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Atrial fibrillation: Ways to refine your care

What's best for your patient: rate or rhythm control? Aspirin or warfarin? These guidelines and tools can help you decide.

Practice recommendations

- Pursue a rate-control strategy for most patients with atrial fibrillation (AF); rhythm control may be preferable for younger (<65 years) symptomatic patients (**A**).
- Use a risk stratification scheme to guide decisions regarding anticoagulation therapy; adjusted-dose warfarin is extremely effective at preventing strokes in patients with AF (**A**).
- Hemodynamically unstable patients require urgent cardioversion, so you should not delay the procedure in order to provide anticoagulation therapy (**C**).

Strength of recommendation (SOR)
A Good quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

IN THIS ARTICLE

Atrial fibrillation (AF), the most common arrhythmia seen in clinical practice, affects an estimated 2.2 million American adults.[1] The condition is associated with a 1.5- to 1.9-fold mortality risk independent of other risk factors[2] and about a 4- to 5-fold increase in the risk of strokes.[3] Achieving rate control; restoring or maintaining sinus rhythm, when it's feasible; and preventing stroke are the primary goals in treating patients with AF. Yet many physicians are not always sure about the best ways to achieve them.

Failure to provide adequate anticoagulation therapy—despite clear evidence that anticoagulation significantly reduces the risk of thromboembolic complications—may be the most common misstep physicians make in treating AF.[4] But anticoagulation is not the only trouble spot. Choosing between a rate-control and rhythm-control strategy also has its share of challenges, as does deciding which drugs are best for which patients.

AF is an age-related condition, with the prevalence increasing from 0.5% among individuals <60 years old to 9% of those >80.[5] An aging population will make your ability to manage AF even more critical in the years ahead. The text and tables that follow will help you refine your care. But first, a quick review.

Classification, causes, and clinical features

AF is classified primarily on the basis of duration:

Paroxysmal AF is the term for brief episodes (lasting <24 hours) and episodes that last up to 7 days but terminate spontaneously. Cardioversion is not needed for this self-limiting condition.

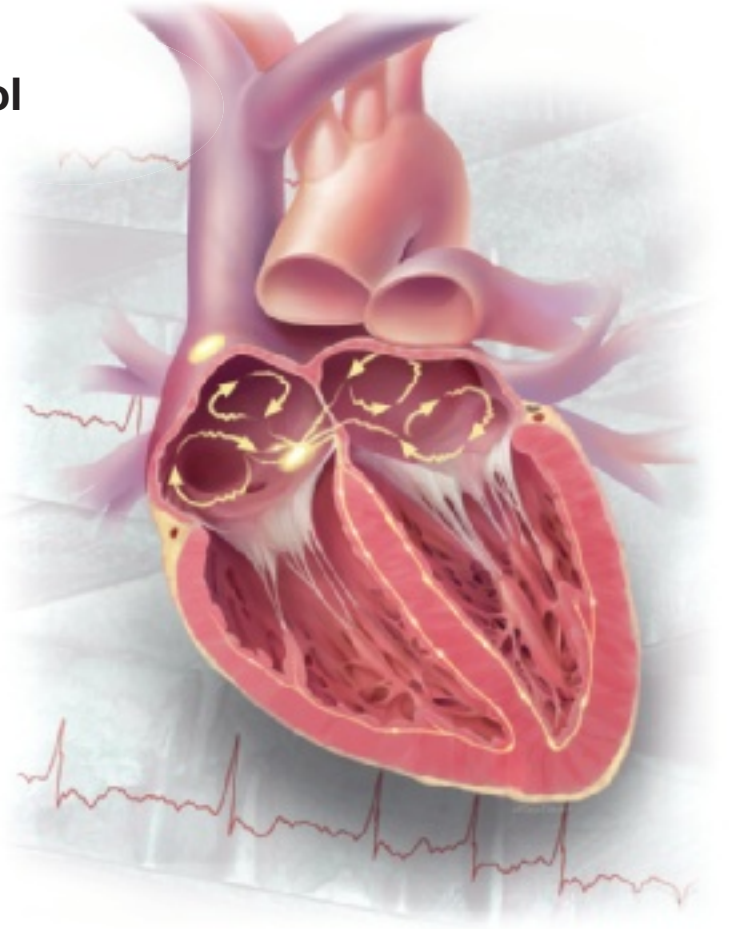
Warfarin or aspirin? An anticoagulation risk tool

