed within the previous year, attempts to maintain sinus rhythm are usually warranted.¹⁹

Rate Control

The ventricular rate in atrial fibrillation is an important determinant of hemodynamic consequences and symptoms. Atrioventricular nodal-blocking agents are usually warranted to reduce the ventricular rate. Beta-blockers and nondihydropyridine calcium-channel blockers (verapamil and diltiazem) are first-line therapies.² Therapy is tailored to the individual patient and is based on consideration of adverse effects (e.g., beta-adrenergic blockers may aggravate depression, and calcium-channel blockers may aggravate heart failure). Therapy is

generally initiated with a beta-blocker at a dose that is adjusted upward, with the aim of controlling symptoms by reducing the heart rate. Although some physicians aim for an average resting heart rate of less than 80 beats per minute, a faster resting rate is acceptable when it is not associated with symptoms, provided that ventricular function remains normal.²⁰ Calcium-channel blockers may be combined with beta-blockers if the beta-blocker alone is not sufficient, but hypotension can complicate this approach, particularly in older adults. Digoxin slows the resting ventricular rate, but rate control is not usually adequate during exertion. Digoxin has been associated with increased mortality in post hoc analyses of trials involving patients with atrial fibrillation.^{2,21,22} A low dose of digoxin may be added to other atrioventricular nodal agents to improve rate control, particularly in patients with heart failure.² In patients with exertional symptoms, it is important to assess the heart rate response to exertion (e.g., after a brisk walk in the office or with ambulatory monitoring) and to adjust the dose of therapy accordingly.

A controlled ventricular response may occur without the use of a rate-controlling agent in healthy patients who have a high vagal tone, as well as in patients with atrioventricular conduction disease. Particularly in older adults, underlying sinus-node disease may lead to symptomatic bradycardia after conversion to sinus rhythm. Permanent pacemaker implantation may be warranted if sinus rhythm is maintained or atrial fibrillation is paroxysmal. Catheter ablation of the atrioventricular node to produce heart block and permanent pacing is a reasonable option for older patients when symptoms due to inadequate rate control continue despite the use of atrioventricular nodal-blocking agents.

Stroke Prevention

Anticoagulation is first-line therapy for prevention of thromboembolism, and its use is guided by estimation of stroke risk according to the CHA₂DS₂-VASc score (Fig. 3).² Anticoagulation is indicated for patients who have at least two risk factors (i.e., an estimated stroke risk >2.2% per year) and should be considered for patients who have one risk factor other than female sex (i.e., estimated stroke risk of ≥1.3% per year).²

A Cochrane Collaboration review estimated that among patients with atrial fibrillation who had a stroke risk of 4.0% per year, long-term

warfarin therapy reduced the risk to 1.4% per year.^{2,23} Several randomized trials have established that direct-acting oral anticoagulants are noninferior to warfarin.²⁴ A meta-analysis showed that in trials with follow-up ranging from 12 weeks to 2.8 years, the risk of stroke or embolic events was 11% lower among patients who received direct-acting oral anticoagulants than among those who received warfarin; the risk of major bleeding was also reduced (from 5% to 4%) as was the risk of intracranial hemorrhage (from 1.3% to 0.6%).²⁵ The risk of stroke among patients who received a direct-acting oral anticoagulant was 1.3% to 1.5% per year.²⁶⁻²⁹ In observational studies, apixaban has been associated with less bleeding risk than rivaroxaban.^{30,31} The major route of elimination is renal for all direct-acting oral anticoagulants, with substantial hepatic elimination for apixaban; dosing adjustment is generally needed in patients with renal dysfunction. Unlike warfarin, direct-acting oral anticoagulants do not require repeated laboratory testing to guide dosing and are generally preferred when their greater cost is not prohibitive. Warfarin is still used in patients with mitral stenosis or mechanical heart valves. Aspirin and other antiplatelet therapies alone do not provide adequate protection from stroke in patients with atrial fibrillation.²

Even in patients who are at low risk for stroke, cardioversion of atrial fibrillation can be followed by atrial thrombus formation and embolization because of delayed recovery of atrial mechanical function. In patients who are at low risk for thromboembolism in whom atrial fibrillation is known to have been present for less than 48 hours, cardioversion is commonly performed without a preceding period of anticoagulation; the reported risk of stroke with this approach is 0.7 to 1.1%, and it occurs mainly in patients with risk factors (Fig. 3).²⁴ When the duration of atrial fibrillation is uncertain or is 48 hours or longer, anticoagulation is recommended for a period of 3 weeks before cardioversion and for another 4 weeks after cardioversion. If cardioversion of atrial fibrillation is warranted sooner, anticoagulation can be initiated and transesophageal echocardiography can be performed. In the absence of left atrial thrombus, cardioversion with continued anticoagulation has a favorable safety profile. After cardioversion, anticoagulation should generally be continued indefinitely in patients with risk factors for stroke.^{2,24,32}

