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ACC/AHA/ESC PRACTICE GUIDELINES—FULL TEXT

ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation)

Developed in Collaboration With the North American Society of Pacing and Electrophysiology

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This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org), the American Heart Association (www.americanheart.org), the European Society of Cardiology (www.escardio.org), and the North American Society of Pacing and Electrophysiology (www.naspe.org). Single reprints of this document (the complete Guidelines) to be published in the mid-October issue of the European Heart Journal are available by calling +44.207.424.4200 or +44.207.424.4389, faxing +44.207.424.4433, or writing Harcourt Publishers Ltd, European Heart Journal, ESC Guidelines – Reprints, 32 Jamestown Road, London, NW1 7BY, United Kingdom. Single reprints of the shorter version (Executive Summary and Summary of Recommendations) published in the October issue of the Journal of the American College of Cardiology and the October issue of Circulation, are available for $5.00 each by calling 800-253-4636 (US only) or by writing the Resource Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814. To purchase bulk reprints specify version and reprint number (Executive Summary 71-0208; full text 71-0209) up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342; or E-mail: pubauth@heart.org.

*Former Task Force Member during this writing effort.

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PREAMBLE

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the management or prevention of disease states. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and affect the overall cost of care favorably by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. The Task Force is pleased to have this guideline co-sponsored by the European Society of Cardiology (ESC). This is the first such joint effort. The Task Force wishes to acknowledge the important contributions of Jean-Pierre L. Bassand, MD, FESC, the previous chair of the ESC Scientific and Clinical Initiatives Committee, who helped initiate this joint effort. Experts in the subject under consideration have been selected from all 3 organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as well as frequency of follow-up and cost-effectiveness.

The ACC/AHA Task Force on Practice Guidelines and the ESC make every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reported orally to all members of the writing panel at the first meeting and updated as changes occur.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The physician and patient must make the ultimate judgment regarding care of a particular patient in light of general information and specific circumstances.

The executive summary and recommendations are published in the October issue of the *Journal of the American College of Cardiology* and the October 23 issue of *Circulation*. The full text of these guidelines is published in the mid-October issue of the *European Heart Journal*. Reprints of the full text guidelines are available from the ESC; single reprints of the executive summary are available from the ACC; bulk reprints of the full text and executive summary are available from the AHA. These guidelines are available on the ACC, AHA, ESC and NASPE World Wide Web sites. The guidelines have been officially endorsed by the North American Society of Pacing and Electrophysiology.

Raymond J. Gibbons, MD, FACC
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I. INTRODUCTION

A. Organization of Committee and Evidence Review

Atrial fibrillation (AF) is the most common sustained rhythm disturbance. Its prevalence is increasing along with the age of the population. AF is often associated with structural heart disease, but a substantial proportion of patients with AF have no detectable heart disease. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and cost. Accordingly, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) created a committee to establish guidelines for better management of this frequent and complex arrhythmia.

The committee was composed of 8 members representing the ACC and AHA, 4 members representing the ESC, 1 member from the North American Society of Pacing and Electrophysiology (NASPE), and a representative of the Johns Hopkins University Evidence-Based Practice Center representing the Agency for Healthcare Research and Quality's report on Atrial Fibrillation in the Elderly. This document was reviewed by 3 reviewers nominated by the ACC, 3 nominated by the AHA, and 3 nominated by the ESC, as well as by the ACC Clinical Electrophysiology

Committee, the AHA ECG and Arrhythmia Committee, NASPE, and 25 additional reviewers nominated by the writing committee. The document was approved for publication by the governing bodies of the ACC, AHA, and ESC and officially endorsed by NASPE. These guidelines will be reviewed annually by the task force and will be considered current unless the task force revises or withdraws them from distribution.

The ACC/AHA/ESC Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation conducted a comprehensive review of the relevant literature from 1980 to June 2000. Literature searches were conducted in the following databases: PubMed/Medline, EMBASE, the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry), and Best Evidence. Searches were limited to English language sources and to human subjects. Major search terms included atrial fibrillation, aged, atrial remodeling, atrioventricular conduction, atrioventricular node, cardioversion, classification, clinical trial, complications, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, heart failure (HF), hemodynamics, human, hyperthyroidism, hypothyroidism, meta-analysis, myocardial infarction, nomenclature, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, risks, sinus rhythm, symptoms, and tachycardia-mediated cardiomyopathy.

Recommendations are evidence based and derived primarily from published data. The weight of evidence was ranked highest (A) when the data were derived from multiple randomized clinical trials and intermediate (B) when based on a limited number of randomized trials, nonrandomized studies, or observational registries. The lowest rank (C) was given when the primary basis for the recommendation was expert consensus.

Recommendations follow the format of previous ACC/AHA guidelines for classifying indications, summarizing both the evidence and expert opinion:

Class I:

Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Class II:

Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa:

The weight of evidence or opinion is in favor of the procedure or treatment.

Class IIb:

Usefulness/efficacy is less well established by evidence or opinion.

Class III:

Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

B. Contents of These Guidelines

These guidelines first present a comprehensive review of the latest information about the definition, classification, epidemiology, mechanisms, and clinical characteristics of AF. The management of this complex and potentially dangerous arrhythmia is then reviewed. This includes conversion to and maintenance of sinus rhythm, control of heart rate, and prevention of thromboembolism. The treatment algorithms include pharmacological and nonpharmacological antiarrhythmic approaches, as well as antithrombotic strategies thought to be most appropriate for each particular patient's condition. Overall, this is a consensus document that attempts to reconcile evidence and opinion from both sides of the Atlantic Ocean. The pharmacological and nonpharmacological antiarrhythmic approaches discussed may include some drugs and devices that do not have the approval of governmental regulatory agencies. Additional information may be obtained from the package inserts.

Because atrial flutter can precede or coexist with AF, special consideration is given in each of these sections to this arrhythmia. There are important differences in the mechanisms of AF and atrial flutter, and the body of evidence available to support therapeutic recommendations is distinct for the 2 arrhythmias. Atrial flutter is not addressed comprehensively in these guidelines but will be addressed in the upcoming ACC/AHA/ESC Guidelines on the Management of Patients With Supraventricular Arrhythmias.

II. DEFINITION

A. Atrial Fibrillation

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is described by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact (1). The ventricular response to AF depends on electrophysiological properties of the AV node, the level of vagal and sympathetic tone, and the action of drugs (2) (Fig. 1). Regular RR intervals are possible in the presence of AV block or interference due to ventricular or junctional tachycardia. In patients with electronic pacemakers, diagnosis of AF may require temporary inhibition of the pacemaker to expose atrial fibrillatory activity (3). A rapid, irregular, sustained, wide-QRS-complex tachycardia strongly suggests AF with conduction over an accessory pathway or AF with underlying bundle-branch block. Extremely rapid rates (over 200 bpm) suggest the presence of an accessory pathway.

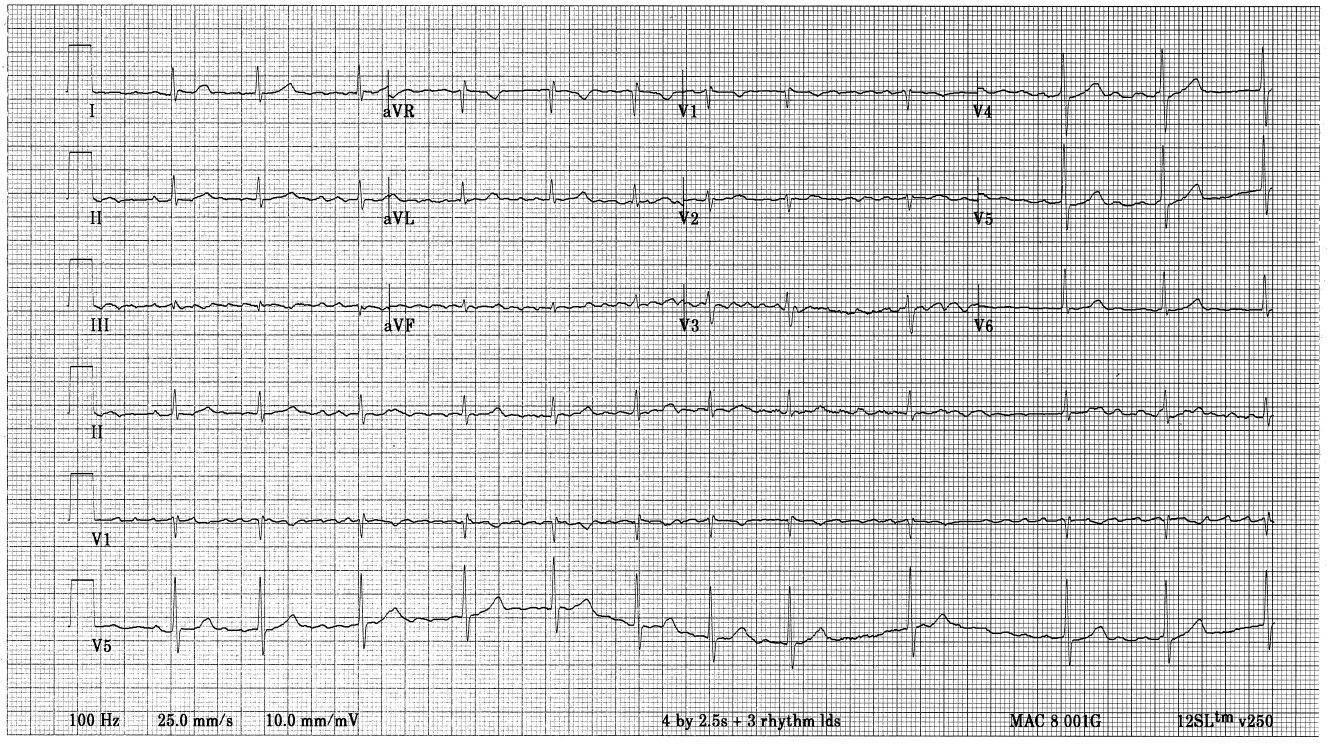

Figure 1. Standard 12-lead surface electrocardiogram showing atrial fibrillation with a controlled rate of ventricular response.

B. Related Arrhythmias

Atrial fibrillation may occur in isolation or in association with other arrhythmias, most commonly atrial flutter or atrial tachycardia. Atrial flutter may arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF. Atrial flutter is a more organized arrhythmia than AF and is characterized by a saw-tooth pattern of regular atrial activation called flutter (f) waves on the ECG, particularly visible in leads II, III, and aVF, without an isoelectric baseline between deflections (Fig. 2). In the untreated state, the atrial rate typically ranges from 240 to 320 beats per minute, with f waves inverted in ECG leads II, III, and aVF and upright in lead V_1. The wave of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and inverted in lead V_1. Atrial flutter commonly occurs with 2:1 AV block, resulting in a ventricular rate of 120 to 160 beats per minute, most characteristically about 150 beats per minute. Several types of atrial flutter have been distinguished, but no consistent nomenclature has been widely accepted. Atrial flutter may degenerate into AF, AF may initiate atrial flutter, or the ECG pattern may alternate between atrial flutter and AF, reflecting changing activation of the atria.

Other atrial tachycardias, AV reentrant tachycardias, and AV nodal reentrant tachycardias may also trigger AF. In other atrial tachycardias, P waves are readily identified and separated by an isoelectric baseline in 1 or more ECG leads. The morphology of the P waves may help localize the origin of the tachycardias. A unique type of atrial tachycardia has recently been identified that commonly originates in the pulmonary veins but may arise elsewhere (4), is rapid (typically faster than 250 beats per minute), and often degenerates into AF. Electrophysiological studies with intracardiac mapping may help differentiate the various types of atrial arrhythmias and elucidate their mechanisms.

III. CLASSIFICATION

Atrial fibrillation has a heterogeneous clinical presentation, occurring in the presence or absence of detectable heart disease or related symptoms. Various classification systems have been proposed for AF. One scheme is based on the ECG presentation (1–3). Another is based on epicardial (5) or endocavitary recordings or noncontact mapping of atrial electrical activity. Several clinical classification schemes have also been proposed, but none fully accounts for all aspects of AF (6–9). To be clinically useful, a classification system must be based on a sufficient number of features and carry specific therapeutic implications.

An episode of AF may be self-limited or require medical intervention for termination. Over time, the pattern of AF may be defined in terms of the number of episodes, duration, frequency, mode of onset and possible triggers, and response to therapy, but these features may be impossible to discern when AF is first encountered in an individual patient. Although the pattern of the arrhythmia can change over time, it may be of clinical value to characterize the arrhythmia at a given moment.

Assorted labels have been used to describe the pattern of AF, including acute, chronic, paroxysmal, intermittent, constant, persistent, and permanent, but the vagaries of

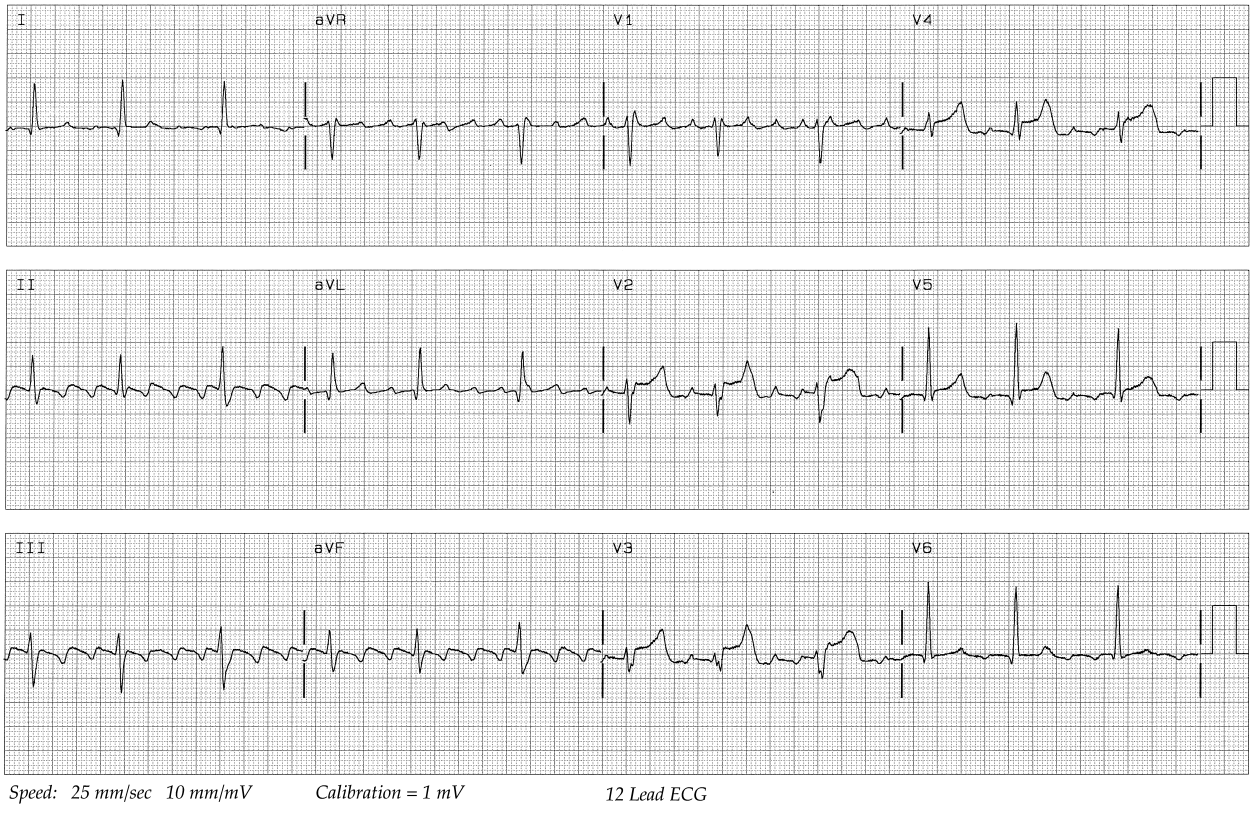

Figure 2. Standard 12-lead surface electrocardiogram showing typical atrial flutter with variable atrioventricular conduction. The recording chart speed and deflection sensitivity are the same as for Fig. 1.

definitions make it difficult to compare studies of AF in terms of the effectiveness of therapeutic strategies based on these designations. The classification scheme recommended in this document represents a consensus driven by a desire for simplicity and clinical relevance.

The clinician should distinguish a first-detected episode of AF, whether or not it is symptomatic or self-limited, recognizing that there may be uncertainty about the duration of the episode and about previous undetected episodes (Fig. 3). When a patient has had 2 or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained, AF is designated persistent. In the latter case, termination with pharmacological therapy or electrical cardioversion does not change the designation. Persistent AF may be either the first presentation of the arrhythmia or the

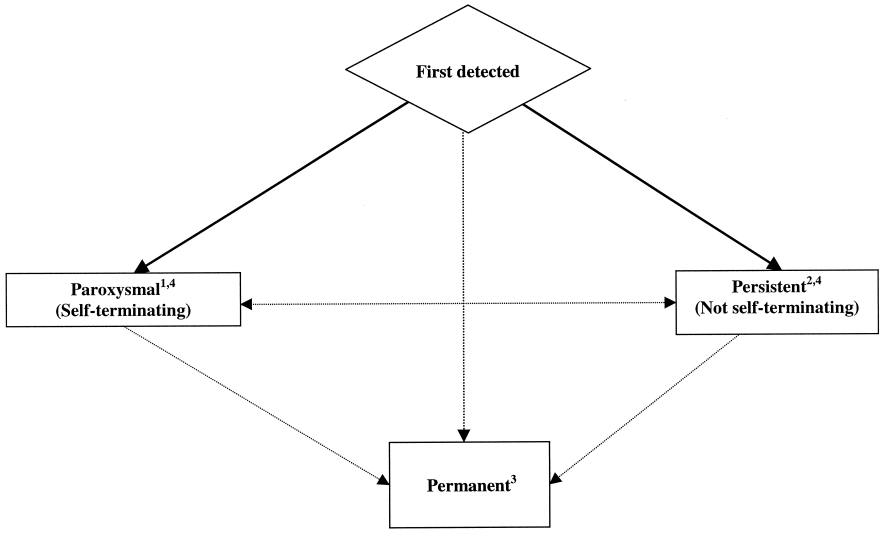

Figure 3. Patterns of atrial fibrillation. 1, episodes that generally last less than or equal to 7 days (most less than 24 h); 2, usually more than 7 days; 3, cardioversion failed or not attempted; and 4, either paroxysmal or persistent AF may be recurrent.

culmination of recurrent episodes of paroxysmal AF. The category of persistent AF also includes cases of long-standing AF (e.g., greater than 1 year) in which cardioversion has not been indicated or attempted, usually leading to permanent AF (Fig. 3).

The terminology defined in the preceding paragraph applies to episodes of AF that lasts more than 30 seconds and that are unrelated to a reversible cause. Secondary AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or acute pulmonary disease is considered separately, because AF is less likely to recur once the precipitating condition is resolved. In these settings, AF is not the primary problem, and treatment of the underlying disorder concurrently with management of the episode of AF usually results in termination of the arrhythmia without recurrence.

The term "lone AF" has been variously defined but generally applies to young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiopulmonary disease (10). These patients have a favorable prognosis with respect to thromboembolism and mortality. As time goes by, however, patients move out of the lone AF category by virtue of aging or the development of cardiac abnormalities such as enlargement of the left atrium (LA), and the risks of thromboembolism and mortality rise accordingly. Lone AF is distinguished from other forms of idiopathic AF because of the criteria of patient age and the absence of identified cardiovascular pathology. By convention, the term nonvalvular AF is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease or a prosthetic heart valve.

IV. EPIDEMIOLOGY AND PROGNOSIS

Atrial fibrillation is the most common arrhythmia encountered in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbance. It has been estimated that 2.2 million Americans have paroxysmal or persistent AF (11). Most of the data regarding the epidemiology, prognosis, and quality of life in AF have been obtained in North America and western Europe.

A. Prevalence

The prevalence of AF is estimated at 0.4% of the general population, increasing with age (12). Cross-sectional studies have found the prevalence to be less than 1% in those under 60 years of age and greater than 6% in those over 80 years (13–15) (Fig. 4). The age-adjusted prevalence is higher in men (15,16). Based on limited data, the age-adjusted risk of developing AF in blacks appears to be less than half that in whites (17,18).

In population-based studies, the frequency of AF in patients with no history of cardiopulmonary disease (lone AF) was less than 12% of all cases of AF (Fig. 5) (10,15,19,20). In some series, however, the observed frequency of lone AF

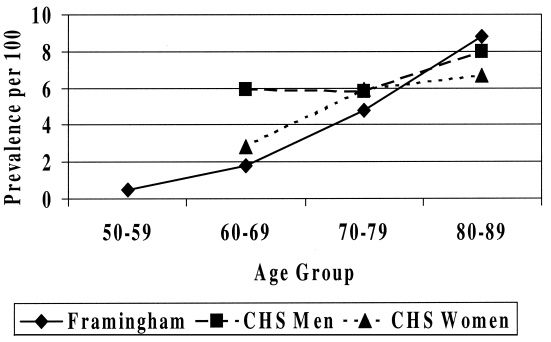

Figure 4. Prevalence of AF in 2 American epidemiological studies. Framingham indicates the Framingham Heart Study (14), CHS, Cardiovascular Health Study (15).

was over 30% (21,22). AF is prevalent in patients with congestive HF or valvular heart disease and increases in prevalence with the severity of these conditions (Table 1).