$CHADS_2$ is a validated risk stratification scheme that offers help in making decisions about anticoagulation therapy. Each of the letters in this acronym represents a risk factor, and carries a certain number of points:

Congestive heart failure (1 point)
Hypertension (1 point)
Age >75 years (1 point)
Diabetes (1 point)
Stroke (2 points)

Patients with a score of ≥3 are at high risk and need to be treated with warfarin; those with a score of 0 are at low risk and can be managed with aspirin. For patients with a score of 1 or 2, the choice of warfarin or aspirin should be based on clinician assessment and patient preference.

Source: Gage BF, et al. *JAMA*. 2001.[24]



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Persistent AF lasts longer than 7 days, and often requires electrical or pharmacological cardioversion.

Permanent AF is used to describe instances in which cardioversion has failed (or has not been attempted) and the arrhythmia is continuous.

These categories are not mutually exclusive—a patient may primarily have paroxysmal AF, with an occasional episode of persistent AF. The term *recurrent AF* is used when 2 or more episodes of paroxysmal or persistent AF occur.

AF typically linked to heart conditions—but not always

Chronic cardiac conditions commonly associated with AF include ischemic heart disease, congestive heart failure (CHF), hypertension, and rheumatic mitral valve disease. Recurrent AF may also be associated with atrial flutter, Wolff-Parkinson-White (WPW) syndrome, or atrioventricular (AV) nodal reentrant tachycardia. It is essential to recognize the presence of such conditions, because treatment of the primary arrhythmia may reduce or eliminate the incidence of recurrent AF. [6]

There are also noncardiac causes of AF—eg, excessive alcohol intake ("holiday heart syndrome"), pulmonary embolism and other pulmonary diseases, and hyperthyroidism and other metabolic disorders. Lone AF, a term used when the patient is younger than 60 years of age and has neither clinical nor echocardiographic evidence of cardiopulmonary disease, is a diagnosis of exclusion. About 30% to 45% of cases of paroxysmal AF and 20% to 25% of persistent AF are considered to be lone AF.[1]

EKG, x-ray, and echo: The role of each

Although some patients are asymptomatic, AF patients typically present with

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During AF, maintaining a ventricular rate of 60 to 80 bpm at rest and 90 to 115 bpm during exercise is recommended.

palpitations, dyspnea, fatigue, chest pain, or dizziness. A stroke may also be the first indication that a patient has AF.

A normal pulse rules out AF,[7] and an irregular pulse should be an indication for an electrocardiogram (EKG). In most cases, a diagnosis can be made from the results of a 12-lead EKG. However, when diagnosis is uncertain or symptoms are paroxysmal, a Holter monitor or event recorder may be required.

Thyroid, renal, and hepatic function tests, serum electrolytes, and hemograms may help to rule out reversible causes of AF. Chest x-ray is valuable in diagnosing CHF, as well as lung pathology. Recent guidelines recommend that all patients who present with AF undergo echocardiography to evaluate for valvular heart disease, left and right atrial size, left ventricular size and function, left ventricular hypertrophy, and pericardial disease.[1] Transesophageal echocardiogram (TEE) should be used to detect intracardiac clots in patients who have had an embolic event or when AF has lasted for more than 48 hours and cardioversion is being considered.

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Electrical cardioversion has a higher success rate than pharmacological cardioversion, and is usually well tolerated.

Rate vs rhythm control: What the research reveals

For hemodynamically unstable patients who present with AF and a rapid rate associated with cardiogenic shock, pulmonary edema, acute myocardial infarction, or unstable angina, urgent direct-current cardioversion is indicated. In less urgent cases, treatment is not so clear cut. Spontaneous conversion to sinus rhythm occurs in up to 60% of patients within 24 hours, and in about 80% of patients within 48 hours.[8]

Intuitively, restoring normal sinus rhythm seems superior to rate control, but several randomized trials[9-12] and one meta-analysis[13] found no support for that belief when researchers looked at mortality, thromboembolic events, and major hemorrhage.

