Strategies for managing atrial fibrillation

MICHAEL S. KATCHER, MD; CAROLINE B. FOOTE, MD; MUNTHER HOMOUD, MD;
PAUL J. WANG, MD; N.A. MARK ESTES III, MD

SUMMARY The limitations of current therapies for atrial fibrillation are forcing a rethinking of how they should be used. Questions are being raised about the use of antiarrhythmic drugs, and new nonpharmacologic procedures are promising alternatives. Most patients with atrial fibrillation still require warfarin therapy, but some low-risk patients can forego it.

KEY POINTS Sinus rhythm spontaneously returns within the first 24 hours in almost half of cases of new atrial fibrillation. Patients with hemodynamic instability due to new-onset atrial fibrillation should proceed directly to electrical cardioversion. Warfarin therapy to maintain an International Normalized Ratio (INR) of 2.0 to 3.0 is currently recommended for all patients with atrial fibrillation with no contraindications to it, except for patients younger than 60 years with lone atrial fibrillation, in whom the risk of stroke is low. Certain antiarrhythmic drugs should be avoided in patients with congestive heart failure, in whom the risks may exceed the benefits. The maze procedure is emerging as an option to restore and maintain sinus rhythm. Radiofrequency atrioventricular node ablation and modification hold promise as options to control the ventricular rate without drugs.

INDEX TERMS: ATRIAL FIBRILLATION
CLEVE CLIN J MED 1996; 63:282–294

From the Cardiac Arrhythmia Service, New England Medical Center Hospitals, Boston.
Address reprint requests to N.A.M.E., New England Medical Center #197, 750 Washington Street, Boston, MA 02111.

TREATMENT STRATEGIES for atrial fibrillation are changing, as studies have shown the limitations of some current pharmacologic therapies and as new surgical techniques have been introduced.

The objectives of treating atrial fibrillation are to control or eliminate hemodynamic symptoms and to prevent thromboembolism. Treatment encompasses three areas: control of ventricular rate, conversion to and maintenance of sinus rhythm, and anticoagulation. Of these, anticoagulation therapy with warfarin has been best studied; although it decreases the risk of stroke, it poses considerable risk for patients older than 75 years.[1] The risks and benefits of antiarrhythmic drugs to restore and maintain normal sinus rhythm have not been evaluated in controlled trials, but retrospective analyses suggest they *increase* the mortality rate in some patients with atrial fibrillation.[2,3]

This paper reviews current strategies and areas of research in treating atrial fibrillation.

TABLE 1
PRECURSORS TO ATRIAL FIBRILLATION

Cardiac precursors
Valvular heart disease (rheumatic and nonrheumatic)
Congenital heart disease
Coronary artery disease (including recent myocardial infarction)
Hypertensive heart disease
Left ventricular hypertrophy
Dilated cardiomyopathy
Pericardial disease
Infiltrative heart disease
Cardiac surgery
Congestive heart failure
Pericarditis
Noncardiac precursors
Diabetes
Hyperthyroidism
Pulmonary embolism
Chronic obstructive pulmonary disease
Pneumonia
Ethanol use ("holiday heart")
Electrolyte imbalance
Acute toxic/metabolic abnormalities
Medications

EPIDEMIOLOGY

Atrial fibrillation is the most common of the sustained arrhythmias. Chronic atrial fibrillation affects approximately 1.8 million Americans.[4] In the Framingham Heart Study, during 22 years of follow-up, atrial fibrillation developed in approximately 2% of men and women.[5] The prevalence increases with age: 0.2% to 0.3% in persons 25 to 35 years old, vs 5% to 9% in those older than 62 years.[4,6,7] The increase is partly due to increases in predisposing illnesses with advancing age.

Atrial fibrillation may result from areas within the atrial myocardium with abnormal conduction or recovery properties. These abnormal areas disrupt normal conduction, resulting in multiple, irregular wavelets of electrical activity. As a result, the atria "quiver" rather than contract (*Figure 1*).

Of the many conditions that predispose to atrial fibrillation (*Table 1*), heart failure and rheumatic heart disease impart the highest risk. However, the most frequent precursors are hypertension and coronary disease.[5] Hyperthyroidism is another frequent precursor and can be insidious, especially in the elderly. Atrial fibrillation arises in 5% to 40% of patients who undergo cardiac surgery, with the highest incidence in the elderly.[8] The incidence is even higher after valvular surgery.

TABLE 2
THROMBOEMBOLIC RISK FACTORS IN ATRIAL FIBRILLATION

Advanced age
Congestive heart failure
Prior embolization
Hypertension
Ventricular aneurysm
Left ventricular dysfunction
Left atrial enlargement
Rheumatic heart disease
Diabetes
Mitral annular calcification
Previous myocardial infarction
Angina

CONSEQUENCES OF ATRIAL FIBRILLATION

Atrial fibrillation causes considerable disease and death. During 22 years of follow-up, Framingham subjects with atrial fibrillation had rates of overall mortality and cardiovascular mortality almost twice those of persons free of atrial fibrillation,[5] likely reflecting a combination of complications of atrial fibrillation and of other comorbid conditions.

Stroke

The lack of organized atrial contraction predisposes to stasis of blood and to clot formation, particularly in the left atrial appendage. Thus, although persons with atrial fibrillation often have other cardiac conditions that predispose them to lacunar and thrombotic strokes, most strokes in this population are thromboembolic.

During 2 years, 7.6% of Framingham subjects with atrial fibrillation suffered strokes, compared with 0.6% of persons without atrial fibrillation.[9] The risk is fivefold higher in persons with chronic nonvalvular atrial fibrillation than in persons free of atrial fibrillation.[10]

Many factors further increase the risk of stroke (*Table 2*). For example, persons with atrial fibrillation plus rheumatic valvular disease have an incidence of embolic stroke as high as 17% per year and require long-term anticoagulation to reduce the risk.[11] The risk also increases with age[9] and in patients with recent congestive heart failure, hypertension, previous thromboembolism, or combinations of these factors.[12]

Definitions

"Lone" atrial fibrillation occurs without predisposing conditions. Some investigators limit the definition to patients younger than 65 years; others use a looser definition and include older patients and those with hypertension, provided there is no electrocardiographic evidence of hypertrophy and no other overt heart disease. Depending on the definition used, lone atrial fibrillation accounts for 2.7% to 11.4% of cases.[1] Patients with lone atrial fibrillation, especially if younger than 60 years, have an excellent prognosis and a low risk of stroke.[2]

Paroxysmal atrial fibrillation refers to transient, self-terminating episodes, although there is no uniform definition. Despite its intermittent nature, paroxysmal atrial fibrillation may predispose to thromboembolism, although the risk is lower in paroxysmal than in chronic atrial fibrillation. Paroxysmal atrial fibrillation is often a precursor to the chronic form.