B. Incidence

In prospective studies, the incidence of AF increased from less than 0.1% per year in those under 40 years of age to greater than 1.5% per year in women over 80 years of age and greater than 2% per year in men over 80 years of age (17,23,24) (Fig. 6). The age-adjusted incidence increased over a 30-year period in the Framingham Study (23), and this may have implications for the future impact of AF on the population. During 38 years of follow-up in the Framingham Study, 20.6% of men who developed AF had congestive HF at inclusion vs. 3.2% of those without AF; the corresponding incidences in women were 26.0% and 2.9% (25). In patients referred for treatment of HF, the 2- to 3-year incidence of AF was 5% to 10% (17,26,27). The incidence of AF may be lower in HF patients treated with angiotensin converting enzyme inhibitors (28).

C. Prognosis

The rate of ischemic stroke among patients with nonrheumatic AF averages 5% per year, which is between 2 and 7 times that of people without AF (13,14,21,23,24,28) (Fig. 7). One of every 6 strokes occurs in patients with AF (29). Additionally, when transient ischemic attacks and clinically occult "silent" strokes detected radiographically are considered, the rate of brain ischemia accompanying nonvalvular AF exceeds 7% per year (25,30–33). In patients with rheumatic heart disease and AF, stroke risk was increased 17-fold compared with age-matched controls in the Framingham Heart Study (34), and attributable risk was 5 times greater than in those with nonrheumatic AF (14). Atrial fibrillation doubled the risk of stroke in the Manitoba Follow-up Study independently of other risk factors (24), and the relative risks for stroke in nonrheumatic AF were 6.9% and 2.3% in the Whitehall and the Regional Heart studies, respectively. Among AF patients from general practices in France, the ALFA Study (Etude en Activité

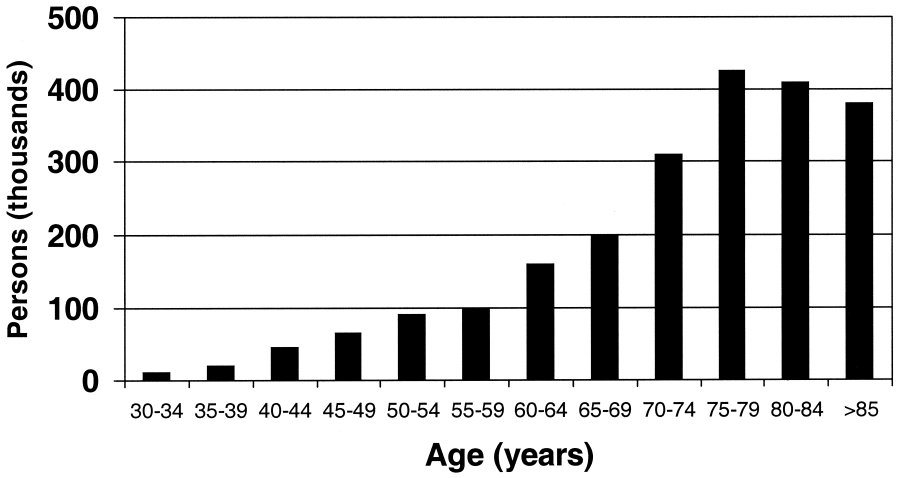

Figure 5. Estimated prevalence of AF in relation to age in the United States, based on 4 population-based surveys. The median age of AF patients is about 75 years. Approximately 70% are between 65 and 85 years old. The overall number of men and women with AF is about equal, but approximately 60% of AF patients over age 75 years are female prevalence, age, distribution, and gender of patients with atrial fibrillation analysis and implications. Vol. 155, pp. 469–73, © 1995 American Medical Association (37).

Liberale sur le Fibrillation Auriculaire) found a 2.4% incidence of thromboembolism over a mean of 8.6 months of follow-up (21). The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF increased from 1.5% in participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years (14).

The mortality rate of patients with AF is about double that of patients in normal sinus rhythm and is linked with the severity of underlying heart disease (13,16,24) (Fig. 7). About two thirds of the 3.7% mortality over 8.6 months in the ALFA study was attributed to cardiovascular causes (21). In patients with mild to moderate HF, however, the data are mixed. The V-HeFT studies (Veterans Administration Heart Failure Trials) did not find increased mortality among patients with concomitant AF (35), whereas in the SOLVD trial (Studies of Left Ventricular Dysfunction), mortality was 34% for those with AF vs. 23% for patients in sinus rhythm (p less than 0.001) (36). The difference was attributed mainly to an increased number of deaths due to HF rather than to thromboembolism.

Table 1. Prevalence of Atrial Fibrillation in Patients With Heart Failure

Predominant NYHA Type	Prevalence of AF, %	Study, y
I	4	SOLVD-prevention (1992)
II–III	10–26	SOLVD-treatment (1991)
		CHF-STAT (1995)
		MERIT-HF (1999)
		Diamond (1999)
III–IV	20–29	Middlekauff (1991)
		Stevenson (1996)
		GESICA (1994)
IV	50	CONSENSUS (1987)

NYHA, New York Heart Association; AF indicates atrial fibrillation; SOLVD, Studies of Left Ventricular Dysfunction; CHF-STAT, Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; GESICA, Grupo Estudio de la Sobrevida en la Insufficienca Cardiaca en Argentina (V); and CONSENSUS, Co-operative North Scandinavian Enalapril Survival Study.

V. PATHOPHYSIOLOGICAL MECHANISMS

A. Atrial Factors

1. Pathology of the Atrium in Patients With AF. Patients with persistent AF predominate in most pathological studies, and only limited information is available about anatomic changes associated with paroxysmal AF. The atria of patients with AF display structural abnormalities beyond the changes caused by underlying heart disease (38). Histological examination has shown patchy fibrosis with juxtaposition of normal and diseased atrial fibers, which may account for nonhomogeneity of atrial refractoriness (39,40). Fibrosis or fatty infiltration may also affect the sinus node and may be a reaction to inflammatory or degenerative processes that are difficult to detect. The role of inflammation in the pathogenesis of AF has not yet been evaluated, but histological changes consistent with myocarditis were reported in 66% of atrial biopsy specimens from patients with lone AF (40). Infiltration of the atrial myocardium may occur in amyloidosis, sarcoidosis, and hemochromatosis.

Atrial fiber hypertrophy has been described as a major

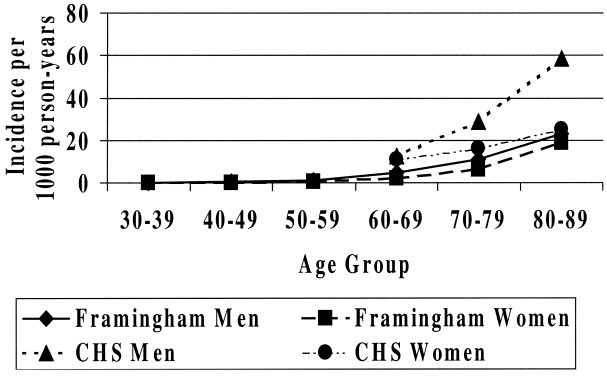

Figure 6. Incidence of atrial fibrillation in 2 American epidemiological studies. Framingham indicates the Framingham Heart Study (23), and CHS indicates Cardiovascular Health Study (17).

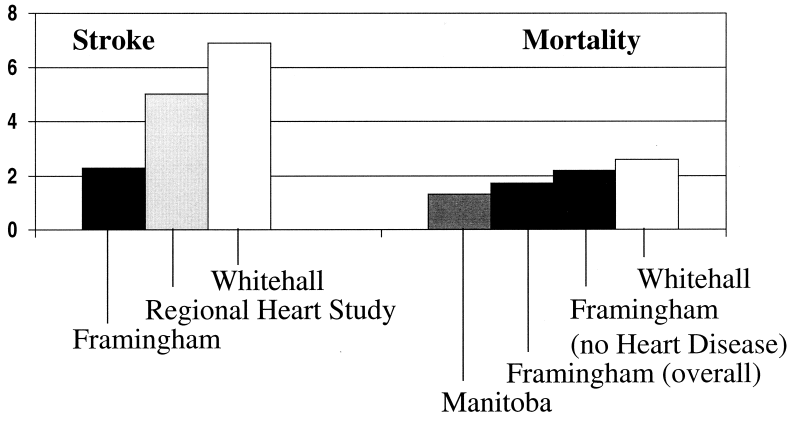

Figure 7. Relative risk of stroke and mortality in patients with AF compared with patients without AF. Source data from the Framingham Heart Study (16), Regional Heart Study (13), Whitehall study (13), and Manitoba study (24).

feature or sometimes the sole histological change in AF patients (39). Atrial hypertrophy and dilatation may be either a cause or a consequence of persistent AF, because progressive atrial enlargement has been demonstrated echocardiographically in patients with AF (41). A recent experimental study showed that HF facilitates the induction of sustained AF, mediated by extensive interstitial fibrosis (42). In most patients, however, it is not possible to identify the underlying anatomic process responsible for the arrhythmia. A role for autoimmune mechanisms in genetically predisposed patients has been suggested by high serum levels of antibodies against myosin heavy chains in patients with paroxysmal AF without identified heart disease (43). This is of particular interest because the prevalence of heart disease is generally lower in patients with paroxysmal AF than in those with permanent AF.

2. Mechanisms of AF. Theories of the mechanism of AF involve 2 main processes: enhanced automaticity in 1 or several rapidly depolarizing foci and reentry involving 1 or more circuits (44,45) (Fig. 8). A focal origin of AF is supported by experimental models of aconitine-induced and pacing-induced AF (46,47) in which the arrhythmia persisted only in isolated regions of atrial myocardium. Rapidly firing atrial foci, located most often in the superior pulmonary veins, may initiate AF in susceptible patients (4,48). Patients may have more than 1 pulmonary vein focus capable of engendering AF (48); foci also occur in the RA and infrequently in the superior vena cava or coronary sinus (4,48,49). Histological studies have demonstrated cardiac muscle with preserved electrical properties extending into the pulmonary veins (50–55). Whether this represents a particular form of AF or a triggering arrhythmia is not clear, nor has the importance of this mechanism of induction among various subsets of AF patients been evaluated sufficiently. The focal origin appears to be more important in patients with paroxysmal AF than in those with persistent AF, and ablation of such foci may be curative (4) (see Section VIII-E-7, Nonpharmacological Correction of AF).

The multiple-wavelet hypothesis as the mechanism of reentrant AF was advanced by Moe and colleagues (44,56), who proposed that fractionation of the wave fronts as they propagate through the atria results in self-perpetuating "daughter wavelets." The number of wavelets present at any time depends on the refractory period, mass, and conduction velocity in different parts of the atria. A large atrial mass with a short refractory period and delayed conduction may

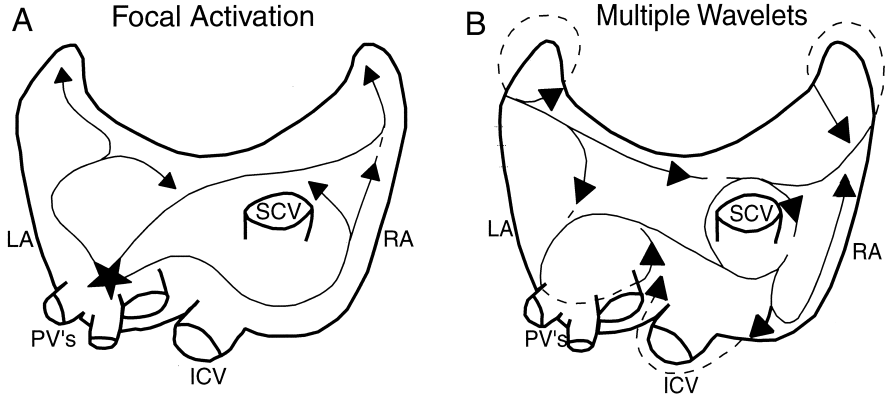

Figure 8. Principal electrophysiological mechanisms of atrial fibrillation. **A**, Focal activation. The initiating focus (indicated by the asterisk) often lies within the region of the pulmonary veins. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. **B**, Multiple-wavelet reentry. Wavelets (indicated by arrows) randomly reenter tissue previously activated by them or by another wavelet. The routes the wavelets travel vary. LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium. Reproduced with permission from Konings KTS (64).

Table 2. Anatomic and Electrophysiological Factors Promoting the Initiation and/or Maintenance of AF

Anatomic Factors	Electrophysiological Factors
Ion channel expression	Shortened atrial effective refractory periods
Altered gap junction distribution	Atrial myocyte calcium overload
Altered sympathetic innervation	Atrial myocyte triggered activity or automaticity
Atrial dilatation	Decreased atrial conduction velocity
Pulmonary vein dilatation	Nonhomogeneity of atrial refractoriness
Atrial myocyte apoptosis	Dispersion of conduction
Interstitial fibrosis	Supersensitivity to catecholamines and acetylcholine

harbor an increased number of wavelets, favoring sustained AF. Simultaneous recordings from multiple electrodes have confirmed the multiple-wavelet hypothesis in canine atria (45,57), and similar observations have been reported in humans (58,59).

Although the patterns of activation underlying the irregular atrial electrical activity of AF have traditionally been described as disorganized or random, recent evidence has emerged that AF is spatially organized. High-resolution video imaging, ECG recordings, and spectral analysis during propagation of AF in sheep hearts identified sequential wave fronts with temporal periodicity and spatial patterns of propagation that appear to arise from reentry in anatomically or functionally determined circuits (60). Unlike other arrhythmias, in which a single reentrant circuit is typically identified, AF may involve several circuits (5,61). The length of the path through which the depolarization wave front must travel, as well as its conduction velocity and refractoriness, is influenced by atrial enlargement, which may favor the development of AF. On the basis of mapping studies of patients undergoing surgery for the Wolff-Parkinson-White (WPW) syndrome, 3 patterns of induced AF have been identified (5). Type I AF involves single wave fronts propagating across the RA. Type II AF involves 1 or 2 wave fronts, and type III AF is characterized by multiple activation wavelets propagating in different directions. Anisotropy related to the orientation of atrial fibers and pectinate muscles within the atria has been investigated by video imaging and mapping (62), with observations of heterogeneous breakthrough patterns over the epicardium, wave collisions, and incomplete reentry. Evolving nonfluoroscopic 3-dimensional electroanatomic recording systems are expected to provide additional information about the mechanisms engendering AF that will allow more precise characterization of its electrophysiological origins (63) (Table 2). Ultimately, a better understanding of the diverse electrophysiological mechanisms responsible for the genesis and maintenance of AF will lead to the development of effective preventive measures.

A. ATRIAL ELECTRICAL REMODELING. Pharmacological or electrical cardioversion of AF has a higher success rate when AF has been present for less than 24 h (65), whereas a longer duration of AF reduces the likelihood of restoring and maintaining sinus rhythm. These observations gave rise to the adage that "atrial fibrillation begets atrial fibrillation." This notion (that atrial fibrillation tends to perpetuate itself) has recently found experimental support in a goat model using an automatic atrial fibrillator that detected spontaneous termination of induced AF and reinduced the dysrhythmia by delivering a burst of electrical stimuli (66). Initially, electrically induced AF terminated spontaneously. After repeated inductions, however, the episodes became progressively more sustained until AF persisted at a more rapid atrial rate (66). The increasing propensity to AF was related to progressive shortening of effective refractory periods with increasing episode duration, a phenomenon known as electrophysiological remodeling. These measurements support clinical observations (67) that the atrial effective refractory period in patients with paroxysmal AF is short and that refractoriness fails to adapt to rate, particularly during bradycardia. Further confirmation has come from recordings of action potentials in isolated tissue from fibrillating atria and in patients after cardioversion (68). The duration of atrial monophasic action potentials in AF patients was shorter after cardioversion and was correlated with instability of the sinus mechanism (69). Decreased inward current through L-type calcium channels probably plays an important role in action potential shortening (70).

Electrophysiological remodeling that takes place in the atria within the first 24 h after the onset of AF involves shortening of the effective atrial refractory periods. Restoration of electrical refractoriness by prompt cardioversion of AF might explain the higher success rate of early intervention (66). Calcium channel blockade may inhibit the atrial remodeling that occurs during AF (71–73). Prolonged periods of AF may also disturb atrial contractile function, and recovery of atrial mechanical function may depend on the duration of AF. After a long period of persistent AF, recovery of atrial contraction can be delayed for days or even weeks after sinus rhythm has been restored. This has important implications for the duration of anticoagulation after cardioversion. (See Section VIII-G, Preventing Thromboembolism.) Electrophysiological studies in dogs and preliminary human data suggest that prolonged AF may lengthen sinus node recovery time (74,75). The implication is that in some patients with the tachycardia-bradycardia syndrome, AF may be partly responsible for sinus node dysfunction.

B. OTHER ELECTROPHYSIOLOGICAL FACTORS. Other factors involved in the induction or maintenance of AF include premature beats, autonomic nervous system activity, atrial ischemia (76), atrial stretch (77), anisotropic conduction (78), and aging. In animal experiments, induction of AF increases oxygen consumption in atrial myocardium (76). In human studies (79,80), refractory periods and conduction velocities are not homogeneous in AF patients, and disper-

sion of refractoriness has been linked to the inducibility and persistence of AF (70). Slowing of conduction is also involved in dispersion of atrial refractoriness, particularly in structurally diseased hearts (80), and interruption of sympathetic and parasympathetic fibers increases the sensitivity of atrial tissue to catecholamines and acetylcholine (77).

A critical mass of atrial tissue appears necessary to sustain AF. This may account for the effectiveness of the maze operation (58,81,82) and of catheter ablation of atrial myocardium with linear lesions. Both methods reduce the mass of contiguous atrial tissue to a point that inhibits sustained AF. Once it is initiated, maintenance of AF may involve specific requirements for the size of the atria and the distance between depolarization wave fronts. When the wavelength (45) exceeds the length of the path, the dysrhythmia stops. For an electrical impulse to propagate around an area of block, conduction must be slow enough to allow the fibers ahead to recover excitability. A short refractory period or slow conduction shortens the excitation wavelength and thus sustains reentry.

Atrial fibrillation may result from increased vagal tone, which leads to episodes during sleep or after meals, most often in patients without organic heart disease. In dog models, vagal denervation of the atria prevents induction of AF (83). In contrast, exercise, emotion, surgical stress, or infusion of isoproterenol may provoke catecholamine-induced AF. One or the other of these mechanisms may predominate in a given patient, but the mode of initiation of AF may vary over time, which makes it difficult to distinguish one type from another based on the history of a single episode. The role of the autonomic nervous system in AF patients has been examined with measurements of heart rate variability, which revealed features of vagal or adrenergic predominance (84).

Even when other factors are involved in AF, premature beats are important initiating events in most cases (4,85,86). Just as rapid ventricular tachycardia may degenerate into ventricular fibrillation, other types of supraventricular tachycardia may degenerate into AF (tachycardia-induced tachycardia) (87). It is important to recognize this mechanism of AF induction, because elimination of the initiating arrhythmia may abolish AF. AV node reentry and AV reentry are examples of arrhythmias that cause AF and are often easily cured by radiofrequency catheter ablation (88–90).

B. AV Conduction

1. General Aspects. In the absence of an accessory pathway or His-Purkinje dysfunction, the AV node limits conduction during AF (90). There appear to be 2 distinct atrial inputs to the AV node, one directed posteriorly via the crista terminalis and the other anteriorly via the interatrial septum. Studies on rabbit AV nodal preparations showed that during AF, propagation of impulses through the AV node to the His bundle depended in part on the relative timing of the anterior and posterior septal activation inputs to the AV node (91). Other factors affecting conduction through the AV node are its intrinsic refractoriness, concealed conduction, and autonomic tone. Concealed conduction, which occurs when atrial impulses traverse part of the AV node but do not conduct to the ventricle, plays a prominent role in determining the ventricular response during AF (56,92,93). These impulses alter AV nodal refractoriness, slowing or blocking subsequent atrial impulses. Moe and colleagues (56) explained that the irregularity of ventricular response during AF was caused in part by concealed AV nodal conduction. When the atrial rate during AF is relatively slow, the ventricular rate tends to increase. Alternatively, an increased atrial rate is associated with a slower ventricular rate.