One of the largest studies was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), which involved more than 4000 patients with paroxysmal and persistent AF who were randomized to either rate control or rhythm control.[9] The research revealed a nonsignificant trend toward an increased death rate with the rhythm-control strategy—a 5-year mortality rate of 24% vs 21% for patients in the rate-control group. A trend toward higher risk of ischemic stroke, particularly associated with the lack of anticoagulation therapy, was also found in the rhythm-control group. That finding emphasizes the need for indefinite anticoagulation, independent of the use of a rate-control or rhythm-control approach.

A retrospective subanalysis of the AFFIRM trial that evaluated patients on the basis of a number of independent treatment variables found that sinus rhythm, in and of itself, was actually associated with a lower risk of death. But the antiarrhythmic agents that are often needed to achieve sinus rhythm are not associated with higher rates of survival. According to the researchers, this finding suggests that the drugs' beneficial antiarrhythmic effects are offset by their adverse effects.[14]

Age is another confounding factor. Most of the AFFIRM subjects were relatively older, with a mean age of 69.7 years. In another study, rhythm control was found to be beneficial in young patients (mean age of 38.6 years) with AF and rheumatic valvular heart disease, in terms of morbidity and mortality.[15]

With no single treatment strategy emerging as the best approach, guidelines offer help in determining whether to pursue a rate-control or rhythm-control strategy for a particular patient. The recommendations of the British National Institute for Health and Clinical Excellence (NICE) guideline for AF,[16] developed on the basis of a systematic literature review as well as expert consensus, are summarized here.

When should you opt for rate control?

The NICE guideline recommends rate control as the initial choice for patients who have persistent AF and:

- are >65 years of age
- have coronary artery disease
- do not have CHF
- are not candidates for cardioversion
- have contraindications to antiarrhythmic drugs.[16]

The American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) guidelines recommend maintaining a ventricular rate during AF of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during exercise.[1]

Which drug for which patient?

Beta-blockers and nondihydropyridine calcium channel blockers (verapamil and diltiazem) and digoxin slow conduction through the AV node. Compared with placebo, beta-blockers and calcium channel blockers are effective for controlling the ventricular rate in patients with AF, both at rest and during exercise.[17] In the AFFIRM trial, rate control was achieved in 70% of patients treated with beta-blockers vs 54% of patients taking calcium channel blockers.[9]

That said, the type of drug you use to achieve rate control should be an individual decision based on characteristics of your particular patient. In general, beta-blockers are preferable for patients with myocardial infarction or ischemia, and for any patient in a high adrenergic state, whereas calcium channel blockers should be used for patients with severe asthma or chronic obstructive pulmonary disease. Consider using digoxin for patients with CHF or hypotension, because both beta-blockers and calcium channel blockers can precipitate hemodynamic deterioration in these patients.

Digoxin has a relatively slow onset of action, however, and is less effective than beta-blockers or calcium channel blockers for rate control. What's more, digoxin is ineffective for slowing the heart rate during exercise or in hyperadrenergic states. Thus, combination therapy will be needed to achieve adequate rate control in many cases.

Agents that predominantly block AV conduction, such as beta-blockers, calcium channel blockers, and digoxin, are contraindicated in patients with WPW syndrome and wide-complex ventricular response related to the preexcitation syndrome. That's because these drugs can trigger an antegrade conduction along the accessory pathway.[18] In this subset of patients, use a Class 1 antiarrhythmic such as flecainide or procainamide, or amiodarone for rate control[1] (**TABLE 1**).

When should you consider cardioversion?

The NICE guidelines recommend rhythm control as the initial choice for patients who:

- are symptomatic
- are <65 years old
- are presenting for the first time with lone AF or AF secondary to a condition that has been treated or corrected
- have CHF.[16]

While the guidelines recommend restoring sinus rhythm in patients with heart failure, a recent study suggests that rhythm control is no more effective for reducing the rate of death from cardiovascular causes compared to a rate-control strategy in this patient population.[19] As with other aspects of AF management for which there is no definitive approach, individualized factors—including patient preference—should be your guide.

Electrical vs pharmacological cardioversion. Sinus rhythm can be established with electrical or pharmacological cardioversion. Electrical cardioversion, in which an external defibrillator delivers an electric shock that's synchronized with the QRS complex, is usually well tolerat-

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When AF is associated with atrial flutter, WPW syndrome, or AV nodal reentrant tachycardia, it is essential to recognize and treat the primary arrhythmia.