Chronic atrial fibrillation, in contrast to paroxysmal atrial fibrillation, does not revert to normal sinus rhythm without therapy.

References

1. **Levine HJ, Estes NAM III.** Medical management of atrial fibrillation. Am J Med 1993; **76 (Suppl):** 3–13.
2. **Pritchett ELC.** Management of atrial fibrillation. N Engl J Med 1992; **326:**1264–1271.

Hemodynamic effects

The rapid ventricular rate in atrial fibrillation limits the duration and degree of diastolic ventricular filling and can predispose to palpitations, fatigue, and congestive heart failure. The rapid heart rate and the increased diastolic filling pressures increase myocardial oxygen demand and, in patients with coronary artery disease, can precipitate ischemia. The loss of atrioventricular synchrony diminishes cardiac output. Patients with diastolic dysfunction and stiff ventricles, who depend heavily on the "atrial kick" for diastolic filling and cardiac output, are at greatest risk for these adverse hemodynamic effects of atrial fibrillation.

CONFIRMING AND TREATING ATRIAL FIBRILLATION

Atrial fibrillation produces a rapid, irregularly irregular heart rate. Normally, the ventricular rate in untreated atrial fibrillation ranges from 100 to 170 beats per minute. More-rapid rates occur in hyperthyroidism, high-catecholamine states (eg, pain, dehydration, fever, blood loss, theophylline toxicity, exercise, heart failure), and ventricular pre-excitation.[13,14] Slower ventricular rates occur in atrioventricular (AV) nodal disease.

At rest, the heart rate may not be exceedingly high; however, even modest activity may markedly increase it. This increase is primarily mediated by enhanced AV nodal conduction, with an increase in sympathetic tone and a decrease in vagal tone.

Electrocardiography is needed to confirm and document atrial fibrillation. All patients with newly diagnosed atrial fibrillation should also undergo echocardiography to detect structural heart disease and to estimate left atrial size. Patients with risk factors for coronary artery disease should undergo an exercise tolerance test. Noncardiac causes of atrial fibrillation, such as hyperthyroidism, should be searched for and ruled out. Factors that trigger episodes of atrial fibrillation should be identified, such as ingestion of alcohol, caffeine, or other drugs or metabolic and electrolyte abnormalities.

Therapy should be individualized on the basis of whether the patient is hemodynamically stable and whether benefits of sinus rhythm outweigh the risks of antiarrhythmic therapy (*Figure 2*). When deciding whether to use anticoagulation with rate control or make an attempt to regain normal sinus rhythm with antiarrhythmic medication, factors to consider include the severity of patient's symptoms, degree of underlying cardiac and noncardiac disease, and suitability for long-term anticoagulation.

HEMODYNAMICALLY UNSTABLE PATIENTS: PERFORM CARDIOVERSION IMMEDIATELY

Hemodynamically unstable patients should undergo urgent direct-current electrical cardioversion rather than attempts at rate control. Afterward, they should receive anticoagulant therapy for 4 weeks (*Figure 2*).

HEMODYNAMICALLY STABLE PATIENTS: BEGIN RATE CONTROL THERAPY FIRST

Hemodynamically stable patients, on the other hand, should undergo rate control therapy first. Drug therapy for rate control in atrial fibrillation falls into two categories: immediate (acute) and long-term (chronic). Patients without symptoms or tachycardia can be given oral agents, started in low doses and gradually increased. In contrast, patients