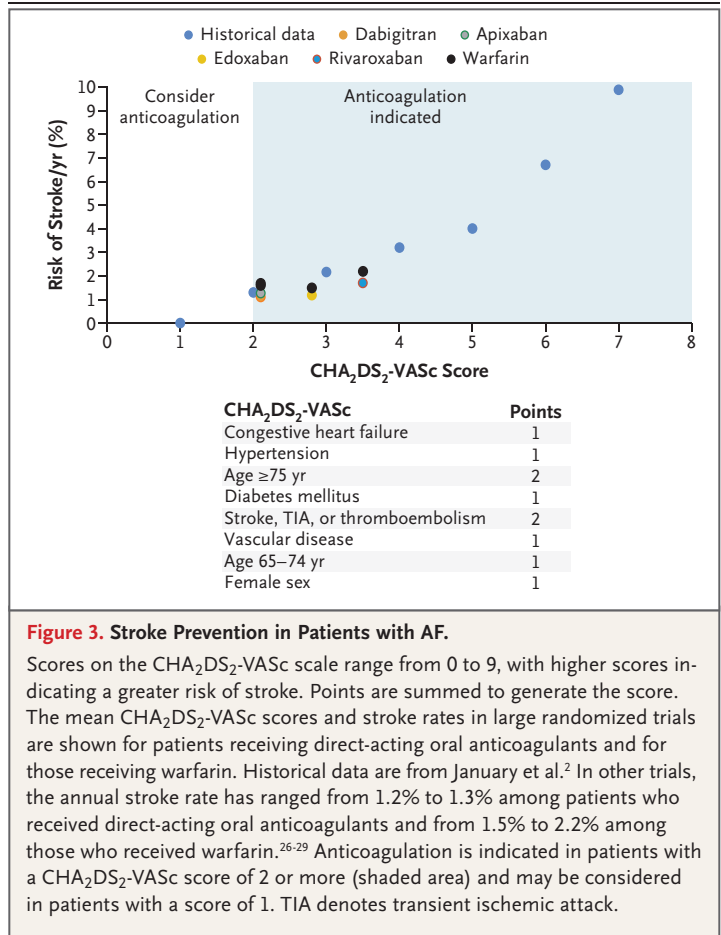


Figure 3. Stroke Prevention in Patients with AF.

Scores on the CHA₂DS₂-VASc scale range from 0 to 9, with higher scores indicating a greater risk of stroke. Points are summed to generate the score. The mean CHA₂DS₂-VASc scores and stroke rates in large randomized trials are shown for patients receiving direct-acting oral anticoagulants and for those receiving warfarin. Historical data are from January et al.² In other trials, the annual stroke rate has ranged from 1.2% to 1.3% among patients who received direct-acting oral anticoagulants and from 1.5% to 2.2% among those who received warfarin.²⁶⁻²⁹ Anticoagulation is indicated in patients with a CHA₂DS₂-VASc score of 2 or more (shaded area) and may be considered in patients with a score of 1. TIA denotes transient ischemic attack.

Maintenance of Sinus Rhythm

The decision regarding whether to pursue maintenance of sinus rhythm is shared between the patient and physician; this decision is informed by the effect of atrial fibrillation on the patient's quality of life and by the risks and toxic effects of therapies. Many patients with paroxysmal atrial fibrillation or recently recognized persistent atrial fibrillation have symptoms and want to receive therapy, but some patients with persistent atrial fibrillation adapt without realizing that the arrhythmia is causing a reduction in their activity. For newly recognized asymptomatic atrial fibrillation, an attempt at cardioversion and maintenance of sinus rhythm is often reasonable to assess the symptomatic effect of atrial fibrillation, which then informs further treatment. The large, randomized Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) trial compared early rhythm control (with antiarrhythmic drugs or catheter ablation) with usual care in patients who had atrial fibrillation that was diag-

nosed within 1 year before enrollment and other cardiovascular disease or stroke risk factors.¹⁹ The early rhythm-control strategy was associated with a significantly lower rate of the composite of death from cardiovascular causes, stroke, or hospitalization for heart failure or acute coronary syndrome (by 1.1 events per 100 person years; a 22% reduction), without an increase in the number of nights spent in the hospital. Serious adverse events related to treatment occurred in 4.9% of the patients in the early rhythm-control group; the most common serious adverse event in that group was drug-induced bradycardia (in 1.0% of the patients).