AV nodal conduction is also affected by autonomic tone (92,94,95). Increased parasympathetic and decreased sympathetic tone exert negative dromotropic effects on AV nodal conduction; the opposite is true in states of decreased parasympathetic and increased sympathetic tone. Vagal tone also enhances the negative dromotropic effects of concealed conduction in the AV node (94,95). Fluctuations in autonomic tone can produce disparate ventricular responses to AF in a given patient. For example, a patient may exhibit slow ventricular rates during sleep but an accelerated ventricular response during exercise. Digitalis, which slows ventricular rate during AF predominantly by increasing vagal tone, may control heart rate at rest but is much less effective during activity. These wide swings in rate due to variations in autonomic tone often create therapeutic challenges.

The conducted QRS complexes during AF are narrow unless there is fixed or rate-related bundle-branch block or an accessory pathway (see below). Aberrant conduction occurs commonly during AF, facilitated by the irregularity of the ventricular response. This often results in a long interval followed by a relatively short interval, with the QRS complex that closes the short interval aberrantly conducted (Ashman phenomenon) (96).

2. AV Conduction in the WPW Syndrome. Accessory pathways are muscle connections between the atrium and ventricle that have the capacity to conduct rapidly in many individuals. Unlike conduction through the AV node, conduction over an accessory pathway during AF can result in a very rapid ventricular response that may be fatal (2,97). Concealed conduction over accessory pathways (98) likely plays a lesser role than the AV node to limit the ventricular response. Whereas a substantial increase in sympathetic tone may increase the preexcited ventricular response, alterations in vagal tone appear to have little effect on conduction over accessory pathways.

Transition of AV reentry into AF in patients with the WPW syndrome can produce a rapid ventricular response that degenerates into ventricular fibrillation leading to sudden cardiac death (97,99). Drugs such as digitalis, calcium channel antagonists, and beta-blockers, which are usually given to slow conduction across the AV node during AF, do not block conduction over the accessory pathway

and may even enhance conduction, resulting in hypotension or cardiac arrest (100). During AF with intermittent conduction over an accessory pathway, drugs such as calcium channel blockers that impair conduction predominantly through the AV node may result in an accelerated preexcited ventricular response because of the loss of concealed retrograde conduction into the accessory pathway.

C. Myocardial and Hemodynamic Consequences of AF

During AF, 3 factors can affect hemodynamic function: loss of synchronous atrial mechanical activity, irregularity of ventricular response, and inappropriately rapid heart rate. A marked decrease in cardiac output may occur with the loss of atrial contraction, especially in patients with impaired diastolic ventricular filling, hypertension, mitral stenosis, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy. The variation in RR intervals during AF may also result in hemodynamic impairment. In a canine model with complete heart block, cardiac output fell by approximately 9% during irregular ventricular pacing at the same mean cycle length as a regularly paced rhythm (101). Importantly, mitral regurgitation was observed only during the irregularly paced rhythm. Cardiac cycle irregularity during AF can also decrease cardiac output in human subjects (102). In fact, myocardial contractility is not constant during AF. When left ventricular (LV) pressure and volume were measured continuously in 6 patients, cycle-to-cycle changes in myocardial contractility were observed in AF because of force-interval relationships associated with cycle length (103). Thus, both the loss of AV synchrony and the irregularity of the ventricular response adversely affect hemodynamics during AF. Although it might seem that restoration of sinus rhythm would result in improved hemodynamic characteristics, this is not always the case (104,105).

A persistently rapid atrial rate can adversely affect atrial mechanical function (tachycardia-induced atrial cardiomyopathy) (2,106). In dogs subjected to sustained rapid atrial pacing, electrophysiological, anatomic, and pathological changes occur over time, including increased mitochondrial size, disruption of sarcoplasmic reticulum, biatrial enlargement, and decreased atrial refractoriness (106). Persistence of AF in chronically instrumented goat atria is associated with marked structural abnormalities in atrial myocytes and progressive but reversible electrophysiological changes, so sustained AF develops much more readily (66,106,107). Such changes in atrial tissue may explain the delayed recovery of atrial contractility in patients after cardioversion to sinus rhythm. In a study of persistent AF, mean LA volume increased over time from 45 to 64 cm^3, and RA volume increased from 49 to 66 cm^3 (108). In another study, restoration and maintenance of sinus rhythm decreased RA and LA volumes (109). Moreover, transesophageal echocardiography (TEE) has demonstrated that LA appendage (LAA) blood flow velocity and contractile function recover over time after cardioversion, which suggests a reversible atrial cardiomyopathy (110,111).

Beyond the effects on atrial function, a persistently elevated ventricular rate during AF—greater than or equal to 130 beats per minute in one study (112)—can produce dilated ventricular cardiomyopathy (tachycardia-induced cardiomyopathy) (2,112–115). It is critically important to recognize this cause of cardiomyopathy, because control of the ventricular response may lead to partial or even complete reversal of the myopathic process. Patients may present with HF as the initial manifestation of AF; HF may thus be a consequence of rather than the cause of AF, offering an avenue for remarkable improvement in LV function. In one study, the median LV ejection fraction increased from 25% to 52% (113) with rate control. This has important implications for the timing of measurements of ventricular performance in patients with AF, because a reduced ejection fraction during or in the days or weeks following tachycardia may not accurately reflect ventricular function after the rate has been controlled. A variety of hypotheses have been proposed to explain tachycardia-mediated cardiomyopathy that involve myocardial energy depletion, ischemia, abnormalities of calcium regulation, and remodeling, but the actual mechanisms responsible for this disorder are still unclear (116).

D. Thromboembolism

Although ischemic stroke and systemic arterial occlusion in AF are generally attributed to embolism of thrombus from the LA, the pathogenesis of thromboembolism is complex (117). Up to 25% of AF-associated strokes may be due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or atheromatous pathology in the proximal aorta (118,119). The frequency of stroke related to AF increases with age to 36% per year for patients aged 80 to 89 years (14). About half of all elderly AF patients have chronic hypertension (a major risk factor for cerebrovascular disease) (28), and approximately 12% harbor cervical carotid artery stenosis. Carotid atherosclerosis is not substantially more prevalent in AF patients with stroke than in patients without AF, however, and is probably a relatively minor contributing factor (120).

1. Pathophysiology of Thrombus Formation. LA thrombus formation begins with Virchow's conditions of stasis, endothelial dysfunction, and a hypercoagulable state. The hemodynamic and hemostatic mechanisms responsible for clinical thromboembolism in AF have been elucidated by serial imaging and coagulation studies. Thrombus associated with AF arises most frequently in the LAA, which cannot be regularly examined by precordial (transthoracic) echocardiography (121). Transesophageal Doppler echocardiography provides a sensitive and specific method to assess LAA function (122) and to detect thrombotic material. Thrombi are more often encountered in AF patients with ischemic stroke than in those without stroke (123). Serial TEE studies of the LA (124) and LAA (125) during

conversion of AF to sinus rhythm have demonstrated reduced LAA flow velocities related to loss of organized mechanical contraction during AF. This substrate of decreased flow within the LA/LAA has been associated with spontaneous echo contrast, thrombus formation, and embolic events (126–132). LAA flow velocities are lower in patients with atrial flutter than what is usually seen with normal sinus rhythm but are higher than with AF. Whether this accounts for the slightly lower prevalence of LAA thrombus and perhaps a lower rate of thromboembolism associated with atrial flutter is uncertain. Although conventional clinical management is based on the presumption that thrombus formation requires continuation of AF for approximately 48 h, thrombi have been identified by TEE within shorter intervals (133,134). (See Section VIII-G-1-c, Therapeutic Implications.)

Endothelial dysfunction has been difficult to demonstrate as a distinct mechanism contributing to thrombus formation in patients with AF, although systemic and atrial tissue levels of von Willebrand factor are elevated in some patients (135–138). Similarly, AF has been associated with biochemical markers of coagulation and platelet activation that may reflect a systemic hypercoagulable state (135,136,139–141). Both persistent and paroxysmal AF have been associated with increased systemic fibrinogen and fibrin D-dimer levels, which indicates active intravascular thrombogenesis (135,136,140–142). Elevated thromboglobulin and platelet factor 4 levels in selected patients with AF indicate platelet activation (135,140,143), but these data are less robust, in line with the lower efficacy of platelet-inhibitor drugs for prevention of thromboembolism in clinical trials of antithrombotic therapy for AF. These biochemical markers of coagulation and platelet activation do not distinguish between a reactive process secondary to intravascular coagulation and a primary hypercoagulable state. The levels of some of these markers of coagulation activity fall to normal during anticoagulation therapy (139), and some markers increase immediately after conversion to sinus rhythm and then normalize (144).

In patients with rheumatic mitral stenosis undergoing transseptal catheterization for mitral balloon valvuloplasty, a regional type of coagulopathy has been demonstrated in the LA. Levels of fibrinopeptide A, thrombin/antithrombin III complex, and prothrombin fragment F1.2 are increased in the LA compared with levels in the RA and femoral vein, which indicates regional activation of the coagulation cascade (145,146). Whether such elevations are related to AF through LA pressure overload or some other mechanism has not been determined, but the regional coagulopathy was associated with spontaneous echo contrast in the LA (146). In contrast, incompetence of the mitral valve reduces stasis in the LAA and is associated with less coagulation activity (147).

Spontaneous echo contrast is a complex phenomenon that is dependent in vitro on blood flow velocity and serum proteins, including fibrinogen, and hematocrit (148). In patients with AF, independent predictors of spontaneous echo contrast include LA size, LAA flow velocity (126,149), LV dysfunction, fibrinogen level (132), hematocrit (131,132), and aortic atherosclerosis (131,132,148,150). This hemorheologic phenomenon may represent an echocardiographic surrogate for regional coagulopathy and is of clinical value, particularly when dense, for identifying AF patients at high risk for thromboembolism (148). The utility of this finding for prospective risk stratification for thromboembolism beyond that achieved by clinical assessment, however, has not yet been determined.

Contrary to the prevalent concept that systemic anticoagulation for 4 weeks results in endocardial adherence and organization of LAA thrombus, TEE studies have verified resolution of thrombus in the majority of patients (151). Similar observations have defined the dynamic nature of LA/LAA dysfunction on conversion of AF, which provides a mechanistic rationale for anticoagulation for several weeks before and after successful cardioversion. Conversely, increased flow within the LA in patients with mitral regurgitation has been associated with less prevalent LA spontaneous echo contrast (152,153) and fewer thromboembolic events, even in the presence of LA enlargement (154).

2. Clinical Implications. Because the pathophysiology of thromboembolism in patients with AF is uncertain, the mechanisms linking risk factors to ischemic stroke in AF are also incompletely defined. The strong association between hypertension and stroke in AF is probably mediated primarily by embolism originating in the LAA (119), but hypertension also increases the risk of noncardioembolic strokes in AF (119,155). Hypertension in AF patients is associated with reduced LAA flow velocity, spontaneous echo contrast, and thrombus formation (148,149,156). Ventricular diastolic dysfunction might underlie the effect of hypertension on LA dynamics, but this relationship is still speculative (157,158). Whether sustained control of systemic hypertension lowers the risk for cardioembolic stroke in AF patients is a vital question, because ventricular diastolic abnormalities associated with hypertension in the elderly are often multifactorial and difficult to reverse (158,159).

The effect of advancing age in increasing stroke risk in AF is multifactorial. In patients with AF, aging is associated with LA enlargement, reduced LAA flow velocity, and spontaneous echo contrast, all of which predispose to LA thrombus formation (41,148,149). Additionally, age is a risk factor for atherosclerosis, including complex aortic arch plaque, and is associated with stroke independently of AF (150). Levels of prothrombin activation fragment F1.2, an index of in vivo thrombin generation, increase with age in the general population (160–162) and in those with AF (11,163), which suggests an age-related prothrombotic diathesis. In the Stroke Prevention in Atrial Fibrillation (SPAF) studies, age was a more potent risk factor when combined with other risk factors such as hypertension or

female gender (163), placing women over age 75 years with AF at particular risk for cardioembolic strokes (164).

LV systolic dysfunction, as indicated by a history of HF or transthoracic echocardiographic measurements, predicts ischemic stroke in AF patients who receive no antithrombotic therapy (165–168) but not in moderate-risk AF patients given aspirin (163,169). Mechanistic inferences are contradictory; LV systolic dysfunction has been associated both with LA thrombus and with noncardioembolic strokes in AF patients (119,170).

In summary, complex thromboembolic mechanisms are operative in AF and involve the interplay of factors related to LA/LAA stasis, endothelial dysfunction, and systemic and possibly local hypercoagulability.

VI. ASSOCIATED CONDITIONS, CLINICAL MANIFESTATIONS, AND QUALITY OF LIFE

A. Causes and Associated Conditions

1. Acute Causes of AF. Atrial fibrillation may be related to acute, temporary causes, including alcohol intake ("holiday heart syndrome"), surgery, electrocution, MI, pericarditis, myocarditis, pulmonary embolism or other pulmonary diseases, and hyperthyroidism or other metabolic disorders. In such cases, successful treatment of the underlying condition may eliminate AF. Atrial fibrillation that develops in the setting of an acute MI portends an adverse prognosis compared with preinfarct AF or sinus rhythm (171). Atrial fibrillation may be associated with another supraventricular tachycardia, the WPW syndrome, or AV nodal reentrant tachycardias, and treatment of these primary arrhythmias reduces the incidence of recurrent AF (87). Atrial fibrillation is a common early postoperative complication of cardiac or thoracic surgery.

2. AF Without Associated Heart Disease. The concept that AF is not a disease by itself and should instead be considered a sign of underlying cardiac disease is reinforced by the fact that it has so many causes. Arguing to the contrary, approximately 30% to 45% of paroxysmal cases and 20% to 25% of persistent cases of AF occur in younger patients without demonstrable underlying disease (lone AF) (19,21,22). Atrial fibrillation can present as an isolated (48) or familial (172) arrhythmia, although an underlying disease may appear over time. Although this may reduce the relative incidence of lone AF in the elderly, development of heart disease in older patients may be coincidental and unrelated to AF.

3. AF With Associated Heart Disease. Specific cardiovascular conditions associated with AF include valvular heart disease (most often mitral valve disease), coronary artery disease (CAD), and hypertension, particularly when LV hypertrophy is present. In addition, AF may be associated with HCM or dilated cardiomyopathy or congenital heart disease, especially atrial septal defect in adults. Sinus node disease, ventricular preexcitation, and supraventricular tachycardias may also underlie AF. The list of etiologies also includes restrictive cardiomyopathies (such as amyloidosis, hemochromatosis, and endomyocardial fibrosis), cardiac tumors, and constrictive pericarditis. Other heart diseases, such as mitral valve prolapse even without mitral regurgitation, calcification of the mitral annulus, cor pulmonale, and idiopathic dilation of the RA, have been associated with a high incidence of AF. Atrial fibrillation is commonly encountered in patients with the sleep apnea syndrome, but whether the arrhythmia is provoked by hypoxia or other biochemical abnormality or mediated by changes in pulmonary dynamics or RA factors has not been determined. Table 3 shows a list of associated heart diseases in the contemporary population of the ALFA study (21).

4. Neurogenic AF. The autonomic nervous system may trigger AF in susceptible patients through heightened vagal or adrenergic tone. Many patients experience onset of AF during periods of enhanced parasympathetic or sympathetic tone, and Coumel described a group of patients that he characterized in terms of a vagal or adrenergic form of AF (173). Vagal AF is characterized by 1) a prevalence that is approximately 4 times greater in men than in women; 2) age approximately 40 to 50 years at onset; 3) frequent association with lone AF; 4) little tendency to progress to permanent AF; 5) occurrence at night, during rest, after eating, or after ingestion of alcohol; and 6) antecedent progressive bradycardia. Because heart rate is relatively slow during the episode of AF, most patients complain of irregularity rather than dyspnea, lightheadedness, or syncope. Importantly, both adrenergic blocking drugs and digitalis may increase the frequency of vagally mediated AF.

Like vagal AF, the age of patients with adrenergic AF is usually about 50 years at onset, and most do not exhibit structural heart disease. In contrast, as originally described by Coumel (173) and subsequently verified by others, adrenergic AF has the following features: 1) a lower incidence than vagally mediated AF; 2) onset predominantly during the daytime; 3) provocation by exercise or emotional stress; 4) polyuria as a common correlate; 5) onset typically associated with a specific sinus rate for a given patient; and 6) no gender differences. In contrast to vagally induced AF, beta-blockers are usually the treatment of choice for AF of the adrenergic type.

Scant data are available on neurogenic AF, which is relatively rare as a pure entity. Although patients with pure vagal or adrenergic AF are uncommon, when the clinical history reveals a pattern of onset of AF that has features of one or the other of these syndromes, the clinician may be able to select agents that are more likely to prevent recurrent episodes.

B. Clinical Manifestations

Atrial fibrillation may be symptomatic or asymptomatic, even in the same patient. The dysrhythmia may present for the first time with an embolic complication or exacerbation of HF, but most patients with AF complain of palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope.

Table 3. Demographics and Associated Conditions Among Patients With Atrial Fibrillation in the ALFA Study

	Total Population	Paroxysmal AF	Chronic AF	Recent-Onset AF
No. of patients	756	167	389	200
Age, y	68.6	65.9	69.9	68.1
Male/female ratio	436/320	91/76	237/152	108/92
Body weight, kg	72.5	72.3	72.4	73
Height, cm	168.4	169.2	168	168.3
Time from first episode of AF, mo	47.3	39.4	65.7	NA
Duration of current episode of AF, mo	NA	NA	54	NA
Underlying heart disease, n (%)				
Coronary artery disease*	126 (16.6)	20 (11.9)	69 (17.7)	37 (18.5)
Hypertensive heart disease	162 (21.4)	28 (16.7)	84 (21.5)	50 (25.0)
Valvular (rheumatic)	115 (15.2)	16 (9.5)	76 (19.5)	23 (11.5)
Dilated cardiomyopathy	70 (9.2)	4 (2.3)	49 (12.5)	17 (8.5)
Hypertrophic cardiomyopathy	37 (4.8)	5 (2.9)	14 (3.5)	18 (9.0)
Nonrheumatic valvular (mitral valve prolapse, other)	25 (3.3)	9 (5.3)	10 (2.5)	6 (3.0)
Cardiomyopathy (other)	9 (1.2)	1 (0.6)	6 (1.5)	2 (1.0)
Sinus node dysfunction	9 (1.2)	3 (1.8)	5 (1.3)	1 (0.5)
Miscellaneous	28 (3.7)	10 (6.0)	13 (3.3)	5 (2.5)
None	222 (29.3)	77 (46.1)	90 (23.1)	55 (27.5)
Other predisposing or associated factors, n (%)				
Hyperthyroidism	24 (3.1)	6 (3.5)	9 (2.3)	9 (4.5)
Hypertension	298 (39.4)	59 (35.3)	148 (38.0)	91 (45.5)
Bronchopulmonary disease	85 (11.2)	16 (9.5)	50 (12.9)	19 (9.5)
Diabetes	81 (10.7)	12 (7.1)	51 (13.1)	18 (9.0)
Congestive HF	226 (29.8)	24 (14.3)	166 (42.6)	36 (18.0)
Prior embolic events	64 (8.4)	14 (8.3)	42 (10.8)	8 (4.0)
Left atrial size, mm	43.8	40	46.5	41.5
Left ventricular ejection fraction, %	58.7	63.3	56.9	58.4

ALFA indicates Etude en Activité Liberale sur le Fibrillation Auriclaire (21); AF, atrial fibrillation; NA denotes not applicable or available; HF, heart failure. Persistent AF includes both patients with recent-onset AF and chronic AF. Recent-onset AF was defined as persistent AF of between 7 and 30 days' duration. Chronic AF was defined as persistent AF more than 30 days' duration. Patients in whom the diagnosis was definite and those in whom it was probable were included. Modified with permission from Levy S et al., Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA Study, Vol. 99, pp. 3028–35, © 1999 by Lippincott Williams & Wilkins.

The association of polyuria with AF may be mediated by release of atrial natriuretic peptide. Atrial fibrillation may be associated with a fast ventricular response, leading to tachycardia-mediated cardiomyopathy, especially in patients who are unaware of the arrhythmia. Syncope is an uncommon but serious complication that is usually associated with sinus node dysfunction or hemodynamic obstruction, such as valvular aortic stenosis, HCM, cerebrovascular disease, or an accessory AV pathway. Symptoms vary with the ventricular rate, underlying functional status, duration of AF, and individual patient perceptions.

C. Quality of Life

Although strokes certainly account for much of the functional impairment associated with AF, the rhythm disturbance can also decrease quality of life directly. In the SPAF study cohort, Ganiats et al. (174) found the New York Heart Association functional classification, developed for HF, to be an insensitive index of quality of life in patients with AF. In another study (175), 47 (68%) of 69 patients with paroxysmal AF considered the dysrhythmia disruptive of their lives, but this perception was not associated with either the frequency or duration of symptoms.

Little is known of the direct effects of antiarrhythmic and rate control therapy on quality of life. In the Canadian Trial of Atrial Fibrillation (CTAF) study, quality of life improved after pharmacological treatment, whether this involved amiodarone, propafenone, or sotalol (176). The postcardioversion EMERALD (European and Australian Multicenter Evaluation Research on Atrial Dofetilide) study (177) showed that dofetilide improved quality of life 1 month after electrical cardioversion. The AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), still in progress, is comparing maintenance of sinus rhythm with rate control in patients with AF and addressing many facets of quality of life, as has been done in the smaller PIAF (Pharmacological Intervention in Atrial Fibrillation) study (178,179).