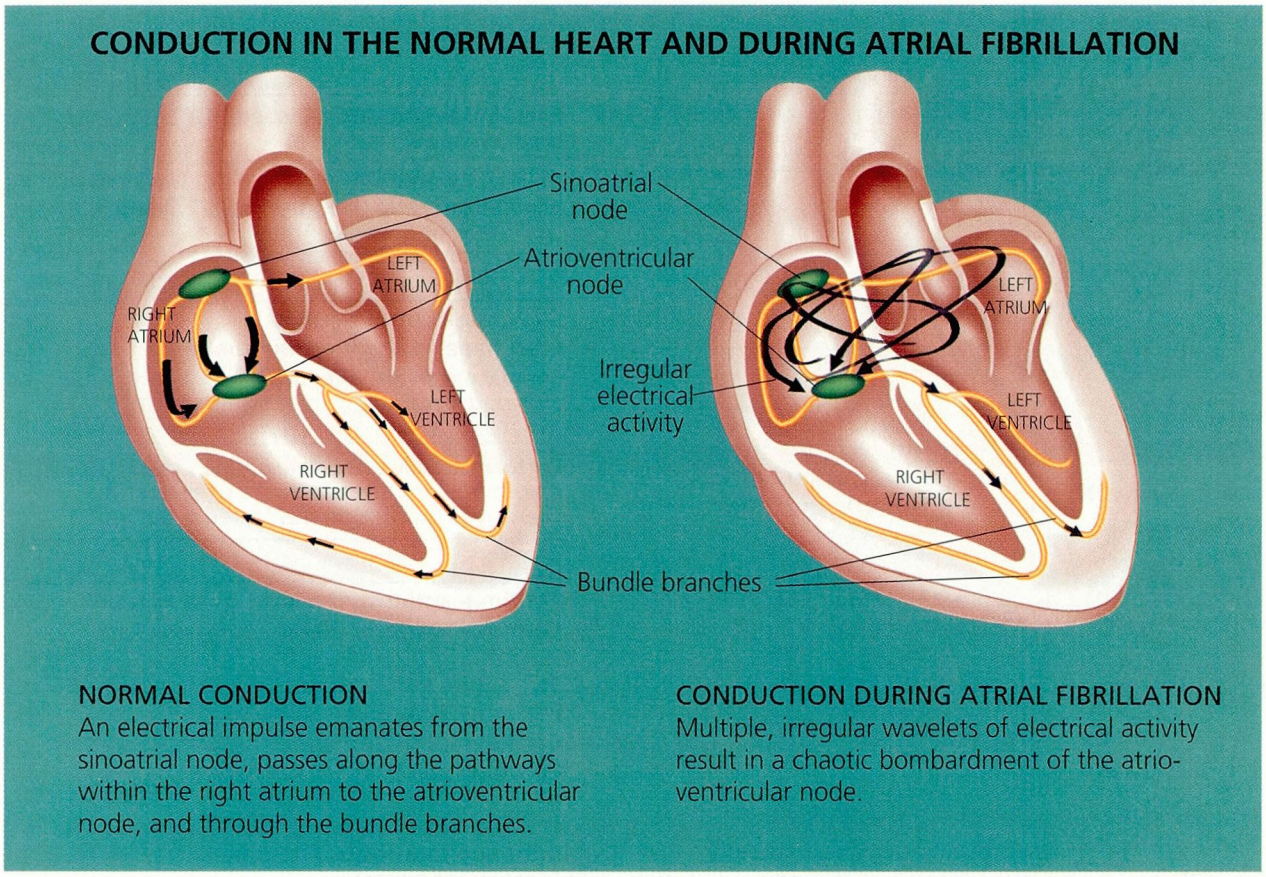

FIGURE 1.

with symptoms or with heart rates greater than 100 beats per minute need immediate heart-rate control, usually with intravenous medications.

Pharmacologic therapy for rate control

The same drugs are used for both immediate and long-term rate control: digoxin, beta blockers, and calcium antagonists (*Table 3*). The choice of agent to slow AV nodal contraction must be individualized, and depends on clinical considerations and the physician's preference. Sometimes it is necessary to combine use of two or more agents to acheive adequate rate control.

Digoxin increases vagal tone and thus slows AV nodal conduction, but has several important limitations in the acute setting. Its onset of action is slow: in one study, oral digoxin took an average of 5.5 hours to slow the heart rate significantly.[13,15] Even if given intravenously, digoxin has a slow onset of action and may require multiple loading doses over several hours. Further, digoxin has a narrow therapeutic window before it reaches toxic levels, which prevents more rapid and aggressive dosing.

On the other hand, digoxin is the principal agent traditionally used for long-term rate control. Its advantage is its long half-life. Digoxin generally controls the heart rate at rest but does little to prevent the rapid ventricular response during exercise.[13] It is most useful in chronic atrial fibrillation in patients with congestive heart failure and systolic dysfunction, who may not tolerate agents with negative inotropic effects. Digoxin has not been shown effective in paroxysmal atrial fibrillation[16]; in fact, in patients with paroxysmal atrial fibrillation that is vagally mediated, it can exacerbate the arrhythmia.[17] A number of cardiac medications (eg, quinidine, propafenone, amiodarone, verapamil) can increase digoxin levels and predispose to toxicity.

Beta blockers. Various intravenous beta blockers have been used to lower the heart rate quickly. Esmolol, given as a continuous intravenous infusion,