TABLE 1

Rate-control agents: A review of the options

DRUG	LOADING DOSE (ONSET)	MAINTENANCE DOSE	MAJOR ADVERSE EFFECTS
Amiodarone*	IV: 150 mg over 10 min (days)	*Acute care*: 0.5-1 mg/min IV *Outpatient:* 200 mg/d oral	Hypotension, HB, bradycardia; pulmonary toxicity; skin discoloration, thyroid dysfunction; corneal deposits, optic neuropathy; warfarin interaction
Digoxin†	IV: 0.25 mg/2h, up to 1.5 mg (≥60 min)	*Acute care*: 0.125-0.375 mg/d IV or oral *Outpatient*: 0.125-0.375 mg/d oral	Digitalis toxicity, HB, bradycardia
Diltiazem	IV: 0.25 mg/kg over 2 min (2-7 min)	*Acute care*: 5-15 mg/h IV *Outpatient*: 120-360 mg/d oral in divided doses (slow release available)	Hypotension, HB, HF
Esmolol‡	IV: 500 mcg/kg over 1 min (5 min)	*Acute care*: 60-200 mcg/kg per min IV	Hypotension, HB, HF, bradycardia; asthma
Metoprolol‡	IV: 2.5-5 mg bolus over 2 min; up to 3 doses (5 min)	*Outpatient*: 25-100 mg BID oral	Hypotension, HB, HF, bradycardia; asthma
Propranolol‡	IV: 0.15 mg/kg (5 min)	*Outpatient*: 80-240 mg/d oral in divided doses	Hypotension, HB, HF, bradycardia; asthma
Verapamil	IV: 0.075-0.15 mg/kg over 2 min (3-5 min)	*Outpatient*: 120-360 mg/d oral in divided doses (slow release available)	Hypotension, HB, HF; digoxin interaction

HB, heart block; HF, heart failure; IV, intravenous.

*Recommended for patients with accessory pathway and those with heart failure without accessory pathway; often useful when other measures are unsuccessful or contraindicated.

†For patients with heart failure without accessory pathway.

‡The beta-blockers listed here are representative; other similar agents can also be used to achieve rate control.

Adapted from: Fuster V, et al. *Circulation*. 2006.[1]

ed; embolization, pulmonary edema, and other arrhythmias are infrequent complications. Cardioversion with biphasic waveform defibrillation typically uses less energy and may have greater efficacy than monophasic waveforms.

The success rate of electrical cardioversion is higher than that of pharmacological cardioversion.[8] But the use of electrical cardioversion is limited by the need for general anesthesia or conscious sedation for pain control. Pharmacological cardioversion is more effective for patients who have had AF for <48 hours; after that, the conversion rate drops considerably, and electrical cardioversion is often needed to restore sinus rhythm in a patient whose AF has lasted more than 7 days. A variety of antiarrhythmic drugs (**TABLE 2**), including propafenone, flecainide, ibutilide, and amiodarone, can be used to restore sinus rhythm. But because of the proarrhythmic potential of most of these agents, patients should be monitored in the hospital while drug therapy is initiated. After sinus rhythm is restored, maintenance therapy may be required.

Whether cardioversion is achieved by electrical or pharmacological means,

TABLE 2

Pharmacological cardioversion: Typical drugs and doses

DRUG	ROUTE OF ADMINISTRATION	TYPICAL DOSAGE	POTENTIAL ADVERSE EFFECTS
Amiodarone	Oral	*Inpatient*: 1.2-1.8 g/d in divided dose to 10 g total, then 200-400 mg/d or 30 mg/kg as single dose	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare); GI upset, constipation; phlebitis (IV)
	IV	5-7 mg/kg over 30-60 min, then 1.2-1.8 g/d continuous	
Dofetilide	Oral	125-500 mcg BID*	QT prolongation, torsades de pointes
Flecainide	Oral	200-300 mg	Hypotension, atrial flutter with high ventricular rate
	IV	1.5-3 mg/kg over 10-20 min	
Ibutilide	IV	1 mg/10 min; repeat 1 mg PRN	QT prolongation, torsades de pointes
Propafenone	Oral	600 mg	Hypotension, atrial flutter with high ventricular rate
	IV	1.5-2 mg/kg over 10-20 min	

AF, atrial fibrillation; BID, twice a day; GI, gastrointestinal; IV, intravenous; PRN, as needed.