In selected patients, radiofrequency catheter ablation of the AV node and pacemaker insertion decreased subjective symptoms of AF and improved quality-of-life scores compared with medical therapy (180–185). Baseline quality-of-life scores appear to be lower for patients with atrial flutter

and fibrillation than for those with other arrhythmias who are undergoing radiofrequency ablation (186). A meta-analysis of 10 published studies of patients with AF (187) found improvement in both symptoms and quality-of-life scores after ablation and pacing. Although these studies followed highly selected patients who remained in AF, such consistent improvement suggests that quality of life was impaired at baseline (before intervention). Two studies have described improvement in symptoms and quality of life after radiofrequency catheter ablation of atrial flutter (188,189).

Long-term oral anticoagulant therapy, which involves frequent blood testing and multiple drug interactions, is another factor with important implications for the quality of life of AF patients. Gage et al. (190) quantified this as a mean 1.3% decrease in utility, a measure of quality of life used in quantitative decision analysis. Eleven patients (16%) felt that their quality of life would be greater with aspirin than with oral anticoagulants, despite its lesser efficacy. Protheroe et al. (191), using decision analysis to assess patient preferences, found that only 59 (61%) of 97 patients preferred anticoagulation therapy to no treatment, a considerably smaller proportion than that for whom treatment has been recommended according to published guidelines. These comparisons could be influenced in the future by the development of more convenient approaches to antithrombotic therapy.

VII. CLINICAL EVALUATION

A. Minimum Evaluation of the Patient With AF

1. Clinical History and Physical Examination. The initial evaluation of a patient with suspected or proven AF includes characterizing the pattern of the arrhythmia as paroxysmal or persistent, determining its cause, and defining associated cardiac and extracardiac factors (Table 4). A careful history will result in a well-planned, focused workup that serves as an effective guide to therapy (2). The workup of an AF patient can usually take place and therapy can be initiated in 1 outpatient encounter. Delay occurs when the rhythm has not been specifically documented and additional monitoring is necessary.

As emphasized, AF may present with a wide array of symptoms. (See Section VI, Associated Conditions, Clinical Manifestations, and Quality of Life.) Factors contributing to symptoms include the rate and irregularity of the ventricular response and the loss of atrial contribution to ventricular filling. Patients with atrial flutter and a regular pulse, even if rapid, are less often symptomatic than in patients with AF (192).

Typically, AF occurs in patients with underlying heart disease, usually hypertensive heart disease (24,193). (See Section VI, Associated Conditions, Clinical Manifestations, and Quality of Life.) Atherosclerotic heart disease or valvular heart diseases are also common substrates, whereas pulmonary pathology, preexcitation syndromes, and thyroid disease are less frequent causes that should still be sought (194). Because reports of genetic transmission of AF have been published, the family history is becoming important as well (172). The setting in which the physician initially encounters the AF patient may be a clue to its origin. Patients seen in the hospital emergency department tend to have a higher incidence of organic heart disease than those seen in an ambulatory clinic setting, where the incidence of lone AF can be higher than 30% (21) (Table 3).

Although various environmental triggers can initiate episodes of AF, this aspect may not emerge from the initial history given spontaneously by the patient and often requires specific inquiry. Commonly mentioned triggers include alcohol, sleep deprivation, and emotional stress, but vagally mediated AF episodes may occur during sleep or after a large meal and are more likely to arise during a period of rest after a period of stress. Stimulants such as caffeine or exercise may also precipitate AF.

Patients with paroxysmal AF may be particularly frightened by the symptoms, and the initial physician encounter must be complete and reassuring. Even when the patient with AF is relatively asymptomatic, the interview should include an effort to characterize the episodes in terms of onset and duration. The clinician should determine whether the onset and termination of palpitations is abrupt or gradual; the former favors AF or another supraventricular tachyarrhythmia, whereas the latter suggests a mechanism other than AF, including sinus tachycardia. As the arrhythmia begins, is the pulse regular or irregular? If it begins as a regular rhythm and then becomes irregular, another atrial arrhythmia should be considered, such as one involving a bypass tract. Are there associated symptoms? Dyspnea may indicate underlying heart disease, whereas angina pectoris points toward CAD. Syncope may be associated with AF, but ventricular arrhythmias should not be overlooked as a possible cause. The patient may relate the onset of AF to environmental factors including food, drink, emotional stress, sleep, or other details. Some of these factors may indicate a provocative vagal component; vagally mediated AF is also suggested when a beta-blocker or digitalis has increased the tendency to AF (173). Finally, an effort should be made to quantify the episodes in terms of frequency and duration, because AF episodes tend to become more frequent and more symptomatic over time.

The physical examination may suggest AF on the basis of irregular pulse, irregular jugular venous pulsations, and variation in the loudness of the first heart sound. Examination may also disclose associated valvular heart disease, myocardial abnormalities, or HF. The findings on examination are similar in patients with atrial flutter, except that the rhythm may be regular and rapid venous oscillations may occasionally be visible in the jugular pulse.

2. Investigations. The diagnosis of AF requires ECG documentation by at least single-lead ECG recording during the dysrhythmia, which may be facilitated by review of emergency department records, Holter monitoring, or transtelephonic or telemetric recordings. A portable ECG

Table 4. Minimum and Additional Clinical Evaluation in Patients With Atrial Fibrillation

Minimum evaluation

1. History and physical examination, to define
   - The presence and nature of symptoms associated with AF
   - The clinical type of AF (first episode, paroxysmal, persistent, or permanent)
   - The onset of the first symptomatic attack or date of discovery of AF
   - The frequency, duration, precipitating factors, and modes of termination of AF
   - The response to any pharmacological agents that have been administered
   - The presence of any underlying heart disease or other reversible conditions (e.g., hyperthyroidism or alcohol consumption)
2. Electrocardiogram, to identify
   - Rhythm (verify AF)
   - LV hypertrophy
   - P-wave duration and morphology or fibrillatory waves
   - Preexcitation
   - Bundle-branch block
   - Prior MI
   - Other atrial arrhythmias
   - To measure and follow the RR, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. Chest radiograph, to evaluate
   - The lung parenchyma, when clinical findings suggest an abnormality
   - The pulmonary vasculature, when clinical findings suggest an abnormality
4. Echocardiogram, to identify
   - Valvular heart disease
   - Left and right atrial size
   - LV size and function
   - Peak RV pressure (pulmonary hypertension)
   - LV hypertrophy
   - LA thrombus (low sensitivity)
   - Pericardial disease
5. Blood tests of thyroid function
   - For a first episode of AF, when the ventricular rate is difficult to control, or when AF recurs unexpectedly after cardioversion

Additional testing

- One or several tests may be necessary

1. Exercise testing
   - If the adequacy of rate control is in question (permanent AF)
   - To reproduce exercise-induced AF
   - To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug
2. Holter monitoring or event recording
   - If diagnosis of the type of arrhythmia is in question
   - As a means of evaluating rate control
3. Transesophageal echocardiography
   - To identify LA thrombus (in the LA appendage)
   - To guide cardioversion
4. Electrophysiological study
   - To clarify the mechanism of wide-QRS-complex tachycardia
   - To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
   - Seeking sites for curative ablation or AV conduction block/modification

AF indicates atrial fibrillation; LV, left ventricular; MI, myocardial infarction; RV, right ventricular; LA, left atrial; and AV, atrioventricular. Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs (see Table 9).

recording tool may help establish the diagnosis in cases of paroxysmal AF and provide a permanent ECG record of the dysrhythmia. If episodes are frequent, then a 24-h Holter monitor can be used. If episodes are infrequent, then an event recorder, which allows the patient to transmit the ECG to a recording facility when the arrhythmia occurs, may be more useful.

A chest radiograph may detect enlargement of the cardiac chambers and HF but is valuable mostly for detection of intrinsic pulmonary pathology and evaluation of the pulmonary vasculature. It is less important than echocardiography for the routine evaluation of patients with AF. Two-dimensional transthoracic echocardiography should be acquired during the initial workup of all AF patients to determine LA and LV dimensions and LV wall thickness and function and to exclude occult valvular or pericardial disease or HCM. LV systolic and diastolic performance help guide decisions regarding antiarrhythmic and anti-

thrombotic therapy. Thrombus should be sought in the LA but is seldom detected without TEE (121,127,195).

Blood tests are routine but can be abbreviated. It is important that thyroid function, serum electrolytes, and the hemogram be measured at least once (196).

B. Additional Investigation of Selected Patients With AF

1. Holter Monitoring and Exercise Testing. Aside from the use of Holter monitoring to establish the diagnosis of AF, this technique and treadmill stress testing will better evaluate the adequacy of rate control over time than a resting ECG (197). Exercise testing should be performed if myocardial ischemia is suspected or if type IC antiarrhythmic drug therapy is planned.

2. Transesophageal Echocardiography. TEE places high-frequency ultrasound transducers in close proximity to the heart to provide high-quality images of cardiac structure (198) and function (199). It is the most sensitive and specific technique to detect sources and potential mechanisms for cardiogenic embolism (200) and has been used in AF to stratify patients in terms of stroke risk and to guide cardioversion. (See Section VIII-G, Preventing Thromboembolism.) TEE of patients with AF before cardioversion has shown an LA or LAA thrombus in 5% to 15% (195,201). Detection of LA/LAA thrombus in the setting of stroke or systemic embolism is convincing evidence of a cardiogenic mechanism (134).

Several TEE features have been associated with thromboembolism in patients with nonvalvular AF, including LA/LAA thrombus, LA/LAA spontaneous echo contrast, reduced LAA flow velocity, and aortic atheromatous abnormalities (156). Although these features are associated with cardiogenic embolism (169,202), further prospective investigation is needed to compare these TEE findings with clinical and transthoracic echocardiographic predictors of thromboembolism.

TEE has also been used to exclude LA/LAA thrombus before elective cardioversion (203,204). In a multicenter observational study, however, 17 cases of thromboembolism in AF patients were reported after conversion to sinus rhythm even after TEE showed no LA/LAA thrombus (205). All of the strokes occurred relatively soon after cardioversion in patients who did not receive therapeutic anticoagulation. These observations reinforce the need to maintain therapeutic anticoagulation in patients with AF undergoing cardioversion even when no thrombus is identified by TEE. For patients with AF of greater than 48 h duration, a TEE-guided strategy and the traditional strategy of anticoagulation for 3 weeks before and 4 weeks after elective cardioversion resulted in similar rates of thromboembolism (less than 1%) during the 8 weeks after randomization (201). (See Section VIII-G-3, Conversion to Sinus Rhythm and Thromboembolism.)

3. Electrophysiological Study. An electrophysiological study is rarely needed to establish the diagnosis of AF but may be useful for other reasons. In patients with paroxysmal AF, an electrophysiological study may help define the mechanism of AF, which is especially important when curative catheter ablation is considered for selected patients. The cause of AF may be a rapidly firing focus, commonly in or near the pulmonary vein(s), or the result of a regular supraventricular tachycardia such as AV reentry, AV node reentry, or atrial flutter that degenerates into AF (tachycardia-induced tachycardia). (See Section V, Pathophysiological Mechanisms.) Electrophysiological studies may be helpful when sinus node dysfunction is suspected and to clarify the mechanism of wide QRS complexes during AF, particularly when the ventricular response is rapid. Rate control by catheter ablation or modification of AV conduction requires electrophysiological study, as does selection of patients for pacemaker therapy to prevent AF.

Table 5. Objectives of Rhythm Control in Patients With Atrial Fibrillation

Relief of symptoms such as palpitations, fatigue, and dyspnea
Prevention of thromboembolism
Prevention of tachycardia-induced myocardial remodeling and HF

HF indicates heart failure.

VIII. MANAGEMENT

The major issues in management of patients with AF are related to the arrhythmia itself and to prevention of thromboembolism. In patients with persistent AF, there are fundamentally 2 ways to manage the dysrhythmia: to restore and maintain sinus rhythm or to allow AF to continue and ensure that the ventricular rate is controlled. Although this decision must be faced often by clinicians because AF is common, remarkably little research has been conducted in the form of controlled trials of antiarrhythmic drugs that take into account the various mechanisms and patterns of AF. Management strategies and therapeutic algorithms must be based on the scant evidence available. Information on prevention of thromboembolism is more substantial, however, enabling recommendations to be based on a higher level of evidence.

A. Rhythm Control vs. Heart Rate Control

Reasons for restoration and maintenance of sinus rhythm in patients with AF include relief of symptoms, prevention of embolism, and avoidance of cardiomyopathy (Table 5). The decision to convert AF (as opposed to controlling the rate and allowing AF to continue) is commonly intended to alleviate all these problems, but evidence documenting the extent to which restoration and maintenance of sinus rhythm achieves these goals is sparse. Conversion to and maintenance of sinus rhythm offers the theoretical advantages of reducing the risk of thromboembolism and consequently the need for chronic anticoagulation, but drugs used to control heart rate are generally considered safer than those with an antiarrhythmic effect. The relative merit of these 2 approaches—rhythm control vs. rate control—is the subject of ongoing clinical trials (178,179). Limited avail-

able data suggest no clear advantage of one approach over the other (179), but a more complete answer awaits the results of studies in progress.

B. Cardioversion

1. Basis for Cardioversion of AF. Cardioversion is often performed electively to restore sinus rhythm in patients with persistent AF. The need for cardioversion may be immediate, however, when the arrhythmia is the main factor responsible for acute HF, hypotension, or worsening of angina pectoris in a patient with CAD. Nevertheless, cardioversion carries a risk of thromboembolism unless anticoagulation prophylaxis is initiated before the procedure, and this risk appears greatest when the arrhythmia has been present more than 48 h.

2. Methods of Cardioversion. Cardioversion may be achieved by means of drugs or electrical shocks. Drugs were commonly used before electrical cardioversion became a standard procedure. The development of new drugs has increased the popularity of pharmacological cardioversion, although some disadvantages persist, including the risk of drug-induced torsade de pointes ventricular tachycardia or other serious arrhythmias. Pharmacological cardioversion is still less effective than electrical cardioversion, but the latter requires conscious sedation or anesthesia, whereas the former does not.

There is no evidence that the risk of thromboembolism or stroke differs between pharmacological and electrical methods of cardioversion. The recommendations for anticoagulation at the time of cardioversion are the same for both methods, as outlined in Section VIII-G, Preventing Thromboembolism.

C. Pharmacological Cardioversion

Pharmacological cardioversion has been the subject of intense research for over a decade. Although pharmacological and electrical cardioversion have not been compared directly, pharmacological approaches appear to be simpler but less efficacious than electrical cardioversion. In selected cases, pharmacological cardioversion may even be attempted at home. The major risk is the toxicity of antiarrhythmic drugs. In this section, emphasis is given to studies in which drugs were administered over short periods of time specifically to restore sinus rhythm. The quality of available evidence is limited by small samples, lack of standard inclusion criteria, variable intervals from drug administration to assessment of outcome, and arbitrary dose selection. In developing these guidelines, placebo-controlled trials of pharmacological cardioversion have been emphasized, but trials in which the control group was given another antiarrhythmic drug have also been considered.

Pharmacological cardioversion appears to be most effective when initiated within 7 days after the onset of AF (206–209). Most such patients have a first documented episode of AF or an unknown pattern of AF at the time of treatment. (See Section III, Classification.) A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 h (210–212). Spontaneous conversion is less frequent in patients with AF of longer duration (greater than 7 days) before treatment was begun, and the efficacy of pharmacological cardioversion is also markedly reduced in patients with persistent AF.

Some drugs have a delayed onset of action, and conversion may not occur for several days (213). In some studies, drug treatment abbreviated the interval to cardioversion compared with placebo without affecting the proportion of patients who remained in sinus rhythm after 24 h (211). Pharmacological cardioversion may accelerate the restoration of sinus rhythm in patients with recent-onset AF, but the advantage over placebo is quite modest after 24 to 48 h, and it is much less effective (and with some drugs ineffective) in patients with persistent AF.

The relative efficacy of various drugs differs for pharmacological cardioversion of AF and atrial flutter, yet many studies of drug therapy for AF have included patients with atrial flutter. The dose, route, and rapidity of administration influence efficacy, and this has been considered as much as possible in developing these guidelines. The designs of randomized trials have seldom fully accounted for concomitant medications, on the assumption that such treatment would be equally distributed among groups. Several investigators have generated multiple reports, and it is not always clear when these involve distinct or overlapping patient cohorts. Diligence in reporting adverse effects varies between trials, but toxicity has been considered in the recommendations that follow. Special populations, such as those with AF after recent heart surgery or MI, are addressed later (Section VIII-H, Special Considerations).

The potential interactions of antiarrhythmic drugs with oral anticoagulants (either increasing or decreasing the anticoagulant effect) are always an issue when these drugs are added or withdrawn from the treatment regimen. The problem is amplified when anticoagulation is initiated in preparation for elective cardioversion. Addition of an antiarrhythmic drug to enhance the likelihood that sinus rhythm will be restored and maintained may perturb the intensity of anticoagulation beyond the intended therapeutic range, raising the risk of bleeding or thromboembolic complications.

A summary of recommendations concerning the use of pharmacological agents for cardioversion of AF is presented in Tables 6, 7, and 8. Algorithms for pharmacological management of AF are given in Figs. 9, 10, 11, and 12. Considerations specific to individual agents are summarized below. The antiarrhythmic drugs listed have been approved by federal regulatory agencies in the United States and Europe for clinical use, but their use for the treatment of AF has not been approved in all cases. Furthermore, not all agents are approved for use in each country. Within each category, drugs are listed alphabetically. The recommendations given in this document are based on published data

Table 6. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Less Than or Equal to 7 Days' Duration

Drug*	Route of Administration	Type of Recommendation	Level of Evidence	References
Agents with proven efficacy				
Dofetilide	Oral	I	A	215, 216, 226–228, 261
Flecainide	Oral or intravenous	I	A	206–208, 210, 220, 229–233
Ibutilide	Intravenous	I	A	234–239
Propafenone	Oral or intravenous	I	A	208, 211, 212, 221, 229, 230, 233, 240–249
Amiodarone	Oral or intravenous	IIa	A	210, 213, 214, 217–225, 262
Quinidine	Oral	IIb	B	206, 208, 209, 211, 218, 219, 247, 250, 251
Less effective or incompletely studied agents				
Procainamide	Intravenous	IIb	C	234, 236, 259
Digoxin	Oral or intravenous	III	A	211, 222, 229, 249, 255–258
Sotalol	Oral or intravenous	III	A	237, 250, 251, 256, 260

*The doses of medications used in these studies may not be the same as those recommended by the manufacturers. Drugs are listed alphabetically within each category of recommendation and level of evidence.

and do not necessarily adhere to the regulations and labeling requirements of governmental agencies.

1. Agents With Proven Efficacy.

A. AMIODARONE. Data on amiodarone are confusing because the drug may be given intravenously, orally, or by both routes concurrently. The drug is modestly effective for pharmacological cardioversion of recent-onset AF (214) but acts less rapidly and probably less effectively than other agents. The conversion rate in patients with AF for longer than 7 days is limited, however, and restoration of sinus rhythm may not occur for days or weeks. Amiodarone is effective for controlling the rate of ventricular response to AF. Both amiodarone and dofetilide (administered separately) have been proven effective for conversion of persistent AF in placebo-controlled trials (214–216). Limited information suggests that amiodarone is equally effective for conversion of AF and atrial flutter. Adverse effects include bradycardia, hypotension, visual disturbances, nausea, and constipation after oral administration and phlebitis after peripheral intravenous administration. Serious toxicity has been reported, including 1 death due to bradycardia ending in cardiac arrest (210,213,214,217–225).

B. DOFETILIDE. Dofetilide, given orally, is more effective than placebo for pharmacological cardioversion of AF that has persisted longer than 1 week, but available studies have not further stratified patients on the basis of the duration of the dysrhythmia. Dofetilide appears to be more effective for cardioversion of atrial flutter than of AF. A response may take days or weeks when the drug is given orally, and the intravenous form is investigational (215,216,226–228).

C. FLECAINIDE. Flecainide administered orally or intravenously was effective for pharmacological cardioversion of recent-onset AF in placebo-controlled trials. It has not been evaluated extensively in patients with persistent AF, but available information suggests lower efficacy in this setting. Limited data suggest that flecainide may be more effective for conversion of AF than of atrial flutter. A response usually occurs within 3 h after oral administration and 1 h

Table 7. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of More Than 7 Days' Duration

Drug*	Route of Administration	Type of Recommendation	Level of Evidence	References
Agents proven effective				
Dofetilide	Oral	I	A	215, 216, 226–228, 261
Amiodarone	Oral or intravenous	IIa	A	210, 213, 214, 217–225, 262
Ibutilide	Intravenous	IIa	A	234–239
Flecainide	Oral	IIb	B	206–208, 210, 220, 229–233
Propafenone	Oral or intravenous	IIb	B	208, 211, 212, 221, 229, 230, 233, 240–249
Quinidine	Oral	IIb	B	206, 208, 209, 211, 218, 219, 247, 250, 251
Less effective or incompletely studied agents				
Procainamide	Intravenous	IIb	C	234, 236, 259
Sotalol	Oral or intravenous	III	A	237, 250, 251, 256, 260
Digoxin	Oral or intravenous	III	C	211, 222, 229, 249, 255–258

*The doses of medications used in these studies may not be the same as recommended in Table 8 or by the manufacturers. Drugs are listed alphabetically within each category of recommendation and level of evidence.