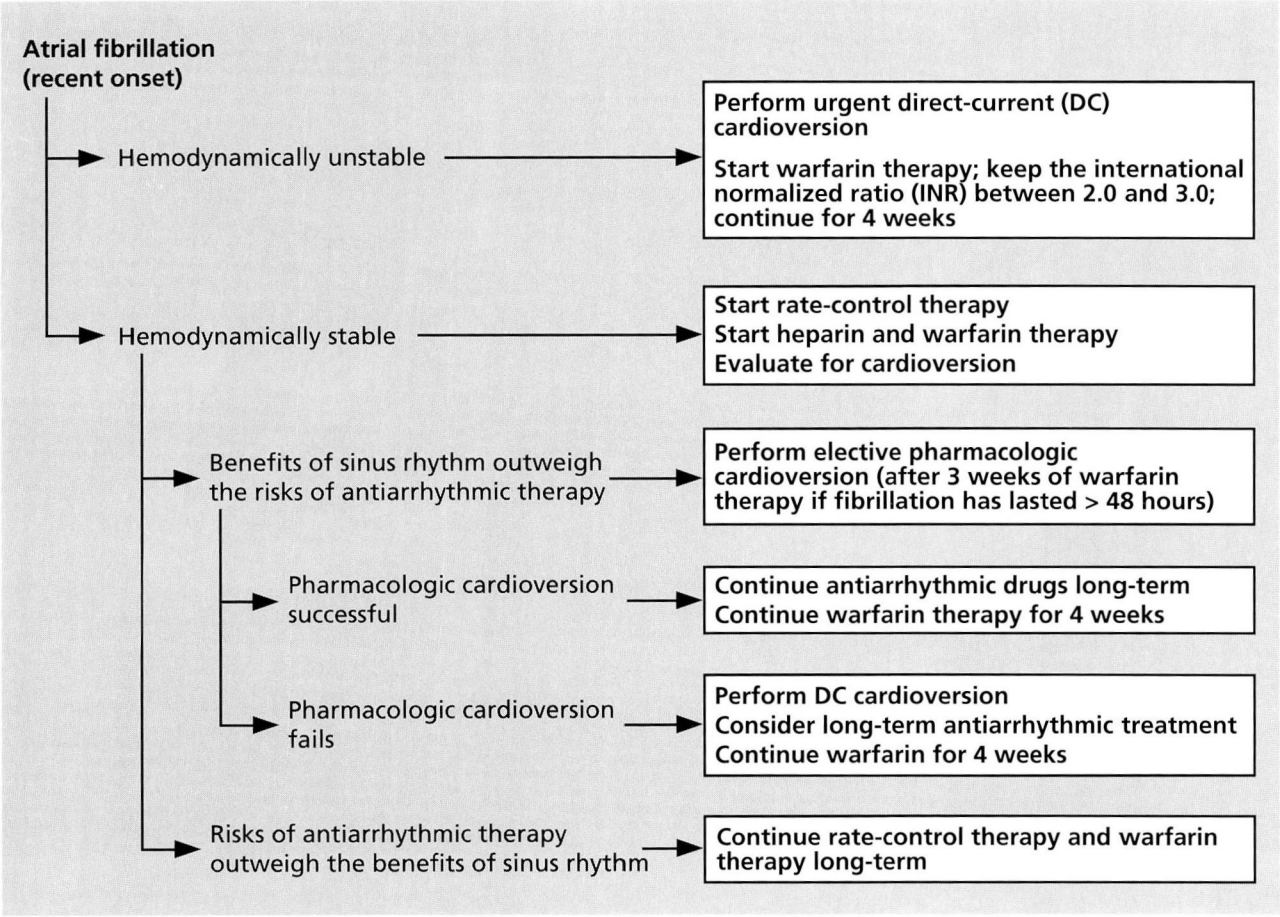

FIGURE 2. Algorithm for the management of atrial fibrillation.

can be titrated to achieve a specific heart rate. Beta blockers can exacerbate congestive heart failure, particularly in patients with diminished left ventricular systolic function.

Because they blunt sympathetic stimulation of the heart, beta blockers are well suited for long-term rate control during exercise in active patients. They are also useful in controlling very rapid heart rates in thyrotoxicosis.

Calcium antagonists. Intravenous verapamil quickly lowers the ventricular rate in atrial fibrillation, but its effect is transient. Its negative inotropic effect can precipitate hypotension and worsen congestive heart failure. Diltiazem has also been used for immediate rate control and is usually well tolerated.[18,19] It is given as an intravenous bolus followed by a continuous infusion or by oral doses. Oral preparations of verapamil and diltiazem are also effective for long-term rate control.

Clonidine, a centrally acting alpha-2 agonist, has also been shown to lower the heart rate quickly, presumably by suppressing the outflow of sympathetic activity from the central nervous system.[20]

Nonpharmacologic therapy for rate control

If the ventricular rate is difficult to control with drugs, nonpharmacologic therapies may be useful.

AV nodal ablation, an electrophysiologic procedure, uses radiofrequency energy to irreversibly destroy AV nodal tissue and thus interrupt or modify AV conduction. Complete AV nodal ablation produces iatrogenic complete heart block and necessitates permanent implantation of a pacemaker. Patients with paroxysmal atrial fibrillation can use a dual-chamber pacemaker that automatically switches to ventricular pacing during episodes of atrial fibrillation.[21,22] AV nodal ablation is safe, and

TABLE 3
DRUGS FOR SLOWING THE VENTRICULAR RESPONSE IN ATRIAL FIBRILLATION*

Drug	Loading dose†	Maintenance dose†	Side effects
Digoxin	0.25–0.5 mg IV, then 0.25 mg IV every 4 hours (1.0–2.0 mg in first 24–48 hours)	0.125–0.375 mg PO daily	Nausea, anorexia, yellow vision, ventricular arrhythmias, AV block
Esmolol	500 μg/kg IV over 1 minute	50 μg/kg IV for 4 minutes Repeat loading dose if needed and increase maintenance dose by 20–50 μg/kg/minute every 5–10 minutes	Bronchospasm, heart failure, hypotension
Propranolol	1 mg IV every 5 minutes to a total of 5 mg	10–80 mg PO three to four times a day	Bronchospasm, heart failure, hypotension
Metoprolol	5 mg IV every 5 minutes to a total of 15 mg	25–100 mg PO twice a day	Bronchospasm, heart failure
Diltiazem	0.25 mg/kg over 2 minutes Repeat if needed after 15 minutes as 0.35 mg/kg over 2 minutes	5–15 mg/hour IV, or 30–90 mg PO four times a day	Hypotension, heart failure, bradycardia
Verapamil	2.5–10 mg IV over 2 minutes	0.005 mg/kg/minute, or 5–10 mg intravenously every 30–60 minutes	Hypotension, heart failure, bradycardia, increased serum, digoxin level

*These agents are useful only in patients with conduction through the AV node and not in those with ventricular pre-excitation (Wolff-Parkinson-White syndrome)
†IV, intravenously; PO, by mouth

acute complications are rare. Long-term success rates range from 80% to 100%.[22–25] However, because the atria continue to fibrillate afterward, this procedure does not lessen the risk of stroke or the need for long-term anticoagulation.

Complete AV nodal ablation is best considered in patients with rapid heart rates refractory to pharmacologic therapy, or who cannot tolerate pharmacologic therapy, or who already require permanent pacing.[22,26] Such patients enjoy marked benefit, including adequate rate control without pharmacotherapy, an enhanced quality of life, improved left ventricular function, and decreased long-term health care costs.[22]

AV nodal modification. Selective ablation of the slow pathway of the AV node slows the ventricular response without creating complete AV block and avoids the need for a permanent pacemaker.[27,28] In an initial series of 19 patients, 14 (74%) had an initial success with this procedure; 4 (21%) developed complete AV block and required permanent pacing.[27] Eight months after the procedure, all of the 14 patients who had an initial success reported improved alleviation of symptoms and had lower exercise heart rates and improved function. Further experience is needed to clarify the role of this therapy.

PATIENT SELECTION FOR CARDIOVERSION

Once the heart rate is under control, a decision can be made whether to perform cardioversion. Unfortunately, the side effects of currently available antiarrhythmic agents may outweigh their benefits.[2,3]

Spontaneous conversion to sinus rhythm without pharmacologic or electrical therapy is common, especially in atrial fibrillation of very recent onset. The rhythm spontaneously converts within the first 24 hours in almost half of cases of new atrial fibrillation.[15,29]

Curently, the guidelines for selecting which atrial fibrillation patients should undergo cardioversion and be maintained in normal sinus rhythm are evolving based on assessment of the risk and benefits of antiarrhythmic agents, rate control agents, and anticoagulant medications. For many atrial fibrillation patients whose rate control is adequate and who have minimal or no symptoms, rate control with anticoagulation may be preferable to the risk and side effects of antiarrhythmic drugs.