Continued therapy with a beta-blocker may reduce episodes of atrial fibrillation in some patients,^{2,33} but it is less effective than antiarrhythmic drugs; atrial fibrillation has been reported to recur in 43 to 67% of patients who receive beta-blockers.³⁴ Reductions in the frequency and duration of atrial fibrillation episodes are often reasonable goals if they improve symptoms. Adverse effects and contraindications (Table 1) are important considerations in drug selection. Several agents have been linked to an increased risk of death among patients with structural heart disease (e.g., flecainide, propafenone, and d-sotalol) or heart failure (dronedaron).^{34,37} Flecainide, propafenone, sotalol, and dofetilide are options for patients who do not have structural heart disease. Patients who receive sotalol and dofetilide must be monitored closely for prolongation of the corrected QT interval, which can lead to potentially fatal ventricular tachycardia (torsades de pointes). This risk is increased among women (because the QT interval is longer in women than in men), among patients with renal insufficiency or bradycardia, and among those who are taking other drugs that prolong the QT interval or alter antiarrhythmic drug absorption or elimination.³⁸ Amiodarone is a highly effective antiarrhythmic drug; however, owing to several potential long-term toxic effects, long-term use should be avoided if possible.^{39,40}

Catheter ablation that is performed with the use of radiofrequency or cryotherapy is more effective than antiarrhythmic drug therapy for maintaining sinus rhythm in patients with paroxysmal atrial fibrillation.^{35,41-44} Two recent randomized trials compared cryoablation with antiarrhythmic medication in patients with primarily paroxysmal atrial fibrillation.^{43,44} Symptomatic atrial fibrillation recurred by 1 year after a 90-day “blinking

period” (i.e., the first 90 days after the index ablation) in 11.0% of the patients who underwent ablation and in 26.2% of those who received antiarrhythmic drugs in one trial.⁴⁴ The percentage of patients with treatment success at 1 year was 74.6% in the ablation group and 45.0% in the drug-therapy group in the other trial.⁴³ Therapies for maintenance of sinus rhythm are generally less effective in patients with persistent atrial fibrillation than in those with paroxysmal atrial fibrillation. In the randomized Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, 57% of the patients had persistent atrial fibrillation at trial entry; after 48.5 months of follow-up, only 16% of the patients in the ablation group had persistent atrial fibrillation, as compared with 26% in the drug-therapy group.⁴² The most common procedure-related adverse events were associated with vascular access (in 3.9% of the patients); serious complications included cardiac perforation with tamponade (in 0.8%), phrenic-nerve injury (in 0.1%), and transient ischemic attacks from cerebral emboli (in 0.3%).⁴² An expert consensus statement noted that procedure-related death occurs in fewer than 1 in 1000 patients.³⁵ Uncommon late complications include pulmonary-vein stenosis and left atrial esophageal fistula (in 0.02 to 0.11% of patients). The latter manifests 1 to 4 weeks after ablation with a clinical syndrome resembling endocarditis and is fatal without prompt recognition and emergency surgery.³⁵ During the first 3 months after ablation of atrial fibrillation, atrial tachycardia or atrial flutter occurs in up to 50% of patients and often resolves spontaneously, although antiarrhythmic drug therapy or cardioversion may be warranted.³⁵ During longer follow-up, atrial fibrillation recurs in 15 to 50% of patients owing to lack of durability of the ablation lesion or the development of a new source of atrial fibrillation.³⁵ Patients with reductions in atrial fibrillation burden and symptoms do not necessarily have to undergo a repeat procedure.

Maintenance of sinus rhythm is improved by the treatment of modifiable risk factors.^{17,45,46} A randomized trial involving 150 patients with atrial fibrillation showed that the addition of an intensive weight loss program to other therapies (including treatment and counseling for hypertension, sleep apnea, alcohol consumption, hyperlipidemia, and diabetes mellitus) resulted in weight loss as well as less atrial fibrillation and