Table 8. Recommended Doses of Drugs Proven Effective for Pharmacological Cardioversion of Atrial Fibrillation

Drug*	Route of Administration	Dosage**	Potential Adverse Effects	References
Amiodarone	Oral	Inpatient: 1.2–1.8 g per day in divided dose until 10 g total, then 200–400 mg per day maintenance or 30 mg/kg as single dose Outpatient: 600–800 mg per day divided dose until 10 g total, then 200–400 mg per day maintenance	Hypotension, bradycardia, QT prolongation, torsade de pointes (rare), GI upset, constipation, phlebitis (IV)	210, 213, 214, 217–225, 262
	Intravenous/oral	5–7 mg/kg over 30–60 min, then 1.2–1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200–400 mg per day maintenance		
Dofetilide	Oral	Creatinine clearance (mL/min) / Dose (mcg BID): >60 / 500; 40–60 / 250; 20–40 / 125; <20 / Contraindicated	QT prolongation, torsade de pointes; adjust dose for renal function, body size, and age	215, 216, 226–228, 261
Flecainide	Oral	200–300 mg†	Hypotension, rapidly conducting atrial flutter	206–208, 210, 220, 229–233
	Intravenous	1.5–3.0 mg/kg over 10–20 min†		
Ibutilide	Intravenous	1 mg over 10 min; repeat 1 mg when necessary	QT prolongation, torsade de pointes	234–239
Propafenone	Oral	450–600 mg	Hypotension, rapidly conducting atrial flutter	208, 211, 212, 221, 229, 230, 233, 240–249
	Intravenous	1.5–2.0 mg/kg over 10–20 min†		
Quinidine‡	Oral	0.75–1.5 g in divided doses over 6–12 h, usually with a rate-slowing drug	QT prolongation, torsade de pointes, GI upset, hypotension	206, 208, 209, 211, 218, 219, 247, 250, 251

GI indicates gastrointestinal; IV, intravenous; BID, twice a day.

*Drugs are listed alphabetically.

**Dosages given in the table may differ from those recommended by the manufacturers.

†Insufficient data are available on which to base specific recommendations for the use of one loading regimen over another for patients with ischemic heart disease or impaired left ventricular function, and these drugs should be used cautiously or not at all in such patients.

‡The use of quinidine loading to achieve pharmacological conversion of atrial fibrillation is controversial, and safer methods are available with the alternative agents listed in the table. Quinidine should be used with caution.

after intravenous administration. Arrhythmias, including atrial flutter with rapid ventricular rates and bradycardia after conversion, are relatively frequent adverse effects. Transient hypotension and mild neurological side effects may also occur. Overall, adverse reactions have been reported slightly more frequently with flecainide than with propafenone, and these drugs should be given cautiously or avoided entirely in patients with underlying organic heart disease involving abnormal ventricular function (206–208,210,220,229–233).

D. IBUTILIDE. In placebo-controlled trials, intravenous ibutilide has proved effective for pharmacological cardioversion within a few weeks after onset of AF. Available data are insufficient to establish its efficacy for conversion of persistent AF of longer duration. Ibutilide is more effective for conversion of atrial flutter than of AF. An effect may be expected within 1 h after administration. There is a small but definite risk of torsade de pointes ventricular tachycardia, so serum concentrations of potassium and magnesium should be measured before administration of ibutilide, and patients should be monitored for at least 4 h afterward. Hypotension is an infrequent adverse response (234–239).

E. PROPAFENONE. Placebo-controlled trials have verified that propafenone, given orally or intravenously, is effective for pharmacological cardioversion of recent-onset AF. Limited data suggest that efficacy is reduced in patients with persistent AF, for conversion of atrial flutter, and in patients with structural heart disease. The effect occurs between 2 and 6 h after oral administration and earlier after intravenous injection. Adverse effects are uncommon but include rapid atrial flutter, ventricular tachycardia, intraventricular conduction disturbances, hypotension, and bradycardia at conversion. Available data on the use of various regimens of propafenone loading in patients with organic heart disease are scant. This agent should be used cautiously or not at all for conversion of AF in such cases and should be avoided in patients with congestive HF or obstructive lung disease (208,211,212,221,229–233,240–249).

F. QUINIDINE. Quinidine is usually administered after digoxin or verapamil has been given to control the ventric-

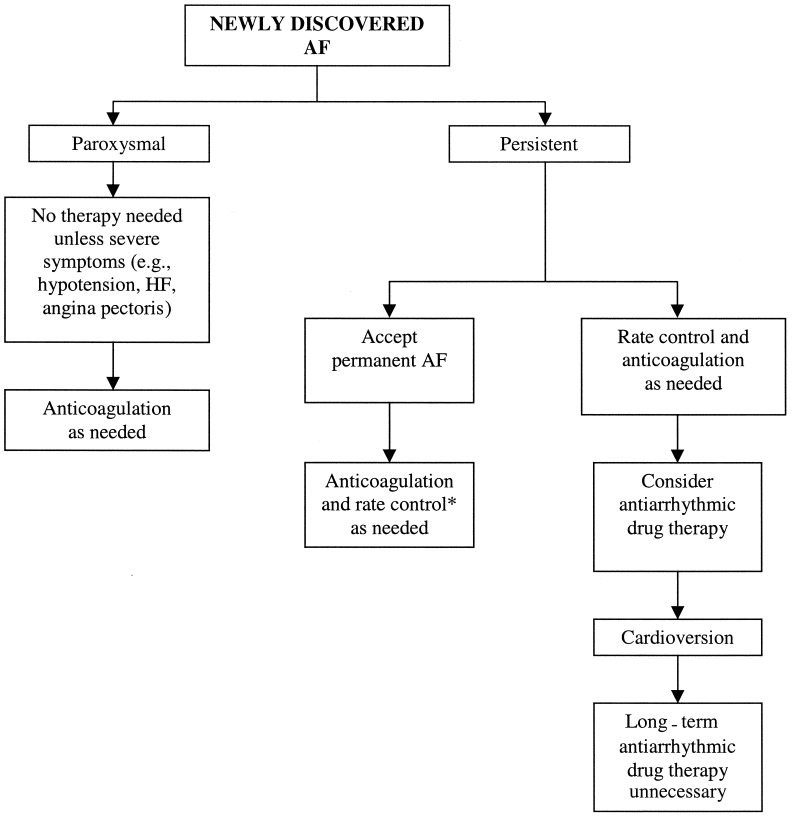

Figure 9. Pharmacological management of patients with newly discovered atrial fibrillation. AF indicates atrial fibrillation; HF, heart failure.

ular response rate. It is probably as effective as most other drugs for pharmacological cardioversion of recent-onset AF and is sometimes effective for correction of persistent AF. No distinction can be made between its efficacy for AF and atrial flutter. Potential adverse effects of quinidine include QT-interval prolongation that may precede torsade de pointes ventricular tachycardia, nausea, diarrhea, fever, hepatic dysfunction, thrombocytopenia, and hemolytic anemia. During the initiation of quinidine therapy, hypotension and acceleration of the ventricular response to AF may occur on a vagolytic basis. A clinical response may be expected 2 to 6 h after administration (206,208,211,218, 219,247,250–252).

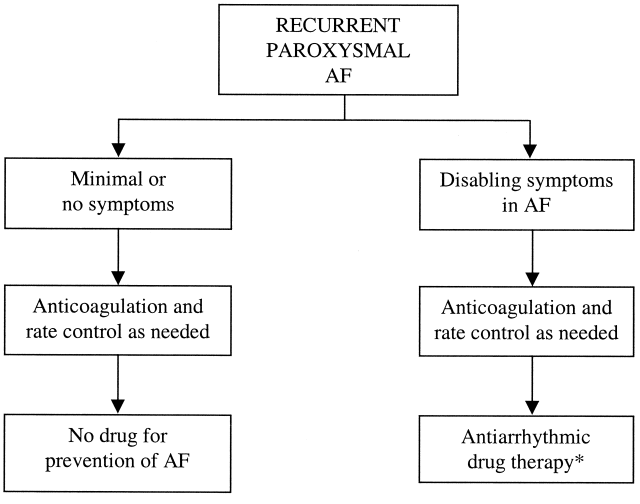

Figure 10. Pharmacological management of patients with recurrent paroxysmal atrial fibrillation. AF indicates atrial fibrillation. *See Fig. 11.

2. Less Effective or Incompletely Studied Agents.

A. BETA-BLOCKERS. When given intravenously, the short-acting beta-blocker esmolol may have modest efficacy for pharmacological cardioversion of recent-onset AF, but this has not been established by comparison with placebo. Esmolol acts rapidly, however, to control the rate of ventricular response to AF. It is not useful in patients with persistent AF, and there are no data comparing its relative efficacy for atrial flutter and AF. A response may be expected within 1 h. Hypotension and bronchospasm are the major adverse effects of esmolol and other beta-blockers (209,253).

B. CALCIUM CHANNEL ANTAGONISTS (VERAPAMIL AND DILTIAZEM). The calcium channel antagonist verapamil has not been shown to be effective for pharmacological cardioversion of recent-onset or persistent AF, but it acts rapidly to control the rate of ventricular response (208,209,224, 232,246). Negative inotropic effects contribute to toxicity, which includes hypotension.

The calcium channel antagonist diltiazem has not been shown to be effective for pharmacological cardioversion of

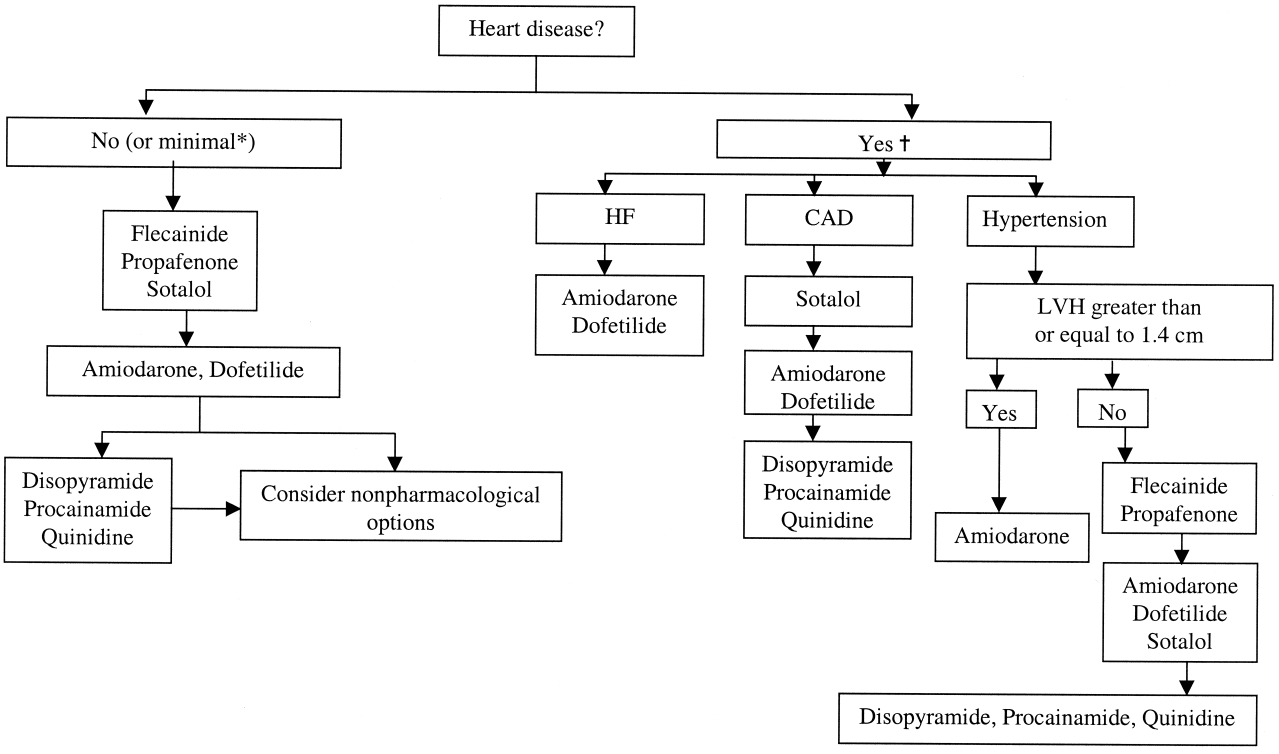

Figure 11. Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. *For adrenergic atrial fibrillation, beta-blockers or sotalol are the initial drugs of choice. †Consider nonpharmacological options to maintain sinus rhythm if drug failure occurs. HF indicates heart failure; CAD, coronary artery disease; and LVH, left ventricular hypertrophy.

recent-onset or long-standing AF, but like verapamil, it is effective for control of heart rate (254).

C. DIGOXIN. Digitalis glycosides are generally no more effective than placebo for conversion of recent-onset AF to sinus rhythm. Digoxin may prolong the duration of episodes of paroxysmal AF in some patients (255), and it has not been evaluated adequately in patients with persistent AF except to achieve rate control. Digoxin has few adverse effects after acute administration in therapeutic doses, aside from AV block and acceleration of ventricular ectopy (211,222,229,249,255–258).

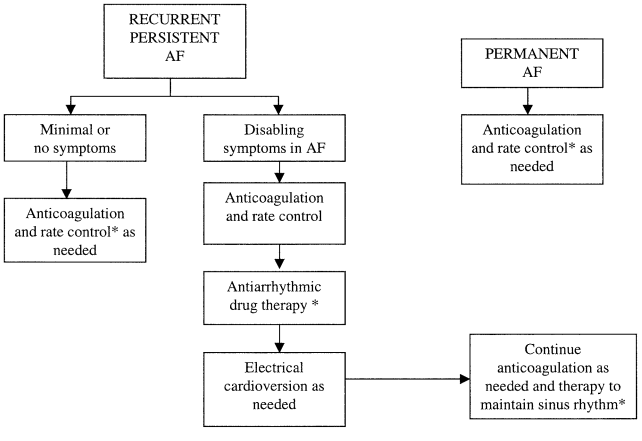

Figure 12. Pharmacological management of patients with recurrent persistent or permanent atrial fibrillation. *See Fig. 11. Initiate drug therapy before cardioversion to reduce the likelihood of early recurrence of AF.

D. DISOPYRAMIDE. Disopyramide has not been tested adequately but may be effective when administered intravenously (254). Adverse effects include dryness of mucosal membranes, especially of the mouth; constipation; urinary retention; and depression of LV contractility. The latter reaction makes it a relatively unattractive option for pharmacological conversion of AF.

E. PROCAINAMIDE. Intravenous procainamide has been used extensively for conversion of AF within 24 h of onset, and several studies suggest that it may be superior to placebo (234,236,259). Procainamide appears to be less useful than some other drugs and has not been tested adequately in patients with persistent AF. Hypotension is the major adverse effect after intravenous administration of procainamide.

F. SOTALOL. Contrary to its relative efficacy for maintenance of sinus rhythm, sotalol has no proven efficacy for pharmacological cardioversion of recent-onset or persistent AF when given either orally or intravenously. It does, however, control the heart rate (237,250,251,256,260).

An issue related to pharmacological cardioversion that arises frequently is whether the antiarrhythmic drug should be started in the hospital or on an outpatient basis. The major concern is the potential for serious adverse effects,

including torsade de pointes ventricular tachycardia. With the exception of those involving low-dose oral amiodarone (225), virtually all studies of pharmacological cardioversion have been limited to hospitalized patients. (For a more extensive discussion of out-of-hospital initiation of antiarrhythmic agents, see Section VIII-E-4, Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients With AF.)

D. Electrical Cardioversion

1. Terminology. Direct-current cardioversion involves delivery of an electrical shock synchronized with the intrinsic activity of the heart, usually by sensing the R wave of the ECG. This technique ensures that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle, from 60 to 80 ms before to 20 to 30 ms after the apex of the T wave (263). Electrical cardioversion is used to normalize all abnormal cardiac rhythms except ventricular fibrillation. The term defibrillation implies an asynchronous discharge, which is appropriate for correction of ventricular fibrillation but not for AF.

2. Technical Aspects. Successful cardioversion of AF depends on the nature of the underlying heart disease and the current density delivered to the atrial myocardium. The latter, in turn, depends on the voltage of the defibrillator capacitor, the output waveform, the size and position of the electrode paddles, and transthoracic impedance. The current density delivered decreases as the impedance increases for a given paddle surface area. The impedance (264) is related to the size and composition of the electrode paddles, the contact medium between the electrodes and the skin, the distance between the paddles, body size, phase of the respiratory cycle, number of shocks delivered, and interval between shocks. Proper attention to each of these variables is important for successful cardioversion.

The electrical resistance between the electrode paddles and the skin should be minimized by the use of electrolyte-impregnated pads. Pulmonary tissue between the paddles and the heart inhibits conduction of current, so shocks delivered during expiration and with chest compression deliver higher levels of energy to the heart. Large electrode paddles result in lower impedance than smaller ones, but when the paddles are too large, current density through cardiac tissue is insufficient to achieve cardioversion, whereas undersized paddles may produce too much current density and cause injury. Animal experiments have shown that the optimum diameter is one that approximates the cross-sectional area of the heart. No definite information has been developed regarding the best paddle size for the specific cardioversion of AF, but a diameter of 8 to 12 cm (264) is generally recommended.

Because the combination of high impedance and low energy reduces the likelihood of successful cardioversion, it has been suggested that impedance be measured to shorten the duration of the procedure, reduce adverse responses, and improve outcome (265,266). Kerber et al. (267) described a technique for automatic impedance-adjusted energy delivery in which energy is automatically increased when the impedance exceeds 70 ohms and claimed improved efficacy in patients with high transthoracic impedances.

The output waveform also influences the amount of energy delivered to the heart during electrical cardioversion. Most equipment used for external cardioversion has a monophasic waveform. In a randomized trial that compared cardioversion with a standard damped sine-wave monophasic waveform with cardioversion applying a rectilinear biphasic waveform, the 77 patients treated with monophasic shocks had a cumulative success rate of 79%, whereas 94% of 88 subjects cardioverted with biphasic shocks were successfully converted to sinus rhythm. Patients in the latter group required less energy for cardioversion. Independent correlates of successful conversion were rectilinear biphasic shocks, thoracic impedance, and the duration of AF (268). In their original description of cardioversion, Lown et al. (269,270) indicated that an anterior-posterior electrode configuration was superior to anterior-anterior positioning, but others disagree (264,271,272). Anterior-posterior positioning allows enough current to reach a sufficient mass of atrial myocardium to effect defibrillation when the pathology associated with AF involves both the RA and the LA (as in patients with atrial septal defect or cardiomyopathy), because the resulting force field encompasses part of the RA wall. A drawback of this configuration is the comparatively wide electrode separation and the amount of pulmonary tissue between the anterior paddle and the heart, particularly in patients with emphysema. Placing the anterior electrode to the left of the sternum reduces electrode separation and the amount of interposed pulmonary tissue. The superiority of one electrode position over another has not been firmly established, but the paddles should be placed directly against the chest wall, under rather than over breast tissue.

Other paddle positions result in less effective current flow through crucial parts of the heart, and their use is discouraged (264). In a randomized controlled study of 301 subjects undergoing elective external cardioversion, patients were allocated to anterior-lateral (ventricular apex and right infraclavicular) or anterior-posterior (sternum and left scapular) paddle positions (273). The overall success (adding the outcome of low-energy shocks to that of high-energy shocks) was greater with the anterior-posterior configuration (87%) than with the anterior-lateral alignment (76%), and the energy requirement was lower with the anterior-posterior paddle configuration. Because the optimum paddle configuration for a given patient is not known before cardioversion, the clinician should consider an alternative arrangement if the initial position proves unsuccessful.

3. Clinical Aspects. Cardioversion is performed with the patient having fasted and under adequate general anesthesia to avoid pain related to delivery of the electrical shock. Short-acting anesthetic drugs or agents that produce conscious sedation are preferred, because cardioversion patients should recover rapidly after the procedure and usually do not require overnight hospitalization (274).