TABLE 4
ANTIARRHYTHMIC DRUGS FOR ATRIAL FIBRILLATION

Class and drug	Dose	Side effects
Class IA agents		
Quinidine	200–400 mg four times a day	Diarrhea, nausea, increased serum digoxin levels, proarrhythmia
Procainamide	10–15 mg/kg intravenously at no greater than 50 mg/minute	Hypotension, heart failure
Procainamide (sustained release)	500–1000 mg every 6 hours	Hypotension, heart failure, lupus, proarrhythmia
Disopyramide	100–300 mg three times a day	Heart failure, anticholinergic effects, proarrhythmia
Class IC agents		
Flecainide	50–100 mg twice a day	Heart failure, proarrhythmia
Propafenone	150–300 mg three times a day	Heart failure, proarrhythmia
Class III agents		
Sotalol	80–320 mg twice a day	Heart failure, bradycardia, proarrhythmia
Amiodarone	100–400 mg daily	Bradycardia, nausea, hyperthyroidism, hypothyroidism, pulmonary toxicity, hepatic toxicity

However, for the younger patient with lone atrial fibrillation, a single attempt to restore normal sinus rhythm is usually considered justifiable. In patients with ventricular systolic or diastolic dysfunction, and who poorly tolerate atrial fibrillation, more aggressive attempts to control sinus rhythms should be made. In such patients, restoration or maintenance of sinus rhythm can improve symptoms and have beneficial effects which outweigh the risks of antiarrhythmic therapy.

Anticoagulant therapy needed before cardioversion

Without prior anticoagulant therapy, the incidence of acute embolization after elective cardioversion is as high as 5.3%.[30] However, thrombi are believed to take at least several days to form after the onset of atrial fibrillation. If atrial fibrillation has lasted less than 48 hours, cardioversion can be performed without prior anticoagulant therapy, with minimal risk of stroke.[31] For atrial fibrillation of longer or indeterminate duration, 3 weeks of warfarin therapy is recommended before cardioversion.[30]

Investigators are using transesophageal echocardiography (TEE) to identify patients in whom it may be safe to proceed to cardioversion without the requisite 3 weeks of warfarin therapy.[32–36] Transthoracic echocardiography cannot rule out atrial thrombi. TEE, with its retroatrial position, is better suited for examining the left atrium and the left atrial appendage. In one study, 78 patients who had left atrial thrombi excluded on the basis of TEE underwent successful cardioversion, and none had an embolic event.[32] TEE can also detect spontaneous echo contrast, which may represent a relative stasis of blood and a prethrombotic state.

Methods of cardioversion

The options for converting atrial fibrillation to normal sinus rhythm are electrical direct-current cardioversion and drugs. Electrical direct-current cardioversion succeeds in more than 90% of cases but requires sedation and general anesthesia. Therefore, it is common to attempt pharmacologic cardioversion first and to reserve electrical cardioversion for patients in whom drugs fail.

Several drugs can restore or maintain normal sinus rhythm in atrial fibrillation (*Table 4*). Digoxin, although historically used for this purpose, is no more effective than placebo.[15] The class IA antiarrhythmic drugs quinidine, procainamide, and disopyramide are effective in up to 50% of cases. Class IC drugs, including flecainide and propafenone, have somewhat less efficacy. Studies vary concerning the efficacy rate of the class III agent amiodarone (from 16% to 71%); however, many of these studies included patients with atrial fibrillation resistant to other therapies.[37,38]

Studies of anticoagulation therapy

Five major placebo-controlled studies examined the utility of anticoagulant therapy in reducing the risk of thromboembolic vascular events in nonrheumatic atrial fibrillation (*Table*).[1–5] These trials all compared warfarin to placebo; two also examined aspirin therapy.[3,4]

Benefit of warfarin therapy

All five studies found warfarin more beneficial than placebo. In total, the incidence of stroke was 1.4% in patients randomized to receive warfarin, compared with 4.5% in controls.[6] The benefit of warfarin may in fact be even greater, since most of the strokes in patients randomized to receive warfarin occurred in persons not taking warfarin at the time of the stroke or who had subtherapeutic anticoagulation (ie, an international normalized ratio [INR] < 1.5). Warfarin has also been shown effective in preventing further strokes in patients with atrial fibrillation and a history of cerebrovascular events.[7]

The level of anticoagulation varied in these primary prevention trials, from a target INR as low as 1.4 to 2.8,[4] to as high as 2.8 to 4.2.[3] (Using the INR compensates for any variability in the thromboplastin used at individual laboratories.[8]) There was no evidence of a greater reduction in risk of stroke with the higher INRs. Nonfatal bleeding was increased in only one of the five trials.[3] In the other four studies, in which lower levels of anticoagulation were maintained, no overall increases in bleeding were reported.

Of the individual studies, only one showed a lower overall mortality rate with warfarin therapy[1]; another showed warfarin to decrease the rate of vascular deaths.[3] A meta-analysis of the five studies found warfarin to decrease the mortality rate by 33%.

Benefit of aspirin

In one of the two trials that compared aspirin with placebo, the incidence of stroke was not significantly lower in patients receiving aspirin; however, the daily dose of aspirin was only 75 mg.[3] In the other trial, in which the dose of aspirin was 325 mg/day, there were 42% fewer embolic events in those treated with aspirin compared with placebo.[4] Currently, aspirin 325 mg/day is recommended for patients with atrial fibrillation deemed poor candidates for warfarin.[9]

Warfarin vs aspirin

The recent, second Stroke Prevention in Atrial Fibrillation (SPAF II) trial compared aspirin therapy with warfarin therapy in atrial fibrillation, and included many of the patients from the earlier SPAF trial.[10] Unlike in the initial SPAF trial, patients older than age 75 were distributed evenly between the two therapy groups.

Patients age 75 or younger had slightly fewer thromboembolic events with warfarin therapy than with aspirin, but the difference was not statistically significant. In such "younger" patients with none of the previous SPAF risk factors (history of hypertension, previous thromboembolism, or recent heart failure) the incidence of thromboembolism was very low (0.5% per year) with aspirin therapy.

In patients older than 75 years, warfarin was associated with a lower embolic event rate than was aspirin (3.6% vs 4.8% per year), although the difference was not statistically significant. In this older population, warfarin therapy caused an increase in intracranial hemorrhage that offset any beneficial decrease in ischemic strokes.