Table 1. Therapies to Maintain Sinus Rhythm.*

Treatment	Efficacy	Adverse Effects	Contraindications	Precautions during Treatment
Drug therapy				
Beta-blockers	Low (sinus rhythm maintained in <20% of patients but symptoms reduced in ≥20%)	Fatigue, bradycardia, hypotension	Bradycardia, hypotension	Monitor for bradycardia
Nondihydropyridine calcium-channel blockers: verapamil and diltiazem	Low (sinus rhythm maintained in <20% of patients but symptoms reduced in ≥20%)	Bradycardia, hypotension, edema	Bradycardia, hypotension, heart failure with depressed left ventricular function	
Other antiarrhythmic agents				
Flecainide	Moderate (AF prevented or reduced in 50–70% of patients)	Adverse effects uncommon	Structural heart disease (proarrhythmia risk)	Evaluate for ischemia before initiation
Propafenone	Moderate (AF prevented or reduced in 50–70% of patients)	Dysgeusia	Structural heart disease (proarrhythmia risk)	Evaluate for ischemia before initiation
Quinidine	Moderate (AF prevented or reduced in 50–70% of patients)	Gastrointestinal side effects in 30% of patients	QT prolongation	Monitor for QT prolongation, polymorphic ventricular tachycardia
Disopyramide	Moderate (AF prevented or reduced in 50–70% of patients)	Vagolytic effects, urinary retention	Heart failure, QT prolongation	Monitor for QT prolongation
Dronedarone	Moderate (AF prevented or reduced in 50–70% of patients)	Adverse effects uncommon	Heart failure	Monitor for fluid retention, hepatitis
Dofetilide	Moderate (AF prevented or reduced in 50–70% of patients)	QT prolongation	QT prolongation, advanced renal disease	Initiate in hospital to monitor for QT prolongation
Sotalol	Moderate (AF prevented or reduced in 50–70% of patients)	QT prolongation, fatigue, bradycardia, hypotension	QT prolongation, bradycardia, advanced renal disease	Monitor for QT prolongation
Amiodarone	High (AF prevented in 80% of patients)	Bradycardia; thyroid, liver, respiratory, and neurologic problems; photosensitivity	Bradycardia, hyperthyroidism	Monitor for toxic effects involving the lungs, liver, thyroid, and nervous system and for drug interactions
Interventional procedures				
Catheter ablation	High (60–90% of patients with paroxysmal AF free from AF at 1 yr and 50% of patients with persistent AF free from AF at 1 yr; reduced AF burden)	Procedure-related, anesthesia, and sedation risks; transient arrhythmias for 3 mo; a second procedure is often needed for persistent AF	High risks associated with sedation and anesthesia; contraindicated in patients for whom vascular access is not possible or presents high risk and in those who are unable to receive anticoagulants	Monitor for postprocedure complications, including tamponade or esophageal injury (within the first 4 wk), pulmonary-vein stenosis within months, and conversion of AF to rapid atrial flutter
Surgical maze†	High (AF prevented in 80% of patients)	Anesthesia and surgery risks	Surgical contraindications	Monitor for complications of thoracic surgery

* Data are from Calkins et al.³⁵ and Lafuente-Lafuente et al.³⁶

† Surgical maze is cardiac surgery with creation of suture lines or ablation lines to isolate the pulmonary veins and interrupt other potential reentry pathways for AF.

fewer symptoms of atrial fibrillation than the standard intervention.⁴⁵ A randomized trial involving patients with atrial fibrillation who consumed more than 10 standard drinks (with 1 standard drink containing approximately 12 g of pure alcohol) per week showed that those assigned to abstain from alcohol (average consumption, ≤ 2 drinks per week) had a lower atrial fibrillation burden during the following 6 months than those assigned to the control group.¹⁸ A recent scientific statement by the American Heart Association suggested a goal of a 10% reduction in weight for patients with a BMI of 28 or higher, along with routine exercise and management of diabetes, hyperlipidemia, and sleep apnea and moderation of alcohol consumption.¹⁷

GUIDELINES

Guidelines for the management of atrial fibrillation have been written collaboratively by the American College of Cardiology, American Heart Association, and Heart Rhythm Society,^{2,24} the European Society of Cardiology,^{47,48} and the Canadian Cardiovascular Society.⁴⁹ Our recommendations are generally concordant with these guidelines.

AREAS OF UNCERTAINTY

Data on the effects of strategies to maintain sinus rhythm on the overall risk of death are lacking. Recent randomized trials have suggested that the risk of death may be decreased among patients in whom the sinus rhythm is maintained early after the diagnosis of atrial fibrillation¹⁹ and in those with depressed left ventricular function who are candidates for and who undergo ablation.^{42,50}

Among some patients with atrial fibrillation

who are thought to be in sinus rhythm, episodes of atrial fibrillation may go undetected and the risk of stroke appears to be increased. Safe strategies for determining whether patients can discontinue anticoagulation when sinus rhythm is maintained require further definition. Data are needed to inform the outcomes of occlusion or resection of the left atrial appendage, particularly in patients in whom anticoagulation poses high risks.

CONCLUSIONS AND RECOMMENDATIONS

For a patient such as the one described in the vignette who has newly recognized atrial fibrillation, we would obtain serum electrolyte, creatinine, and thyrotropin levels; identify and treat reversible risk factors; and initiate anticoagulation with a direct-acting oral anticoagulant and therapy with a beta-blocker (adjusting the dose to achieve rate control). Further evaluation would include echocardiography and assessment of possible coronary artery disease with stress testing or angiography. We would perform direct-current cardioversion after a 4-week course of anticoagulation. If atrial fibrillation recurred, decisions regarding further therapy would be guided by symptoms, risks, and benefits and would include consideration of catheter ablation to maintain sinus rhythm.^{43,44}

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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