*Dosage adjusted based on renal function, body size, and age.

Adapted from: Fuster V, et al. *Circulation*. 2006.[1]

it is associated with an increased risk of thromboembolism, especially in patients whose AF has persisted for >48 hours. Adequate anticoagulation with warfarin (international normalized rate of 2-3) should be achieved 3 weeks prior to cardioversion and continued for 4 weeks thereafter. Alternatively, excluding atrial thrombus by TEE paves the way for early cardioversion, using IV heparin or low-molecular-weight heparin for anticoagulation.

Maintaining sinus rhythm: Choosing the right drug

Without chronic antiarrhythmic therapy, only about 30% of patients with AF will remain in normal sinus rhythm after a year.[20] Of the drugs that can be used to maintain sinus rhythm—amiodarone, disopyramide, flecainide, propafenone, and sotalol—amiodarone is the most effective. In the Canadian Trial of Atrial Fibrillation,[21] 403 patients treated with amiodarone, sotalol, or propafenone were followed for 16 months. The recurrence rate for the amiodarone group was 35%, compared with 63% for those being treated with sotalol or propafenone.

Adverse effects to consider

Amiodarone is less proarrhythmic than the other antiarrhythmic agents, but it is associated with serious noncardiac toxicities, including pulmonary, thyroid, neurologic, hepatic, optic, and dermatologic adverse effects. In addition, amiodarone can increase plasma levels of several drugs, including digoxin and warfarin, and periodic monitoring of the doses of these medications is essential. Adding enalapril, an angiotensin-converting enzyme inhibitor, or irbesartan, an angiotensin receptor blocker, can enhance the efficacy of amiodarone in maintaining normal sinus rhythm after cardioversion.

Thus, the choice of medication to maintain sinus rhythm should be in-

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Amiodarone and dofetilide are the preferred agents for maintaining sinus rhythm in patients with heart failure.

TABLE 3

Maintaining sinus rhythm in patients with AF

DRUG	DAILY DOSE	INDICATION	POTENTIAL ADVERSE EFFECTS	COMMENTS
Amiodarone	100-400 mg	Hypertension with LVH, impaired LV function, HF, ischemic heart disease	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications	Use with care in patients with asthma or bradycardia.
Disopyramide	400-750 mg	Asthma, thyroid disease	Torsades de pointes, HF, glaucoma, urinary retention, dry mouth	
Dofetilide	500-1000 mcg	Cardiomyopathy, ischemic heart disease, significant LV dysfunction	QT prolongation, torsades de pointes	In inpatient setting, adjust dose for renal function and QT-interval response. Avoid in patients with renal failure.
Flecainide	200-300 mg	First-line therapy for patients with a structurally normal heart	VT, HF, conversion to atrial flutter with rapid conduction through AV node	May be used in patients with asthma and thyroid disease.
Propafenone	450-900 mg	First-line therapy for patients with a structurally normal heart	VT, HF, conversion to atrial flutter with rapid conduction through AV node	Use with care in patients with asthma or bradycardia.
Sotalol	160-320 mg	Ischemic heart disease, thyroid disease	Torsades de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease	In inpatient setting, adjust dose for renal function and QT-interval response. Avoid in patients with renal failure.

AF, atrial fibrillation; AV, atrioventricular; GI, gastrointestinal; HF, heart failure; LV, left ventricular; LVH, left ventricular hypertrophy; VT, ventricular tachycardia.
Adapted from: Fuster V, et al. *Circulation*. 2006.[1]

dividualized, based on the patient's underlying cardiac condition and the safety profile of the antiarrhythmics being considered. (**TABLE 3**). The ACC/AHA/ESC guidelines recommend class 1C agents flecainide and propafenone as first-line therapy for maintaining sinus rhythm in patients with structurally normal hearts.[1] But because of their proarrhythmic and negative ionotropic effects, class 1C agents should not be given to patients who have heart failure or ischemia. Amiodarone and dofetilide are the preferred agents for maintaining sinus rhythm in patients with heart failure and severe left ventricular hypertrophy, and dofetilide, amiodarone, and sotalol are best suited for patients with ischemic heart disease.