After cardioversion, all patients require anticoagulation for 4 additional weeks to prevent strokes, because normal atrial contraction may not resume for several weeks.[30,33] Even patients in whom thrombi are excluded by TEE before cardioversion require this, because new thrombi are often seen on repeat TEE.[34] The role of TEE therefore is to shorten the duration of anticoagulation and obviate a second hospitalization for cardioversion in some patients.[32,35] Larger trials are currently ongoing to better assess the utility of TEE.

MAINTAINING SINUS RHYTHM

If antiarrhythmic drugs are not given after cardioversion, the rate of recurrence of atrial fibrillation is high: 75% at 1 year in an analysis of six studies.[2] Predictors of recurrence include coronary artery disease, female sex, long duration of atrial fibrillation, untreated thyrotoxicosis, mitral valve disease, congestive heart failure, left atrial enlargement, and first-degree AV block.[39–41]

Do antiarrhythmic drugs increase the mortality rate?

In the meta-analysis cited above, 50% of patients receiving quinidine remained in sinus rhythm at 1 year.[2] However, the 1-year mortality rate in treated patients was three times that in controls (2.9% vs 0.8%), raising the possibility of excess mortality with quinidine use.

Further evidence that antiarrhythmic therapy might increase the mortality rate was seen in the Stroke Prevention in Atrial Fibrillation (SPAF) study.[3] Patients receiving antiarrhythmic therapy (which was not given in a randomized fashion) had a

TABLE
TRIALS OF WARFARIN THERAPY IN ATRIAL FIBRILLATION:
ANNUAL INCIDENCE OF PRIMARY ENDPOINTS AND DEATH

Study*	Vascular events, %		Bleeding, %		Death, %	
	Warfarin	Control	Warfarin	Control	Warfarin	Control
AFASAK[3]	2.0†	5.5	5.5†	0	0.9†	4.0
BAATAF[1]	0.4†	3.0	1.4	1.6	5.2†	12.5
SPAF[2]	2.3†	7.4	1.5	1.6	2.9	3.8
CAFA[5]	2.6‡	4.6	2.5	0.5	7.0	5.2
SPINAF[4]	0.9†	4.3	1.3	1.1	7.1	8.9

*AFASAK, the Atrial Fibrillation, Aspirin, Anticoagulation study; BAATAF, the Boston Area Anticoagulation Trial for Atrial Fibrillation; SPAF, the Stroke Prevention in Atrial Fibrillation study; CAFA, the Canadian Atrial Fibrillation Anticoagulation study; SPINAF, the Stroke Prevention in Nonrheumatic Atrial Fibrillation study
†Statistically significant difference
‡CAFA was stopped prematurely on the basis of the results of other trials of warfarin in atrial fibrillation; at the time of termination there was a trend towards benefit in the treatment group but this did not reach statistical significance

References

1. **The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators.** The effect of low-dose warfarin on the risk of stroke in patients with atrial fibrillation. N Engl J Med 1990; **323:**1505–1511.
2. **Ezekowitz MD, Bridgers SL, James K, et al.** Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992; **327:**1406–1412.
3. **Petersen P, Godtfredsen J, Boysen G, Andersen ED, Andersen B.** Placebo-controlled randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. Lancet 1989; **1:**175–179.
4. **Stroke Prevention in Atrial Fibrillation investigators.** Stroke prevention in atrial fibrillation study: final results. Circulation 1991; **84:**527–539.
5. **Connolly S, Laupacis A, Gent M.** Canadian atrial fibrillation anticoagulation (CAFA) study. J Am Coll Cardiol 1991; **18:**349–355.
6. **Atrial fibrillation investigators.** Risk factors for stroke and efficacy of antithrombolitic therapies in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994; **154:**1449–1457.
7. **European Atrial Fibrillation Trial Study Group.** Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. Lancet 1993; **324:**1255–1262.
8. **Hirsh J.** Oral anticoagulation drugs. N Engl J Med 1991; **324:**1865–1875.
9. **Laupacis A, Albers G, Dunn M, Feinberg W.** Antithrombolic therapy in atrial fibrillation. Third ACCP Consensus Conference on Antithrombotic Therapy. Chest 1992; **Suppl 102:**426S–433S.
10. **Stroke Prevention in Atrial Fibrillation Investigators.** Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke prevention in atrial fibrillation II Study. Lancet 1994; **343:**687–691.

cardiac mortality rate 2.5 times higher and an arrhythmic mortality rate 2.6 times higher than did patients not receiving antiarrhythmic drugs. The excess risk was confined to patients with congestive heart failure.

All antiarrhythmic agents can cause side effects.[42] Because episodes of ventricular proarrhythmia can occur at the start of therapy, hospitalization is recommended for at least five drug half-lives (2 to 4 days for most agents).

Class IA agents

Several agents are used for maintaining sinus rhythm (*Table 4*). Quinidine, the most commonly used agent, frequently causes gastrointestinal intolerance. Disopyramide has negative inotropic and anticholinergic effects that may make it intolerable to patients with left ventricular dysfunction or prostate disease. Procainamide is used less frequently long-term because it can cause lupus-like reactions.

Class IC agents

The Cardiac Arrhythmia Suppression Trial[43] demonstrated an excess in mortality in patients treated with the IC agents encainide and flecainide after myocardial infarction. In atrial fibrillation, class IC agents should be reserved for patients without evidence of structural heart disease and without ventricular arrhythmia. Flecainide has proved particularly useful in patients with episodes of atrial fibrillation that are frequent (two or more in 4 weeks), symptomatic, and paroxysmal, in whom it was shown to decrease the number of episodes of atrial fibrillation and the frequency of symptoms.[16] However, in a 60-day follow-up, over two thirds of patients had at least one episode of atrial fibrillation,

and 11% experienced adverse cardiac effects.

Class III agents

Class III agents, including sotalol and amiodarone, have also been used to prevent recurrence of atrial fibrillation. Amiodarone in low doses is the most effective agent available for this purpose; in one large study in patients with atrial fibrillation resistant to other drugs, 53% remained in sinus rhythm at 3 years with amiodarone therapy.[44] Outside the United States, amiodarone is frequently a first-line drug for atrial fibrillation.