The electric shock should be properly synchronized with the QRS complex, which calls for triggering by monitoring the R wave with an appropriately selected lead. In addition to R-wave amplitude, it is important that the monitored lead give a good view of P waves, which facilitates assessment of the outcome of the procedure. The initial energy delivered with a monophasic waveform may be low (50 J) for cardioversion of atrial flutter. Higher energy is required for AF cardioversion, starting with at least 200 J. The energy output is increased successively in increments of 100 J until a maximum of 400 J is reached. Some physicians begin with higher energies to reduce the number of shocks (and thus the total energy) delivered. Lower energies are required with a biphasic waveform. To avoid myocardial damage, the interval between 2 consecutive shocks should not be less than 1 minute (275).

In a recent study (276), 64 patients were randomly assigned to initial monophasic waveform energies of 100, 200, or 360 J. Higher initial energy was significantly more effective than lower levels (immediate success rates were 14% with 100, 39% with 200, and 95% with 360 J, respectively), resulting in fewer shocks and less cumulative energy when 360 J was delivered initially. These data indicate that an initial shock of 100 J is often too low, and an initial energy of 200 J or greater is recommended for electrical cardioversion of AF. Devices that deliver current with a biphasic waveform are available, and these appear to achieve cardioversion at lower energy levels than those using a monophasic waveform.

Rates of electrical cardioversion of AF vary from 70% to 90% (277–279). This variability is explained in part by differences in patient characteristics and in part by the definition of success. The interval at which the result is evaluated ranges in the literature from immediately after cardioversion to several days afterward. Restoration and maintenance of sinus rhythm are less likely to occur through cardioversion when AF has been present for longer than a year than in patients with AF of shorter duration.

Over time, the proportion of AF caused by rheumatic heart disease has declined and the average age of the population has increased (277,279,280), whereas the incidence of lone AF has remained constant. These factors make it difficult to compare recent and older data on the outcome of cardioversion. In a large consecutive series of patients undergoing cardioversion of AF, 24% were classified as having ischemic heart disease, 24% rheumatic valvular disease, 15% lone AF, 11% hypertension, 10% cardiomyopathy, 8% nonrheumatic valvular disease, 6% congenital heart disease, and 2% treated hyperthyroidism (277). Seventy percent of the patients were in sinus rhythm 24 h after cardioversion. Multivariate analysis revealed that short duration of AF, presence of atrial flutter, and younger age were independent predictors of success, whereas LA enlargement, underlying heart disease, and cardiomegaly predicted failure. These authors developed a scheme expressing the likelihood of success to facilitate clinical decision making and improve cost-effectiveness by avoiding cardioversion in patients unlikely to sustain sinus rhythm.

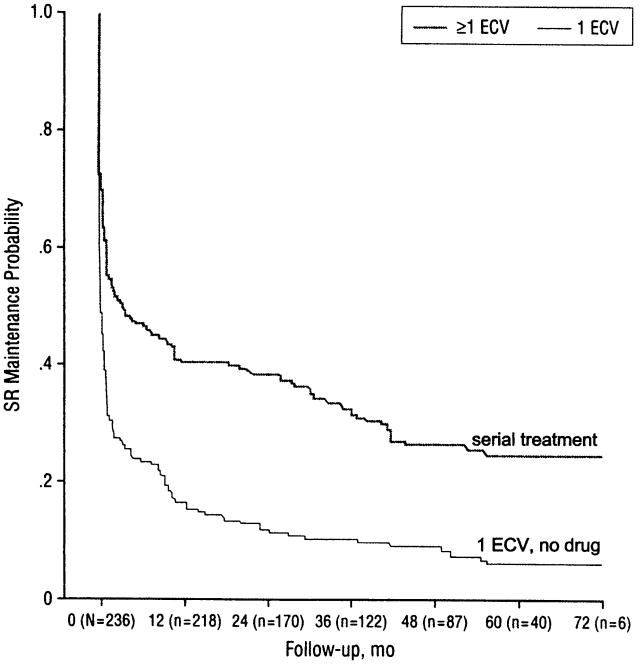

Figure 13. Arrhythmia-free survival after electrical cardioversion in patients with persistent atrial fibrillation. The lower curve represents outcome after a single shock when no prophylactic drug therapy was given. The upper curve depicts the outcome with repeated electrical cardioversions in conjunction with antiarrhythmic drug prophylaxis. ECV indicates electrical cardioversion; SR, sinus rhythm. Reproduced with permission from van Gelder et al., Arch Intern Med 1996;156:2585–92, © 1996, American Medical Association (304).

The primary success rate as measured 3 days after cardioversion in 100 consecutive subjects (279) was 86%; this increased to 94% when the procedure was repeated during treatment with quinidine or disopyramide after an initial failure to convert the rhythm. Only 23% of the patients remained in sinus rhythm after 1 year and 16% after 2 years; in those who relapsed, repeated cardioversion with antiarrhythmic medication resulted in sinus rhythm in 40% and 33% after 1 and 2 years, respectively. For patients who relapsed again, a third cardioversion resulted in sinus rhythm in 54% at 1 year and 41% at 2 years. Thus, sinus rhythm can be restored in a substantial proportion of patients by direct-current cardioversion, but the rate of relapse is high unless concomitant antiarrhythmic drug therapy is given (Fig. 13). For patients for whom initial attempts at cardioversion fail, available adjunctive strategies include alternative electrode positions, concomitant administration of intravenous ibutilide, and delivery of higher energy with the use of 2 defibrillators. It is anticipated that external cardioversion with a biphasic shock waveform will reduce the need for these adjunctive maneuvers.

4. Transvenous Electrical Cardioversion. A technique for delivering high-energy (200 to 300 J) direct current internally for cardioversion of AF was introduced by Lévy et al. in 1988 (281,282), using an RA catheter and a backplate. In

a randomized trial, internal cardioversion was superior to external countershock, particularly in obese patients and patients with chronic obstructive lung disease, but the frequency of recurrence of AF over the long term did not differ between the 2 methods. A monophasic shock waveform was used for external cardioversion in the study; use of a biphasic waveform would likely necessitate internal cardioversion considerably less frequently. Other techniques for internal cardioversion apply low-energy (less than 20 J) shocks via a large-surface cathodal electrode in the RA and an anode in the coronary sinus or left pulmonary artery (283–286). These techniques have been successful for restoration of sinus rhythm in 70% to 90% of mixed cohorts, including those who did not respond to external cardioversion (285–287). Low-energy internal cardioversion does not require general anesthesia but is performed under sedation. Indications might include implanted pacemakers, defibrillators, or drug infusion pumps, but these are presently under investigation.

5. Electrical Cardioversion in Patients With Implanted Pacemakers and Defibrillators. Cardioversion of patients with implanted pacemaker and defibrillator devices is feasible and safe when appropriate precautions are taken to prevent damage. Pacemaker generators and defibrillators are designed with circuits protected against sudden external electrical discharges, but programmed data may nevertheless be altered by sudden current surges. Electricity conducted along an implanted electrode lead to the endocardium may cause myocardial injury associated with a temporary or permanent increase in stimulation threshold. When pronounced, this may cause exit block that results in failure of ventricular capture. The implanted device should be interrogated immediately before and after cardioversion to verify appropriate pacemaker function and should be reprogrammed if necessary to increase generator output. Devices are typically implanted anteriorly, and the paddles used for external cardioversion should be positioned as distant as possible from them, preferably in the anterior-posterior configuration. The risk of exit block is greatest when one paddle is positioned near the impulse generator and the other over the cardiac apex, or lower with the anterior-posterior electrode configuration and in pacemakers with bipolar lead systems (288,289). Low-energy internal cardioversion in patients with implanted pacemakers and electrodes positioned in the RA and coronary sinus or left pulmonary artery does not interfere with pacemaker function (290).

6. Risks and Complications. The risks of electrical cardioversion are mainly related to embolic events and cardiac arrhythmias.

A. EMBOLISM. Thromboembolic events have been reported in between 1% and 7% of patients who did not receive prophylactic anticoagulation before cardioversion of AF (291,292). Prophylactic antithrombotic therapy is discussed below.

B. ARRHYTHMIAS. Various benign arrhythmias may arise after cardioversion that commonly subside spontaneously, especially ventricular and supraventricular premature beats, bradycardia, and short periods of sinus arrest (293). More dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may be precipitated in patients with hypokalemia or digitalis intoxication (294,295). Serum potassium levels should be in the normal range for safe, effective cardioversion. Cardioversion is contraindicated in cases of digitalis toxicity because the ventricular tachyarrhythmias that are provoked may be difficult to terminate. A serum digitalis level in the therapeutic range does not exclude clinical toxicity but is not generally associated with malignant ventricular arrhythmias during cardioversion (296), so it is not routinely necessary to interrupt digoxin use before elective cardioversion of AF. It is important to exclude clinical and ECG signs of digitalis excess and to delay cardioversion until the toxic state has been eliminated, which usually requires more than 24 h.

In patients with long-standing AF, cardioversion commonly unmasks underlying sinus node dysfunction. A slow ventricular response to AF in the absence of drugs that slow conduction across the AV node may indicate an intrinsic conduction defect. The patient should be evaluated before cardioversion with these issues in mind to avoid symptomatic bradycardia (297). When this risk is anticipated, a transvenous or transcutaneous pacemaker can be used prophylactically.

C. MYOCARDIAL INJURY. Animal experiments show a wide margin of safety between the energy required for cardioversion of AF and that associated with clinically relevant myocardial depression (298,299). Even without apparent myocardial damage, however, transient ST-segment elevation may appear on the ECG after cardioversion (300,301), and blood levels of creatine kinase may rise. In a study of 72 elective cardioversion attempts involving an average energy greater than 400 J (range 50 to 1280 J), serum troponin-T and -I levels did not rise significantly. There was a small increase in creatinine kinase-MB mass levels above the proportion attributable to skeletal muscle trauma in 10% of patients, and this was related to the energy delivered (302). Myocardial damage, even on a microscopic level, related to direct-current cardioversion has not been confirmed and is probably not clinically significant.

Before electrical cardioversion, prophylactic drug therapy to prevent early recurrence of AF should be considered individually for each patient. For example, a patient with lone AF of relatively short duration is less likely to develop early recurrence than a patient with heart disease and a longer duration of AF. The latter patient stands to gain more potential benefit from prophylactic antiarrhythmic drug therapy before cardioversion. Should relapse (particularly early relapse) occur, antiarrhythmic therapy is recommended in conjunction with the second attempt. Further cardioversion is of limited value, and patients should be

selected carefully. In patients who are highly symptomatic, for example, infrequently repeated cardioversion may be an acceptable approach.

Recommendations for Pharmacological or Electrical Cardioversion of AF

Class I

1. **Immediate electrical cardioversion in patients with paroxysmal AF and a rapid ventricular response who have ECG evidence of acute MI or symptomatic hypotension, angina, or HF that does not respond promptly to pharmacological measures. (*Level of Evidence: C*)**
2. **Cardioversion in patients without hemodynamic instability when symptoms of AF are unacceptable. (*Level of Evidence: C*)**

Class IIa

1. **Pharmacological or electrical cardioversion to accelerate restoration of sinus rhythm in patients with a first-detected episode of AF. (*Level of Evidence: C*) (See Tables 6, 7, and 8 for recommended drugs.)**
2. **Electrical cardioversion in patients with persistent AF when early recurrence is unlikely. (*Level of Evidence: C*)**
3. **Repeated cardioversion followed by prophylactic drug therapy in patients who relapse to AF without antiarrhythmic medication after successful cardioversion. (*Level of Evidence: C*)**

Class IIb

1. **Pharmacological agents for cardioversion to sinus rhythm in patients with persistent AF. (*Level of Evidence: C*) (See Tables 6, 7, and 8 for recommended drugs.)**
2. **Out-of-hospital administration of pharmacological agents for cardioversion of first-detected, paroxysmal, or persistent AF in patients without heart disease or when the safety of the drug in the particular patient has been verified. (*Level of Evidence: C*) (See Table 8.)**

Class III

1. **Electrical cardioversion in patients who display spontaneous alternation between AF and sinus rhythm over short periods of time. (*Level of Evidence: C*)**
2. **Additional cardioversion in patients with short periods of sinus rhythm who relapse to AF despite multiple cardioversion procedures and prophylactic antiarrhythmic drug treatment. (*Level of Evidence: C*)**

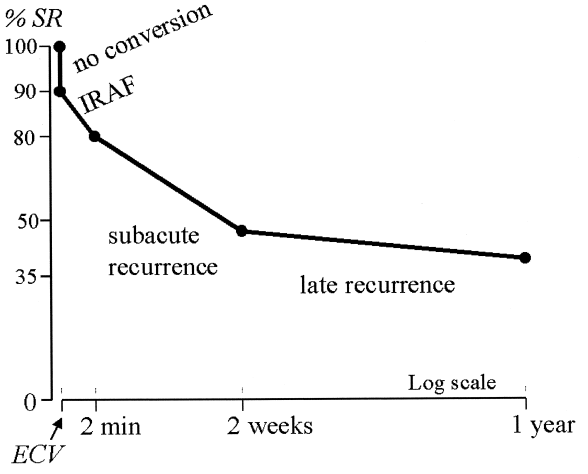

Figure 14. Hypothetical illustration of cardioversion failure. Three types of recurrences after electrical cardioversion of persistent AF are shown. The efficacy of drugs varies in enhancement of shock conversion and suppression of recurrences. ECV indicates external cardioversion; IRAF, first recurrence of AF after cardioversion; and SR, sinus rhythm. Modified with permission from van Gelder IC, et al. Am J Cardiol Vol. 84, Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation, pp. 147R–151R. 1999, with permission from Excerpta Medica Inc. (388).

E. Maintenance of Sinus Rhythm

1. Pharmacological Therapy to Prevent Recurrence of AF.

A. GOALS OF TREATMENT. Maintenance of sinus rhythm is relevant in patients with paroxysmal AF (in whom episodes terminate spontaneously) and persistent AF (in whom electrical or pharmacological cardioversion is necessary to restore sinus rhythm). Whether paroxysmal or persistent, AF is a chronic disorder, and recurrence is likely at some point in most patients (Figs. 13 and 14) (303,304,388). Most patients with AF will therefore need prophylactic treatment with antiarrhythmic drugs if sinus rhythm must be maintained.

The goal of maintenance therapy is suppression of symptoms and sometimes prevention of tachycardia-induced cardiomyopathy due to AF. It is not yet known whether maintenance of sinus rhythm prevents thromboembolism, HF, or death (178,305). Because the clinical factors that predispose a patient to recurrent AF (advanced age, history of HF, hypertension, LA enlargement, and LV dysfunction) are also risk factors for thromboembolism, the risk of stroke may not be reduced by correction of the rhythm. Pharmacological maintenance of sinus rhythm may reduce morbidity in patients with HF (227,306), but one observational study demonstrated that the strategy of serial cardioversion of persistent AF did not prevent complications (307). Pharmacological therapy to maintain sinus rhythm is indicated in patients who have troublesome symptoms related to paroxysmal AF or recurrence after cardioversion and who can tolerate antiarrhythmic drugs.

Throughout this document, reference is made to the Vaughan Williams classification of antiarrhythmic drugs (308), which has been modified to include drugs that

Table 9. Vaughan Williams Classification of Antiarrhythmic Drug Actions

Type IA
Disopyramide
Procainamide
Quinidine
Type IB
Lidocaine
Mexiletine
Type IC
Flecainide
Moricizine
Propafenone
Type II
Beta-blockers (e.g., propranolol)
Type III
Amiodarone
Bretylium
Dofetilide
Ibutilide
Sotalol
Type IV
Calcium-channel antagonists (e.g., verapamil and diltiazem)

Modified with permission from Vaughn Williams EM. A classification of antiarrhythmic action as reassessed after a decade of new drugs. J Clin Pharmacol 1984;24:129–47, © 1984 by Sage Publications Inc. (308) to include compounds introduced after publication of the original classification.

became available after the original classification was developed (Table 9).

B. END POINTS IN ANTIARRHYTHMIC DRUG STUDIES. Over the past decades, various antiarrhythmic drugs have been investigated for maintenance of sinus rhythm in patients with AF. The number and quality of studies with each drug are limited (few meet current standards of good clinical practice), and end points vary. In studies of paroxysmal AF, the proportion of patients without recurrence at the end of follow-up, the time to first recurrence, the number of recurrences over a specified interval (an example of arrhythmia burden), or combinations of these data have been reported. The arrhythmia burden and quality-of-life assessments from the patient's viewpoint have not been quantified consistently in studies of maintenance antiarrhythmic therapy.

In studies of persistent AF, the proportion of patients in sinus rhythm at the end of follow-up is a useful end point, but this is a less useful measure in studies of paroxysmal AF. Most studies involving patients with persistent AF used electrical cardioversion to restore sinus rhythm, with antiarrhythmic drug prophylaxis started before or after electrical cardioversion. Because transtelephonic monitoring reveals clustering of the majority of recurrences in the first few weeks after cardioversion (309,310), the median time to first recurrence may not differ between drug and placebo. Because recurrent AF tends to persist, neither the interval between recurrences nor the number of episodes in a given period of time (arrhythmia burden) represents a suitable end point unless a serial cardioversion strategy is used.

Given these differences, the appropriate end points for evaluation of treatment efficacy in patients with paroxysmal and persistent AF have little in common. This hampers evaluation of treatment strategies aimed at maintenance of sinus rhythm in cohorts containing both paroxysmal and persistent AF patients. Studies of mixed cohorts have not contributed heavily to the development of these guidelines.

Recurrence of AF is not equivalent to treatment failure. In several studies (311,312), patients with recurrent AF often chose to continue treatment with a drug, perhaps because episodes of AF were less frequent, shorter, or associated with milder symptoms. A reduction in arrhythmia burden may constitute therapeutic success for some patients, whereas any recurrence of AF may seem intolerable to others. Assessment based on time to recurrence in paroxysmal AF or the number of patients in sinus rhythm after cardioversion in persistent AF may overlook potentially valuable treatment strategies. The duration of follow-up varied considerably among studies and was generally insufficient to permit meaningful extrapolation to years of treatment in this often lifelong cardiac rhythm disorder.

Available studies are far from uniform in many other respects as well. Underlying heart disease or extracardiac disease is present in 80% of patients with persistent AF, but this is not always described in sufficient detail. It is also not always clear when patients had a first episode of AF and whether it was recent or persistent AF, and the frequency of previous episodes and previous electrical cardioversions are not uniformly described. The efficacy of treatment for atrial flutter and AF is usually not reported separately. Controlled trials of antiarrhythmic drugs usually contain few high-risk patients (those at risk of drug-induced HF, proarrhythmia, or conduction disturbances), and this should be kept in mind in applying the recommendations below.

C. PREDICTORS OF RECURRENT AF AFTER RESTORATION OF SINUS RHYTHM. Most patients with AF, except those with postoperative AF, eventually experience recurrence. Risk factors for frequent recurrence of paroxysmal AF (more than 1 episode per month) include female gender and underlying heart disease (313). In one study of patients with persistent AF, the 4-year arrhythmia-free survival rate was less than 10% after single-shock electrical cardioversion without prophylactic drug therapy (304). Predictors of recurrences within that interval included hypertension, age greater than 55 years, and AF duration greater than 3 months. Even serial cardioversions and prophylactic drug therapy resulted in freedom from recurrent AF in only approximately 30% of patients in the same study (304). With this serial approach, predictors of recurrence included age greater than 70 years, AF duration greater than 3 months, and HF (304). Other risk factors for recurrent AF include atrial enlargement and rheumatic heart disease; some of the above parameters are interrelated (e.g., duration of AF and atrial size).

2. General Approach to Antiarrhythmic Drug Therapy. Before any antiarrhythmic agent is administered, reversible cardiovascular and noncardiovascular precipitants of AF

should be addressed. Most of these relate to CAD, valvular heart disease, hypertension, and HF. Those who develop AF in association with alcohol intake should practice abstinence. Prophylactic drug treatment is not usually indicated in case of a first-detected episode of AF. Antiarrhythmic drugs may also be avoided in patients with infrequent and well-tolerated paroxysmal AF. Similarly, when recurrences are infrequent and tolerated, patients experiencing breakthrough arrhythmias may not require a change in antiarrhythmic drug therapy. In patients who develop AF only during exercise, administration of a beta-blocker may be effective, but a single specific inciting cause accounts for all episodes of AF in relatively few patients, and a majority will not sustain sinus rhythm without antiarrhythmic drug treatment. Selection of an appropriate agent is based first on safety and is tailored to any underlying heart disease that may be present, as well as the number and pattern of previous episodes of AF (314).

In patients with lone AF, a beta-blocker may be tried first, but flecainide, propafenone, and sotalol are particularly effective. Amiodarone and dofetilide are recommended as alternative therapy. Quinidine, procainamide, and disopyramide are not favored unless amiodarone fails or is contraindicated. For patients with vagally induced AF, however, the anticholinergic activity of long-acting disopyramide makes it a relatively attractive choice. Flecainide and amiodarone represent secondary and tertiary treatment options, respectively, in this situation, whereas propafenone is not recommended because its (weak) intrinsic beta-blocking activity may aggravate vagally mediated paroxysmal AF. In patients with adrenergically mediated AF, beta-blockers represent first-line treatment, followed by sotalol and amiodarone. In patients with adrenergically mediated lone AF, amiodarone should be chosen later in the sequence of drug therapy (Fig. 11).