Pill-in-the-pocket. For selected patients with paroxysmal AF and a structurally normal heart, a "pill-in-the-pocket" strategy is an option—provided it has been tried in the hospital and proven to be safe. A patient using this strategy would self-administer a single dose of a class 1C antiarrhythmic agent—eg, 600 mg propafenone or 300 mg flecainide—at the onset of an acute episode of AF. Concomitant administration of a beta-blocker or calcium channel blocker is recommended to prevent development of atrial flutter with rapid AV conduction.

Using anticoagulation as prophylaxis

Judicious use of antithrombotic prophylaxis can significantly reduce the inci-

dence of strokes associated with AF, regardless of whether you pursue a rate-control or rhythm-control strategy. Despite clear evidence of the efficacy of warfarin and aspirin in this patient population, anticoagulation remains underused in clinical practice.

If AF recurs or the patient develops chronic AF, the AFFIRM trial suggests the need for long-term anticoagulation for patients with thromboembolic risk factors.[9]

Adjusted-dose warfarin gets best results. A meta-analysis of 29 randomized trials from 1996 to 2007 involving 28,044 patients (mean age, 71 years; mean follow-up, 1.5 years) assessed the benefits of antithrombotic therapy for patients with AF.[22] Compared with the controls, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% confidence interval [CI], 49%-74%) and 22% (95% CI, 6%-35%), respectively.

Adjusted-dose warfarin was substantially more effective than antiplatelet therapy (12 trials, 12,963 participants; relative risk reduction, 39% [95% CI, 22%-52%]). The absolute risk reduction (ARR) with adjusted-dose warfarin in all strokes was 2.7% per year (number needed to treat [NNT] for 1 year to prevent 1 stroke was 37) for primary prevention and 8.4% per year (NNT, 12) for secondary prevention. Aspirin showed an ARR of 0.8% per year (NNT, 125) for primary prevention trials and 2.5% per year (NNT, 40) for secondary prevention trials. The absolute increase in major extracranial hemorrhage was small (≤0.3% per year).[22]

A recent Cochrane review of 8 randomized trials with a total of 9598 patients concluded that adjusted-dose warfarin reduces stroke and other major vascular events in patients with nonvalvular AF by about one third, compared with antiplatelet therapy alone.[23]

Warfarin or aspirin? Tools to help you decide

The risk of stroke varies considerably among patients with AF, depending on age and history of thromboembolic events, among other risk factors. What's more, anticoagulation therapy carries an inherent risk of increased bleeding, making its use a complicated decision. A validated stroke risk stratification scheme like the $CHADS_2$ can help.[24] (See "Warfarin or aspirin? An anticoagulation risk tool" on page 65.)

The ACC/AHA/ESC guidelines recommend an alternate means of determining when anticoagulation is needed. The recommended risk stratification scheme divides risk factors for stroke into 3 categories:

- **weak/less validated** (female gender, age 65-74 years, coronary artery disease, thyrotoxicosis)
- **moderate** (≥75 years of age, hypertension, heart failure, LV ejection fraction ≤35%, diabetes mellitus)
- **high** (previous stroke, TIA, or embolism; mitral stenosis, prosthetic heart valve).

The guidelines recommend warfarin therapy for any patient with any high-risk factor or 2 or more moderate-risk factors; aspirin therapy for patients with no moderate- or high-risk factors; and aspirin or warfarin for patients with 1 moderate-risk factor.[1]

When conventional therapy fails

For patients who do not respond to conventional therapy, other options, including radiofrequency catheter ablation and pacemakers, may be effective in controlling symptoms and improving quality of life. In a recent RCT of 70 patients 18 to 75 years of age who experienced monthly symptomatic episodes of AF, the recurrence rate at the end of the 12-month follow-up was 13% after pulmonary vein isolation with radiofrequency ablation compared with 63% after treatment with antiarrhythmic drugs ($P<.001$). The rate of hospitalization was also signifi-

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cantly lower in the radiofrequency ablation group: 9% compared with 54% in the antiarrhythmia group ($P<.001$).[25] Another option to consider for patients who require cardiac surgery for other reasons is left atrial appendage (LAA) occlusion or ligation at the time of surgery. This may prevent cardiac embolization, because the vast majority of thrombi in nonvalvular AF involve the LAA. ■

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Disclosures

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