At the higher doses used for ventricular arrhythmias, amiodarone has multiple toxic effects. Cardiac effects include bradyarrhythmias, hypotension, heart failure, and ventricular proarrhythmia; noncardiac effects include thyroid disease (both hyperthyroidism and hypothyroidism), pulmonary toxicity, hepatic toxicity, corneal deposits, neuropathy, photodermatitis, and skin discoloration.[45] Noncardiac toxic effects appear to be dose-related and may reflect cumulative dose.

In atrial fibrillation, in which lower doses are used but long-term therapy may be required, amiodarone's long-term safety has yet to be determined. At present, amiodarone is best used in patients with severe symptoms of atrial fibrillation that is refractory to other therapy (or who cannot tolerate other agents).

The maze procedure

The "maze" procedure consists of multiple incisions made in a complex pattern throughout the atria, isolating the atrial segments and eliminating the critical mass of atrial tissue needed to sustain atrial fibrillation. Sinus impulses can therefore successfully depolarize the entire atrium, and organized contraction can take place.[46] Initial experience, although limited, has shown the maze procedure highly successful at maintaining sinus rhythm without antiarrhythmic drugs in patients with atrial fibrillation previously refractory to drug therapy.[46,47] Preliminary results suggest that the maze procedure may also be performed percutaneously, via a catheter.

Wolff-Parkinson-White syndrome:

The combination of atrial fibrillation and Wolff-Parkinson-White syndrome, in which an accessory pathway bypasses the AV node, can be life-threatening, since rapid ventricular rates can progress into ventricular fibrillation.[48]

Digoxin and verapamil should be avoided in such patients, as these agents can speed conduction through the bypass tract. Instead, medications such as procainamide that inhibit conduction through the bypass tract and prolong its refractory period should be used for rate control short-term. If the patient is hemodynamically compromised, urgent cardioversion is the most appropriate therapy.

The same types of drugs (ie, the class IA, IC, or III antiarrhythmic agents; *Table 3*) can be used for long-term therapy. Patients with rapid conduction via the bypass tract or with supraventricular tachycardia and Wolff-Parkinson-White syndrome should undergo radiofrequency ablation.

LONG-TERM ANTICOAGULATION THERAPY

In light of recent trials (see summary on page 290), treatment to prevent thromboembolic complications of atrial fibrillation must be individualized.[49] Patients younger than 60 years with lone atrial fibrillation may not require antithrombotic therapy, given their low risk.[12,50–52] Aspirin may suffice for patients younger than 75 years with no SPAF risk factors; however, further long-term trials are needed before this can be formally recommended. Other patients younger than 75 years should receive warfarin if they have no contraindications to it. The target INR is from 2.0 to 3.0.[31]

Treating elderly patients is more difficult, as they have the highest embolic risk from atrial fibrillation and have not been reliably shown to benefit from aspirin.[53,54] Elderly patients may benefit from warfarin, but are at increased risk of associated complications. When warfarin is used in the elderly, the patient and the INR should be followed closely. It has yet to be determined if lower levels of anticoagulation are safer or effective.

REFERENCES

1. **Stroke Prevention in Atrial Fibrillation Investigators.** Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke prevention in atrial fibrillation II Study. Lancet 1994; **343**:687–691.
2. **Coplen SE, Antman EM, Berlin JA, Hewitt HP, Chalmers TC.** Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized control trials. Circulation 1990; **82**:2248–2250.
3. **Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halpern JL, Hart RG.** Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. J Am Coll Cardiol 1992; **20**:527–532.
4. **Kannel WB, Wolf PA.** Epidemiology of atrial fibrillation. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and