When treatment with a single drug fails, combinations of antiarrhythmic drugs may be tried. Useful combinations include a beta-blocker, sotalol or amiodarone, plus a type IC agent. A drug that is initially safe may become proarrhythmic when the patient develops CAD or HF or starts other medication that in combination may be arrhythmogenic. Thus, the patient should be alerted to the potential significance of such symptoms as syncope, angina pectoris, or dyspnea and warned about the use of noncardiac drugs that can prolong the QT interval. A useful source of information is the Internet site http://www.torsades.org. Monitoring of antiarrhythmic drug treatment varies with the agent involved and with patient factors. Prospective trial data on upper limits of drug-induced increased in QRS duration or QT prolongation are not available. The following recommendations are the consensus of the writing committee. With type IC drugs, QRS widening should not be permitted to exceed 150% of the pretreatment QRS duration. Exercise testing may be helpful to detect QRS widening that occurs only at rapid heart rates (use-dependent conduction slowing). For type IA or type III drugs, with the possible exception of amiodarone, the corrected QT interval in sinus rhythm should remain below 520 ms. During follow-up, plasma potassium and magnesium levels and renal function should be checked periodically, because renal insufficiency leads to drug accumulation and predisposes to proarrhythmia. In individual patients, serial noninvasive tests may be appropriate to reevaluate LV function, especially if clinical HF develops during treatment of AF.

3. Pharmacological Agents to Maintain Sinus Rhythm. Fourteen controlled trials of drug prophylaxis involving patients with paroxysmal AF have been published, and there have been 22 published trials of drug prophylaxis for maintenance of sinus rhythm in patients with persistent AF. Comparative data are not sufficient to permit subclassification by drug or etiology. Individual drugs, listed alphabetically, are described below, and dosages for maintenance of sinus rhythm are given in Table 10.

A. AMIODARONE. Available evidence suggests that amiodarone is effective for maintenance of sinus rhythm in patients with AF but is associated with a relatively high incidence of side effects compared with placebo (315). Amiodarone is usually used as a second-line or last-resort agent. Of the 403 patients in the CTAF study (316), most had first-time paroxysmal (46%) or persistent (54%, duration less than 6 months) AF. AF was considered persistent when more than half the previous episodes had required pharmacological or electrical intervention. This definition implies that many of the patients designated as having persistent AF actually had spontaneously terminating paroxysmal AF. Amiodarone prevented further attacks beyond the first month in 69% of patients, significantly more than did propafenone or sotalol (each of which achieved complete suppression in 39% of 101 patients). Nevertheless, 11% of the patients assigned to sotalol or propafenone stopped treatment because of side effects after a mean of 468 days, compared with 18% of patients given amiodarone. A placebo-controlled study of amiodarone and sotalol that predominantly involved patients with paroxysmal AF (317) produced results similar to those in the CTAF study. Other uncontrolled, observational studies in patients with paroxysmal AF refractory to 1 or more type I agents support the antiarrhythmic efficacy of amiodarone (318–320).

The selection of a pharmacological agent should be based on the arrhythmia burden, type of underlying heart disease, severity of symptoms, risk of side effects, and patient preferences. Considering the paucity of adequate data from randomized trials, as well as its side effect profile, amiodarone should only be used cautiously as a first-line agent in paroxysmal AF. An exception is its use in patients with HF, for whom amiodarone appears to offer distinct advantages over other agents in terms of relative risks and benefits.

There are scant prospective comparative data available on the use of amiodarone to maintain sinus rhythm in patients with persistent AF, but a favorable outcome has been reported when amiodarone was given as a last-resort agent in uncontrolled studies. Amiodarone is particularly useful in AF complicated by HF, but its use is limited by potentially severe extracardiac side effects. The use of low-dose amio-

Table 10. Typical Doses of Drugs Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation**

Drug*	Daily Dosage	Potential Adverse Effects
Amiodarone†	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsade de pointes (rare), hepatic toxicity, thyroid dysfunction
Disopyramide	400–750 mg	Torsade de pointes, HF, glaucoma, urinary retention, dry mouth
Dofetilide‡	500–1000 mcg	Torsade de pointes
Flecainide	200–300 mg	Ventricular tachycardia, congestive HF, enhanced AV nodal conduction (conversion to atrial flutter)
Procainamide	1000–4000 mg	Torsade de pointes, lupus-like syndrome, GI symptoms
Propafenone	450–900 mg	Ventricular tachycardia, congestive HF, enhanced AV nodal conduction (conversion to atrial flutter)
Quinidine	600–1500 mg	Torsade de pointes, GI upset, enhanced AV nodal conduction
Sotalol‡	240–320 mg	Torsade de pointes, congestive HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

GI indicates gastrointestinal; AV, atrioventricular; and HF, heart failure.
*Drugs are listed alphabetically.
**The drugs and doses given here have been determined by consensus based on published studies.
†A loading dose of 600 mg per day is usually given for one month or 1000 mg per day over 1 week.
‡Dose should be adjusted for renal function and QT-interval response during in-hospital initiation phase.

darone (200 mg daily or less) may be effective and may be associated with fewer side effects (218,316,322).

To date, only a few randomized studies have been performed with amiodarone after cardioversion in patients with persistent AF. Amiodarone was tested as a first-line agent in a study confined to postcardioversion patients (322). After electrical cardioversion, but before randomization, patients were stratified according to age, duration of AF, mitral valve disease, and cardiac surgery. After 6 months, amiodarone was more effective than quinidine; 83% of patients remained in sinus rhythm with amiodarone vs. 43% who were given quinidine. Amiodarone therapy was associated with fewer side effects than quinidine over this interval, but side effects tend to occur after more prolonged treatment with amiodarone. In a single-crossover study of 32 patients randomized to amiodarone or quinidine (218) in which patients with persistent AF for more than 3 weeks were treated with amiodarone when pharmacological conversion did not occur with quinidine (electrical cardioversion was not used), amiodarone was better tolerated, and considering the patients whose treatment crossed over, it was far more effective in achieving conversion of AF and long-term maintenance of sinus rhythm. After 9 months, 18 (67%) of 27 amiodarone-treated patients were in sinus rhythm vs. 2 (12%) of 17 patients taking quinidine.

Among uncontrolled studies (223,318,319,323–326), one involved 89 patients with persistent AF for whom previous treatments had failed; actuarially, 53% of these patients were in sinus rhythm after 3 years of amiodarone therapy (323). In another study (318) of 110 patients with refractory AF or atrial flutter for whom a median of 2 type I agents had failed (57 with paroxysmal AF) and who were followed up for 5 years, amiodarone (268 plus or minus 100 mg daily) was associated with recurrence in 9% of patients with persistent AF and 40% of those with paroxysmal AF. Several other uncontrolled studies support the use of amiodarone as a last-resort agent (319,324–326). In one, a dose of 200 mg per day appeared to be effective in patients for whom cardioversion had failed; 52% underwent repeated cardioversion with success for 12 months (223).

B. BETA-BLOCKERS. One randomized, open-label, crossover study showed that atenolol 50 mg once daily was as effective as sotalol 80 mg twice daily and better than placebo at suppressing ECG-documented episodes of AF, reducing their duration and associated symptoms (327). The study involved stable, nonpostoperative patients. The dose of sotalol was lower than that generally used for suppression of recurrent AF, and both drugs were well tolerated. Beta-blockers have the advantage of controlling the ventricular rate in the event AF recurs during treatment, and they thereby reduce or abolish associated symptoms, but the patient's unawareness of recurrent AF may be a disadvantage in certain cases. These agents may benefit postoperative patients but may aggravate vagally mediated AF. One placebo-controlled study (328) of 394 patients found metoprolol to be moderately effective in preventing postshock recurrences of AF (reduced to 49% vs. 60%, respectively).

C. DIGOXIN. The evidence available does not support a role for digitalis in suppressing recurrent AF in most patients. The lack of an AV blocking effect during sympathetic stimulation results in poor rate control with digoxin, and hence its use does not usually reduce symptoms associated with recurrent paroxysmal AF (22).

D. DISOPYRAMIDE. Several small randomized studies support the efficacy of disopyramide to prevent recurrent AF after electrical cardioversion. One study comparing

propafenone and disopyramide showed equal efficacy, but propafenone was better tolerated (329). Treatment with disopyramide for more than 3 months after cardioversion was associated with an excellent long-term outcome in an uncontrolled study (98 of 106 patients were free of recurrent AF; of these, 67% remained in sinus rhythm after a mean of 6.7 years). Although the duration of AF was more than 12 months in most of these patients, few had significant underlying cardiac disease other than previously treated thyrotoxicosis. It is not clear, therefore, whether disopyramide was the critical factor in suppressing AF (330). Disopyramide has negative inotropic and negative dromotropic effects that respectively may cause HF or precipitate AV block (329–333).

E. DOFETILIDE. Several large-scale, double-blind, randomized studies support the efficacy of dofetilide for prevention of AF or atrial flutter (261,334). To reduce the risks of proarrhythmia, dofetilide should be initiated in the hospital at a dose titrated to renal function and the QT interval. This provides a measure of safety in the event of early proarrhythmic toxicity. Combined results from 966 patients in the SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) and EMERALD studies found dofetilide treatment to be associated with conversion to sinus rhythm, and this effect was dose related: 6%, 10%, and 30% of patients responded within 72 h to 125, 250, and 500 mcg twice a day, respectively (261,334). Most (87%) conversions occurred within 30 h after treatment was initiated. The incidence of torsade de pointes was 0.8%. Four of 5 of these incidents occurred in the first 3 days. In SAFIRE-D, dofetilide was associated with 40%, 52%, and 66% of patients in sinus rhythm at 6 months in the 125-, 250-, and 500-mcg-daily dosage groups, respectively, compared with 21% with placebo (261). In EMERALD, suppression of recurrence of AF by dofetilide was also dose dependent: 51%, 57%, and 71% of patients were in sinus rhythm with 125, 250, and 500 mg daily, respectively, compared with approximately 25% with placebo and 60% with sotalol (334).

F. FLECAINIDE. Two placebo-controlled studies (311,335) found flecainide to be effective in postponing the first recurrence of AF and the overall time spent in AF; and other randomized studies (336,337) found its efficacy to be comparable to that of quinidine, with fewer side effects. Efficacy is further supported by uncontrolled studies (312,338).

Van Gelder et al. (339) showed that time to recurrence of AF was significantly longer with flecainide than without treatment, and severe ventricular proarrhythmia or sudden death was not observed with a mean dose of 199 mg daily. Side effects occurred in 5 patients (9%) and were predominantly related to negative dromotropism, with or without syncope. Compared with long-acting quinidine (1,100 mg daily), flecainide (200 mg daily) was superior in preventing recurrent AF after cardioversion and was associated with fewer side effects, but 1 patient died suddenly a month after entry, presumably due to proarrhythmia (339).

G. MORIZICINE. Although few data are presently available regarding the efficacy of moricizine (340), further studies may define a role for its use in patients with AF.

H. PROCAINAMIDE. No adequate studies are available. Long-term treatment with procainamide is frequently associated with development of antinuclear antibodies and is occasionally associated with arthralgias or agranulocytosis.

I. PROPAFENONE. The UK PSVT (paroxysmal supraventricular tachycardia) study was a large, randomized, placebo-controlled trial of propafenone in which transtelephonic monitoring was used to detect and document relapses of AF (341). The primary end point was time to first recurrence or adverse event. A dose of 300 mg twice daily was effective; 300 mg 3 times a day was even more effective but caused more frequent side effects. In one small, placebo-controlled study (342), only those patients who tolerated an initial average propafenone dose of 688 mg per day were randomized to the drug group. Compared with placebo, propafenone reduced the percentage of days in AF from 51% to 27%. Propafenone was more effective than quinidine in another randomized comparison (343). In an open-label randomized study involving 100 AF patients (approximately half with paroxysmal and half with persistent AF), propafenone and sotalol were equally effective in maintaining sinus rhythm (30% vs. 37% of patients in sinus rhythm at 12 months, respectively) (344). The pattern of AF (paroxysmal or persistent), LA size, and previously unsuccessful drug therapy did not predict the response, but statistical power was quite limited. Other uncontrolled studies, usually involving selected patients previously refractory to other antiarrhythmic drugs, also support the efficacy of propafenone (345–349).

Like other highly effective type IC drugs, propafenone should not be used in patients with ischemic heart disease or LV dysfunction. Close follow-up is necessary to avoid adverse effects due to changes in cardiac condition (e.g., development of ischemia or HF).

In a randomized study, propafenone and disopyramide appeared to be equally effective in preventing postcardioversion AF, but propafenone was better tolerated. As mentioned previously, in the study by Reimold et al. (344), propafenone was as effective as sotalol. The effect of propafenone in the CTAF study (316) is discussed above. A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF have shown propafenone to be effective in terms of maintenance of sinus rhythm and reduction of arrhythmia-related complaints (348).

J. QUINIDINE. Quinidine has not been evaluated extensively in patients with paroxysmal AF but appears to be approximately as effective as type IC drugs (336,337,350). In one study (343), quinidine was less effective than propafenone

(22% of patients were attack free with quinidine vs. 50% with propafenone). Side effects are more prominent than with other antiarrhythmic drugs, and proarrhythmia is a particular concern. A meta-analysis involving patients treated with quinidine to maintain sinus rhythm after cardioversion of AF showed an increase in mortality compared with placebo, but this was based on a total of 12 deaths (351).

A meta-analysis of 6 trials found quinidine to be superior to no treatment (50% vs. 25% of patients, respectively, remained in sinus rhythm over a 1-year period). Total mortality was significantly higher among patients given quinidine (12 of 413 patients; 2.9%) than among those not given quinidine (3 of 387 patients; 0.8%) (351). In a registry analysis (352), 6 of 570 patients less than 65 years old died suddenly shortly after restoration of sinus rhythm while taking quinidine. Up to 30% of patients taking quinidine experience intolerable side effects, most commonly diarrhea. Other investigators (353) found sotalol and quinidine to be equally effective for maintaining sinus rhythm after electrical cardioversion of AF. Sotalol but not quinidine reduced heart rate significantly in patients with recurrent AF, contributing to fewer symptoms with sotalol therapy (278,333,351,353–361).

K. SOTALOL. Sotalol is not effective for conversion of AF to sinus rhythm, but it may be used to prevent AF. To date, 2 placebo-controlled studies (362,363) have been published involving AF patients who were in sinus rhythm at entry and who had at least 1 documented prior episode of AF. Patients considered at risk of proarrhythmia, HF, or AV conduction disturbances were excluded. Whether any of these patients had undergone previous electrical cardioversion was not reported. Sotalol appeared to be safe and effective at doses ranging from 80 to 160 mg twice daily in these carefully selected patient populations (316,344,362).

In another study (344), sotalol and propafenone appeared to be equally effective for maintenance of normal sinus rhythm. In the CTAF study, sotalol and propafenone (separately) were less effective than amiodarone in terms of the number of patients without documented recurrence of AF. The difference between outcomes with these drugs was less marked when the number of patients continuing treatment without side effects was considered. In an uncontrolled study of a stepped-care approach using propafenone and, after failure of propafenone, sotalol in refractory patients, paroxysmal AF occurred in nearly 50% of patients, but only 27% of patients with persistent AF converted to sinus rhythm at 6 months (349).

In a multicenter study, sotalol was as effective as slow-release quinidine sulfate (353) in preventing recurrent AF, was better tolerated than quinidine, and was more effective in suppressing symptoms in patients who relapsed into AF, probably because it induces a slower ventricular rate. Several studies found sotalol and the combination of quinidine and verapamil to be equally effective after cardioversion of AF, although significant ventricular arrhythmias (including torsade de pointes) were more frequent with quinidine (250,364).

L. VERAPAMIL AND DILTIAZEM. There is no evidence to support the antiarrhythmic efficacy of calcium channel antagonist drugs in patients with paroxysmal AF, but they reduce heart rate during an attack such that symptoms may disappear despite recurrences of AF.

4. Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients With AF. Recommendations for out-of-hospital initiation or intermittent use of antiarrhythmic drugs differ for patients with paroxysmal and persistent AF. The aims also differ from those listed in Table 5. In patients with paroxysmal AF, the aims are to stop an attack ("pill-in-the-pocket" approach), to prevent recurrences, or a combination of both. In patients with persistent AF, the aims of out-of-hospital drug initiation are to achieve pharmacological cardioversion of AF, thereby obviating the need for electrical cardioversion, or to enhance the success of electrical cardioversion (by lowering the defibrillation threshold) and prevent early recurrence of AF. Preadmission treatment may also be designed to ensure adequate plasma concentrations of the drug at the moment recurrences are most likely to occur (beginning after electrical cardioversion), because the pharmacokinetics of most antiarrhythmic drugs are such that peak plasma concentrations do not develop for several days.

Few prospective data are available on the safety of outpatient initiation of antiarrhythmic drug therapy. The most worrisome problem is proarrhythmia (Table 11), which rarely occurs in patients without HF who have normal ventricular function and baseline QT intervals (100,365), and who do not have profound bradycardia. In these patients, as long as sinus or AV node dysfunction is not suspected, propafenone or flecainide may be initiated out of the hospital. Sudden death related to idiopathic ventricular fibrillation in a structurally normal heart may occur in patients with the Brugada syndrome, an inherited cardiac disease characterized by ST-segment elevation in the right precordial ECG leads and frequently accompanied by right bundle-branch block. Cases in which administration of type I antiarrhythmic drugs have unmasked this condition have been reported (366,367). Before therapy with these agents is begun, a beta-blocker or calcium channel antagonist should be given to prevent rapid AV conduction or 1:1 AV conduction if atrial flutter develops (368–372). Because termination of paroxysmal AF with flecainide or propafenone may be associated with bradycardia due to sinus node or AV node dysfunction, an initial conversion trial should be undertaken in the hospital before a patient is declared fit for outpatient "pill-in-the pocket" use of these agents for conversion of subsequent recurrences. Out-of-hospital drug termination should be avoided in patients with symptomatic sick sinus syndrome, AV conduction disturbances, or bundle-branch block. Table 12 lists

Table 11. Types of Proarrhythmia During Treatment With Various Antiarrhythmic Drugs for Atrial Fibrillation or Atrial Flutter According to the Vaughan Williams Classification

A. Ventricular proarrhythmia
- Torsade de pointes (VW type IA and type III drugs)
- Sustained monomorphic ventricular tachycardia (usually VW type IC drugs)
- Sustained polymorphic ventricular tachycardia/VF without long QT (VW types IA, IC, and III drugs)

B. Atrial proarrhythmia
- Provocation of recurrence (probably VW types IA, IC, and III drugs)
- Conversion of AF to flutter (usually VW type IC drugs)
- Increase of defibrillation threshold (a potential problem with VW type IC drugs)

C. Abnormalities of conduction or impulse formation
- Acceleration of ventricular rate during AF (VW type IA and type IC drugs)
- Accelerate conduction over accessory pathway (digoxin, intravenous verapamil, or diltiazem)
- Sinus node dysfunction, atrioventricular block (almost all drugs)

VW indicates the Vaughan Williams classification of antiarrhythmic drugs (308). VF indicates ventricular fibrillation; AF, atrial fibrillation.

other factors associated with proarrhythmic toxicity to type IC agents.

Sotalol may be initiated in outpatients with little or no heart disease as long as the baseline uncorrected QT interval is less than 450 ms, serum electrolytes are normal, and none of the type III drug–related proarrhythmia risk factors are present (Table 12). Safety is greatest when sotalol is started when the patient is in sinus rhythm. Amiodarone can usually be given safely on an outpatient basis, even in patients with persistent AF (323), but in-hospital loading may be more appropriate when earlier restoration of sinus rhythm is needed, as in patients with HF. Some loading regimens involve giving either 600 mg per day for 4 weeks (323) or 1 g per day for 1 week (223), followed by lower maintenance doses. Quinidine, procainamide, and disopyramide should generally not be started out of hospital, but an exception may be made for disopyramide in patients without heart disease in whom the QT interval is normal. Currently, the standards for use of dofetilide do not permit out-of-hospital initiation. These recommendations are general guidelines regarding out-of-hospital initiation of drug therapy, but the decision should be individualized for each patient.