management. New York: Raven Press, 1992:81–92.
5. **Kannell WB, Abbott RD, Savage DD, McNamara PM.** Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl J Med 1982; **306**:1018–1022.
6. **Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM.** Prevalence of atrial fibrillation in elderly subjects (the cardiovascular health study). Am J Cardiol 1994; **74**:236–241.
7. **Cobbe S.** Incidence of risks associated with atrial fibrillation. PACE Pacing Clin Electrophysiol 1994; **17**:1005–1010.
8. **Lauer MS, Eagle KA.** Atrial fibrillation following cardiac surgery. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:127–144.
9. **Wolf PA, Abbott RD, Kannel WB.** Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med 1987; **147**:1561–1564.
10. **Repique LJ, Shah SN, Marais GE.** Atrial fibrillation 1992: Management strategies. Chest 1992; **101**:1095–1103.
11. **Petersen P.** Anticoagulation therapy for atrial fibrillation. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:307–320.
12. **The Stroke Prevention in Atrial Fibrillation Investigators.** Predictors of thromboembolism in atrial fibrillation: clinical features in patients at risk. Ann Intern Med 1992; **116**:1–5.
13. **Falk RH.** Control of the ventricular rate in atrial fibrillation. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:255–282.
14. **Stebbins D, Kowey P, Buxton AE.** Contemporary management of atrial fibrillation. Rhythm: contemporary perspectives in arrhythmia. 1994; 6.
15. **Falk RH, Knowlton AA, Bernard S, Gotlieb NE, Battinelli NJ.** Digoxin for converting recent onset atrial fibrillation: a randomized double blind trial. Ann Intern Med 1987; **106**:503–506.
16. **Anderson JL, Gilbert EM, Alpert BL, et al.** Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. Circulation 1989; **80**:1557–1570.
17. **Coumel P.** Neural aspects of paroxysmal atrial fibrillation. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:109–126.
18. **Ellenbogen KA, Dias VC, Plumb VJ, Heywood TJ, Mirvis DM.** A placebo-controlled trial of continuous intravenous diltiazem infusion for 24-hour heart rate control during atrial fibrillation and atrial flutter. A multi-center study. J Am Coll Cardiol 1991; **18**:891–897.
19. **Salerno DM, Dias VC, Kleiger RE, et al.** Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. The diltiazem-atrial fibrillation/flutter study group. Am J Cardiol 1989; **63**:1046–1051.
20. **Roth A, Kaluski E, Felner S, Heller K, Laniado S.** Clonidine for patients with rapid atrial fibrillation. Ann Intern Med 1992; **116**:388–390.
21. **Griffin JC.** Nonpharmacologic therapy of supraventricular tachycardias: an overview. ACC Current Journal Review 1994; **3**:36–38.
22. **Scheinman MM.** The role of atrioventricular junctional ablation for patients with atrial fibrillation. ACC Current Journal Review 1994; **3**:38–39.
23. **Morady F, Calkins H, Langberg JJ, et al.** A prospective randomized comparison of direct current and radiofrequency ablation of the atrioventricular junction. J Am Coll Cardiol 1993; **21**:102–109.
24. **Olgin JE, Scheinman MM.** Comparison of high energy direct current and radiofrequency catheter ablation of the atrioventricular junction. J Am Coll Cardiol 1993; **21**:557–564.
25. **Manolis AS, Wang PJ, Estes NAM III.** Radiofrequency catheter ablation for cardiac tachyarrhythmias. Ann Intern Med 1994; **121**:452–461.
26. **Feld GK.** Catheter ablation versus pharmacologic therapy for atrial fibrillation. ACC Current Journal Review 1994; **3**:39–40.
27. **Wiliamson BD, Man KC, Daoud E, Niebauer M, Strickberger SA, Morady F.** Radiofrequency catheter modification of atrioventricular conduction to control the ventricular rate during atrial fibrillation. N Engl J Med 1994; **331**:910–917.
28. **Fleck RP, Chen PS, Boyce K, Ross R, Dittrich HC, Feld GK.** Radiofrequency modification of atrioventricular conduction by selective ablation of the low posterior septal right atrium in a patient with atrial fibrillation and a rapid ventricular response. PACE Pacing Clin Electrophysiol 1993; **16**:377–381.
29. **Fromer MA.** Indications and limitations of class I drugs in atrial fibrillation. PACE Pacing Clin Electrophysiol 1994; **17**:1016–1018.
30. **Bjerkelund CJ, Orning OM.** The efficacy of anticoagulation therapy in preventing embolization related to D.C. electrical cardioversion of atrial fibrillation. Am J Cardiol 1969; **23**:208–216.
31. **Laupacis A, Albers G, Dunn M, Feinberg W.** Antithrombolic therapy in atrial fibrillation. Third ACCP Consensus Conference on Antithrombotic Therapy. Chest 1992; **Suppl 102**:426S–433S.
32. **Manning WJ, Silverman DI, Gordon SPF, Krumholz HM, Douglas PS.** Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombus. N Engl J Med 1993; **328**:750–755.
33. **Manning WJ, Leeman DE, Gotch PJ, Come PC.** Pulsed doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. J Am Coll Cardiol 1989; **13**:617–623.
34. **Black IW, Fatkin D, Sagar KB, et al.** Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. A multicenter study. Circulation 1994; **84**:2509–2513.
35. **Grimm RA, Stewart WJ, Black IW, Thomas JD, Klein AL.** Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation? J Am Coll Cardiol 1994; **23**:533–541.
36. **Grim RA, Stewart WJ, Maloney JD, Cohen GI, Salcedo EE, Klein AL.** Impact of electrical cardioversion of atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterized by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993; **22**:1356–1366.
37. **Fuchs T, Podrid PJ.** Pharmacologic therapy for reversion of atrial fibrillation and maintenance of sinus rhythm. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:233–254.
38. **Honloser SH.** Indications and limitations of class II and III antiarrhythmic drugs in atrial fibrillation. PACE Pacing Clin Electrophysiol 1994; **17**:1019–1025.
39. **Suttorp MJ, Kingma JH, Koomen EM, Van't Hof A, Tijssen JGP, Lie KI.** Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal LV function. J Am Coll Cardiol 1993; **71**:710–713.
40. **Dittrich HC, Erickson JS, Schneiderman BS, Blacky AR, Savides T, Nicod PH.** Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. Am J Cardiol 1989; **63**:193–197.
41. **Ewy GA.** Optimal technique for electrical cardioversion of atrial fibrillation. Circulation 1992; **86**:1645–1647.
42. **Falk RH.** Proarrhythmia in patients treated for atrial fibrillation or flutter. Ann Intern Med 1992; **117**:141–150.
43. **Echt DS, Liebson PR, Mitchell LB, et al.** Mortality and morbidity in patients receiving encainide, flecainide, or placebo. N Engl J Med 1991; **324**:781–788.
44. **Gosselink ATM, Crijns HJGM, VanGelder IC, Hillige H, Wiesfeld ACP, Lie KI.** Low dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. JAMA 1992; **267**:3289–3293.
45. **Estes NAM III.** Evolving strategies for the management of atrial fibrillation: the role of amiodarone. JAMA 1992; **267**:3332–3333.
46. **Cox JL, Schuessler RB, D'Agostino HJ Jr, et al.** The surgical treatment of atrial fibrillation. III. Development of a definitive surgical treatment. J Thorac Cardiovasc Surg 1991; **101**:569–583.

47. **McCarthy PM, Castle LW, Maloney JD, et al.** Initial experience with the More procedure for atrial fibrillation. J Thorac Cardiovasc Surg 1993; **105:**1077–1087.
48. **Wellens HJJ, Smeets JLRM, Rodriquez LM, Gorgels APM.** Atrial fibrillation in Wolff-Parksinson-White Syndrome. In: Falk RH, Podrid PT, eds. Atrial fibrillation: mechanisms and management. New York: Raven Press, 1992:333–344.
49. **Albers GW.** Atrial fibrillation and stroke: three new studies, three remaining questions. Arch Intern Med 1994; **154:**1443–1448.
50. **The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators.** The effect of low-dose warfarin on the risk of stroke in patients with atrial fibrillation. N Engl J Med 1990; **323:**1505–1511.
51. **Ezekowitz MD, Bridgers SL, James K, et al.** Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992; **327:**1406–1412.
52. **Kopecky SL, Gersh BJ, McGoon MD, et al.** The natural history of lone atrial fibrillation: a population-based study over three decades. N Engl J Med 1987; **317:**669–674.
53. **Hirsh J.** Oral anticoagulation drugs. N Engl J Med 1991; **324:**1865–1875.
54. **SPAF investigators.** Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. N Engl J Med 1990; **322:**863–868.