Transtelephonic monitoring or other ECG surveillance methods may be used to monitor conduction disturbances as pharmacological antiarrhythmic therapy is initiated in patients with AF. Specifically, the PR interval (flecainide, propafenone, sotalol, and amiodarone), QRS duration (flecainide and propafenone), and QT interval (sotalol, amiodarone, and disopyramide) should be measured. As a gen-

Table 12. Factors Predisposing to Drug-Induced Ventricular Proarrhythmia

VW Type IA and Type III Agents	VW Type IC Agents
Long QT interval (QTc greater than 460 ms)	Wide QRS duration (more than 120 ms)
Long QT-interval syndrome	Associated VT
Structural heart disease, LVH	Structural heart disease
Depressed LV function*	Depressed LV function*
Hypokalemia/hypomagnesemia*	
Female gender	
Renal dysfunction*	
Bradycardia*	Rapid ventricular response rate*
1. (Drug-induced) sinus node disease or AV block	1. During exercise
2. (Drug-induced) conversion of AF to sinus rhythm	2. During rapid AV conduction
3. Ectopy producing short-long RR sequences	
Rapid dose increase	Rapid dose increase
High dose (sotalol, dofetilide), drug accumulation*	High dose, drug accumulation*
Addition of drugs*	Addition of drugs*
1. Diuretics	1. Negative inotropic drugs
2. Other QT-prolonging antiarrhythmic drugs	
3. Non-antiarrhythmic drugs listed in: http://www.torsades.org	
Previous proarrhythmia	
After initiation of drug	
Excessive QT lengthening	Excessive (more than 150%) QRS widening

*Some of these factors may develop later after initiation of drug treatment.

VW indicates Vaughan Williams classification (308); QT_c, corrected QT interval; VT, ventricular tachycardia; LVH, left ventricular hypertrophy; LV, left ventricular; AV, atrioventricular; AF, atrial fibrillation.

Table 13. Pharmacological Treatment Before Cardioversion in Patients With Persistent Atrial Fibrillation: Effects of Various Antiarrhythmic Drugs on Acute and Subacute Outcome of Transthoracic Direct Current Shock

	Enhance Conversion by DC Shock and Prevent IRAF*	Suppress SRAF and Maintenance Therapy Class	Recommendation Class	Level of Evidence
Effective	Amiodarone Flecainide Ibutilide Propafenone Propafenone+verapamil Quinidine Sotalol	All drugs in recommendation Class I (except ibutilide) plus beta-blockers	I	B
Uncertain/unknown	Beta-blockers Disopyramide Diltiazem Dofetilide Procainamide Verapamil	Diltiazem Dofetilide Verapamil	IIb	B

All drugs (except beta-blockers and amiodarone) should be initiated in hospital. IRAF indicates immediate recurrence of atrial fibrillation; SRAF, subacute recurrence of atrial fibrillation; and DC, direct current.
*Drugs are listed alphabetically within each class of recommendation.

eral rule, antiarrhythmic drugs should be started at a relatively low dose with upward titration as needed, and the ECG should be reassessed as each dose change is made. The dose of other medication used for rate control should be reduced approximately 6 weeks after initiation of amiodarone and stopped if the rate slows excessively. Concomitant drug therapies (Table 10) should be monitored closely, and both the patient and the physician should be alert to possible deleterious drug interactions.

5. Recurrence of AF After Cardioversion: Implications for Drug Treatment. Although it has long been known that most recurrences of AF occur within the first month after electrical cardioversion, recent research with internal atrial cardioversion (373), as well as day-to-day postconversion studies (309), have established several patterns of recurrence (Fig. 14). In some cases, there is complete failure of direct-current countershock to elicit even a single isolated sinus or ectopic atrial beat, tantamount to a high atrial defibrillation threshold. In others, AF reappears within 1 to 2 minutes after a period of sinus rhythm (374,375). Sometimes recurrence is delayed from 1 day to 2 weeks (309) or more after the shock. Complete shock failure and immediate recurrences occur in approximately 25% of patients undergoing electrical cardioversion, and subacute recurrences occur within 2 weeks in about an equal proportion (374).

Although beta-blockers are unlikely to prevent complete shock failure (lower the defibrillation threshold) or suppress immediate or late recurrences of AF, they may reduce subacute recurrences (328). Conversely, type III drug effects may be less effective for suppression of subacute recurrences than for reducing late recurrences of AF (Table 13). Controlled studies are needed to determine the most effective treatment of immediate and subacute recurrences, but available data suggest that starting pharmacological therapy before electrical cardioversion may enhance immediate success and suppress early recurrences. As a corollary, it seems appropriate to establish therapeutic plasma drug concentrations at the time of cardioversion and for a few weeks thereafter to optimize the chance of success. After cardioversion to sinus rhythm, patients receiving drugs that prolong the QT interval should be observed in the hospital for 24 to 48 h to evaluate the effects of heart rate slowing and to allow for prompt intervention in the event that torsade de pointes develops.

Pretreatment with pharmacological agents may be started out of hospital (see Section VIII-E-4, Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients With AF) or in hospital, immediately before electrical cardioversion. The primary aims are to enhance conversion (e.g., by lowering the cardioversion threshold) and prevent recurrent AF. The risks of pretreatment include the possibility of a paradoxical increase in the defibrillation threshold, as has occurred with flecainide (339); accelerated ventricular rate during loading with type IA or IC drugs in the absence of an AV nodal blocking agent (368–372,376); and ventricular proarrhythmia (Table 11). A loading dose of quinidine (1,200 mg 24 h before electrical cardioversion) was associated with a significant reduction in the number of shocks given and a decreased energy requirement in patients with persistent AF. Quinidine prevented immediate recurrences in almost all of 25 cases compared with 7 of 25 controls (374). When quinidine was administered for approximately 3 days and then patients who did not convert to sinus rhythm were randomized to withdraw or continue quinidine (600 to 800 mg 3 times a day), there was no difference in defibrillation threshold between patients in whom quinidine was continued or withdrawn (278). In-hospital treatment with oral propafenone started 2 days before electrical cardioversion did not influence either the mean defibrillation threshold or the rate of conversion compared with placebo (84% vs. 82%, respectively), but propafenone completely suppressed immediate recurrences (within 10 minutes), so that 84% versus 65% of patients were in sinus rhythm at the end

of the procedure and 74% vs. 53% were in sinus rhythm after 2 days (245).

Propafenone combined with verapamil prevented immediate recurrences of AF after cardioversion, and prophylaxis against subacute recurrences was enhanced by this combination given for 3 days before and 3 days after the shock (310). In a study of 100 patients randomly assigned to electrical cardioversion with or without pretreatment with the type III antiarrhythmic drug ibutilide, 36 of 50 patients in the control group were successfully converted to sinus rhythm compared with all 50 patients in the group treated with ibutilide. In the 14 patients in whom electrical cardioversion was initially unsuccessful, sinus rhythm was subsequently restored when electrical cardioversion was repeated after treatment with ibutilide (377). Others described similar results with ibutilide (378). Amiodarone pretreatment also appears to be effective in patients for whom an initial attempt at electrical cardioversion fails (223,379). Standard therapy with dofetilide includes pretreatment that may produce conversion before the electrical procedure and may decrease the cardioversion threshold, but whether the drug enhances shock conversion or reduces immediate recurrences is not known. Magnesium supplementation does not appear to enhance cardioversion (380).

Pretreatment with pharmacological agents is most appropriate in patients who have previously failed to respond to electrical cardioversion and in those who developed immediate or subacute recurrence of AF. In patients with late recurrence and those undergoing initial cardioversion of persistent AF, pretreatment is optional.

6. Selection of Antiarrhythmic Agents in Patients With Certain Cardiac Diseases.

A. HEART FAILURE. Patients with congestive HF are particularly prone to the ventricular proarrhythmic effects of antiarrhythmic drugs related to underlying myocardial dysfunction and electrolyte disturbances. Randomized trials have demonstrated the safety of amiodarone and dofetilide (given separately) in patients with HF (227,381), and these are the recommended drugs for maintenance of sinus rhythm.

In a subgroup analysis of data from the CHF-STAT study (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) (306), amiodarone reduced the incidence of AF over 4 years to 4% from 8% with placebo in patients with HF. In those patients who had AF, conversion to sinus rhythm occurred in 31% of 51 patients taking amiodarone vs. only 8% with placebo, and this was associated with significantly better survival. A trial of 1,518 patients with symptomatic HF who were randomized to dofetilide or placebo established the clinical advantage of antifibrillatory treatment in HF (227). Dofetilide, initiated in hospital, was associated with a lower incidence of AF (1.9%, 11 of 556 patients) than placebo (6.6%, 35 of 534 patients) after an average of 18 months. With dofetilide, 25 cases of torsade de pointes occurred, three fourths of which occurred within 3 days after treatment was begun. Mortality was equal in both groups (41% and 42%), but dofetilide was associated with a significantly reduced hospital readmission rate for HF.

B. CORONARY ARTERY DISEASE. In stable patients with CAD, beta-blockers may be considered first, but their use is supported by only 2 studies (327,328), and the data on their efficacy for maintenance of sinus rhythm in patients with persistent AF after cardioversion are not convincing (328). Sotalol has substantial beta-blocking activity and may therefore be chosen as the initial antiarrhythmic agent in AF patients with ischemic heart disease because it is associated with less long-term toxicity than amiodarone. Both sotalol and amiodarone have reasonable short-term safety profiles, and amiodarone may be preferred in patients with HF (382–384). Flecainide (385) and propafenone are not recommended in these situations. Quinidine, procainamide, and disopyramide may be considered as third-line treatment choices in patients with CAD. Given the results of the DIAMOND-MI trial (Danish Investigations of Arrhythmias and Mortality on Dofetilide in Myocardial Infarction), dofetilide may be considered as a second-line rather than a third-line antiarrhythmic agent, but this study involved selected post-MI patients in whom the antiarrhythmic benefit balanced the risk of proarrhythmic toxicity. In a straightforward CAD population without MI or HF, it is uncertain whether benefit will outweigh risk, and more experience with the use of dofetilide as a third-line agent is needed before it can be advocated as a second-line agent in these patients.

C. HYPERTENSIVE HEART DISEASE. Patients with LV hypertrophy may be at increased risk of developing torsade de pointes related to early ventricular afterdepolarizations (314,386,387). Thus, a drug that does not prolong the QT interval is preferable as first-line therapy, and in the absence of CAD or marked ventricular hypertrophy (LV wall thickness greater than or equal to 1.4 cm), propafenone and flecainide are reasonable choices. Proarrhythmia with one agent does not predict this type of response to another type of pharmacological agent. For example, patients with LV hypertrophy who develop torsade de pointes during treatment with a type III agent may tolerate a type IC agent uneventfully. Amiodarone prolongs the QT interval but carries a very low risk of ventricular proarrhythmia; its extracardiac toxicity profile relegates it to second-line therapy in these individuals, but amiodarone becomes first-line therapy when marked LV hypertrophy is present. When amiodarone and sotalol either fail or are inappropriate, disopyramide, quinidine, or procainamide may be used as alternatives.

D. WPW SYNDROME. Radiofrequency ablation of the accessory pathway is usually the preferred therapy for patients with preexcitation syndromes and AF. Antiarrhythmic drugs may be useful in selected cases. Digoxin should be

avoided because of the risk of paradoxical acceleration of the ventricular rate during AF in some patients with accessory pathways. Beta-blockers do not decrease conduction over accessory pathways during preexcited periods of AF and could cause hypotension or other complications in patients with tenuous hemodynamics.

Recommendations for Pharmacological Therapy to Maintain Sinus Rhythm

Pharmacological management strategies or algorithms to maintain sinus rhythm in patients with AF (Figs. 9, 10, 11, and 12) are based on available evidence and extrapolated from experience with these agents in other situations.

Class I

1. **Base selection of pharmacological therapy to maintain sinus rhythm in patients with disabling or otherwise troublesome symptoms during AF predominantly on safety. (*Level of Evidence: B*)**
2. **Treat precipitating or reversible causes of AF before initiation of antiarrhythmic drug therapy. (*Level of Evidence: C*)**

Class IIa

1. **Administer pharmacological therapy to maintain sinus rhythm to prevent progression of tachycardia-induced cardiomyopathy due to AF. (*Level of Evidence: C*)**
2. **Infrequent and well-tolerated recurrence of AF may in some cases be deemed a successful outcome of antiarrhythmic drug therapy. (*Level of Evidence: C*)**
3. **Outpatient initiation of antiarrhythmic drug treatment is appropriate in selected patients. (*Level of Evidence: C*)**

Class IIb

1. **Administer pharmacological therapy to maintain sinus rhythm in asymptomatic patients to prevent atrial remodeling. (*Level of Evidence: C*)**
2. **Administer pharmacological therapy to maintain sinus rhythm to prevent thromboembolism or HF in selected patients. (*Level of Evidence: C*)**
3. **Administer combinations of antiarrhythmic agents to maintain sinus rhythm when single-drug therapy fails. (*Level of Evidence: C*)**

Class III

1. **Use of a particular pharmacological agent to maintain sinus rhythm in patients with well-defined proarrhythmia risk factors for that agent. (*Level of Evidence: A*)**
2. **Use of pharmacological therapy to maintain sinus rhythm in patients with advanced sinus node or AV node dysfunction in the absence of a functioning electronic cardiac pacemaker. (*Level of Evidence: C*)**

7. Nonpharmacological Correction of AF. The limited efficacy and proarrhythmic risks of antiarrhythmic drug therapies have led to the exploration of a wide spectrum of alternative nonpharmacological therapies for AF.

A. SURGICAL ABLATION. Based on mapping studies of animal and human AF, Cox (58,81,82,389) developed a surgical procedure (maze operation) that controls AF in more than 90% of selected patients. The mechanism by which the procedure prevents recurrent AF has not been established conclusively, but the creation of barriers to conduction within the RA and LA limits the amount of myocardium available to propagate reentrant wave fronts, thereby inhibiting sustained AF. Incisions encircling the pulmonary veins may prevent initiation of AF by isolating potentially arrhythmogenic foci within or near the pulmonary veins from the remainder of the atria or by isolating atrial regions with the shortest refractory periods. Modifications of the Cox maze operation involve encircling the pulmonary veins by surgical incisions within the LA and radial incisions in both atria that join the mitral and tricuspid valve annuli (390–392).

Surgical operations for AF have been combined successfully with operative correction of a variety of structural cardiac conditions. In patients with highly symptomatic AF who require open-heart operations for valvular, ischemic, and congenital heart disease, consideration should be given to performing a concomitant maze operation for AF or atrial flutter, although this may entail additional risk. The mortality rate of an isolated maze operation is less than 1%, but mortality is higher when the procedure is combined with other types of operative repair. The morbidity associated with the maze operation includes consequences common to median sternotomy and cardiopulmonary bypass, as well as a risk of short-term fluid retention (due to reduced release of atrial natriuretic peptide), transient reduction in LA and RA transport function, and early postoperative atrial tachyarrhythmias. In addition, when the blood supply to the sinus node is disrupted, sinus node dysfunction may require permanent pacemaker implantation. Progressive iterations of these operations have reduced the risk of this complication to less than 10%. Echocardiographic studies suggest that LA and RA transport function is regained postoperatively in more than 90% of patients.

B. CATHETER ABLATION. Given the success of surgical approaches to AF, several catheter ablation strategies have been designed to produce similar effects (393–395). Ablation strategies limited to the RA produce marginal improvement (393), whereas linear ablation in the LA has been more successful in controlling AF. Improvement in as many as 70% to 80% of selected patients with medically refractory AF has been reported with these investigational procedures (395). It has also been recognized that the pulmonary veins are a common location of rapidly depolarizing arrhythmogenic foci that induce paroxysmal AF (48,49,85,396–398). The recognition that foci triggering AF often originate within the pulmonary veins has led to ablation strategies that target this zone or electrically isolate the pulmonary

vein from the LA. Other sites of arrhythmogenic foci that may initiate AF have been found in the superior vena cava, the RA and LA, and the coronary sinus. Ablation of these foci eliminates or reduces the frequency of recurrent AF in more than 60% of patients, but the risk of recurrent AF after a focal ablation procedure is still 30% to 50% over the first year and even higher when more than 1 pulmonary vein is involved. Thus, many patients continue to require antiarrhythmic drug therapy after ablative therapy of AF (399). Potential complications of catheter ablation for AF include systemic embolism, pulmonary vein stenosis, pericardial effusion, cardiac tamponade, and phrenic nerve paralysis. Thus, although these procedures have produced promising results, they have not yet been widely applied.

Atrial flutter may develop not only as a distinct arrhythmia but also during antiarrhythmic drug therapy of AF, especially with type IC agents. Catheter ablation is more effective than antiarrhythmic drugs for treatment of atrial flutter, reducing the recurrence rate from 93% to 5% when used as first-line therapy (400). In addition, the risk of developing AF may also be lower after catheter ablation of atrial flutter than with pharmacological therapy (29% vs. 60% over the first year).

C. SUPPRESSION OF AF BY PACING. Several studies have examined the role of atrial pacing, either from the RA alone or from more than 1 atrial site, to prevent recurrent paroxysmal AF. In patients with standard indications for pacemaker therapy, the risk of AF is lower with atrial than with ventricular pacing (401). Despite this observation, the utility of atrial pacing as a treatment for paroxysmal AF in patients without conventional indications for pacing was not proven in a large controlled trial (402). It has been suggested that the frequency of AF may be lower with dual-site atrial pacing than with single-site pacing (403). A randomized trial of biatrial pacing to prevent recurrent AF (SynbiaPace [Synchronous Biatrial Pacing Therapy]) reported no significant benefit, but a larger trial of dual-site RA pacing (406) is in progress. Although atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing for patients requiring pacemakers for bradyarrhythmias, the use of pacing as a primary therapy for prevention of recurrent AF has not been validated.

D. INTERNAL ATRIAL DEFIBRILLATORS. There has been an interest in internal cardioversion of AF for the past 10 years. Early work using a sheep model (283,407) showed that delivery of a synchronous shock between the high RA and coronary sinus was effective for the termination of AF. A clinical trial of a low-energy transvenous atrial cardioverter/defibrillator that used a 3/3-ms biphasic waveform shock synchronized to the R wave established that internal cardioversion was safe, although the energy required in patients with persistent AF was relatively high (a mean of 3.5 J) (6). An intense amount of basic and clinical research ensued as investigators attempted to find shock waveforms that would reduce the energy requirements for cardioversion, thereby making the shock tolerable to awake patients.

One implantable cardioverter/defibrillator capable of atrial sensing and defibrillation as well as ventricular sensing and pacing was evaluated in 290 AF patients (408). Each had experienced failed therapy with 4 antiarrhythmic drugs. The mean LV ejection fraction was greater than 0.50. In total, 614 episodes of AF were treated with 1,497 shocks, a mean of 2.4 shocks per episode. The conversion rate to sinus rhythm was 93%. The data also suggested that as spontaneous episodes were treated quickly, the interval between episodes of AF lengthened.

Another device with dual-chamber sensing, pacing, and cardioversion capabilities and a maximum output of 27 J has both atrial and ventricular cardioversion/defibrillation capabilities. The device, which weighs 93 g, was designed to treat both atrial and ventricular arrhythmias with pacing modalities before delivering low-energy shocks. A number of investigators are pursuing other techniques to terminate AF by pacing, but the efficacy of this technique may be limited to atrial tachycardia and atrial flutter. Because these units record the number of AF episodes, they provide a very accurate representation of AF control.

An important limitation of this procedure, unrelated to safety or efficacy, is that discharge energy greater than 1 J is uncomfortable to most patients, and the mean cardioversion threshold in the earlier trial was approximately 3 J. Shocks at this amplitude are generally intolerable without sedation in a medical setting, which makes the routine use of the device in its current form not widely acceptable. Another weakness is that some systems do not use atrium-based pacing as a means of maintaining sinus rhythm after atrial cardioversion. Currently, potential candidates for atrial cardioverters/defibrillators (such as those with infrequent episodes of poorly tolerated AF) are usually also suitable for catheter ablation.

E. EVOLVING STRATEGIES FOR NONPHARMACOLOGICAL CORRECTION OF AF. The current absence of a single drug or procedure that can safely and effectively cure AF has engendered the development of a wide array of nonpharmacological approaches. Although each has limitations, these techniques may bring clinical improvement to a large number of patients in the future. In some patients, nonpharmacological therapies may render AF responsive to previously ineffective pharmacological agents. It is also likely that combinations of approaches may be required in treating AF in selected patients. For example, an electronic pacemaker may be a useful adjunct to antiarrhythmic drug therapy in patients with sinus node dysfunction to permit administration of an effective agent that could not otherwise be given because of unacceptable bradycardia.

F. Rate Control During AF

1. Pharmacological Approaches. An alternative to maintenance of sinus rhythm in patients with paroxysmal or

Table 14. Intravenous Pharmacological Agents for Heart Rate Control in Patients With Atrial Fibrillation

Drug*	Loading Dose	Onset	Maintenance Dose	Major Side Effects	Class Recommendation
Diltiazem	0.25 mg/kg IV over 2 min	2–7 min	5–15 mg per hour infusion	Hypotension, heart block, HF	I†
Esmolol‡	0.5 mg/kg over 1 min	5 min	0.05–0.2 $mg \cdot kg^{-1} \cdot min^{-1}$	Hypotension, heart block, bradycardia, asthma, HF	I
Metoprolol‡	2.5–5 mg IV bolus over 2 min; up to 3 doses	5 min	NA	Hypotension, heart block, bradycardia, asthma, HF	I†
Propranolol‡	0.15 mg/kg IV	5 min	NA	Hypotension, heart block, bradycardia, asthma, HF	I†
Verapamil	0.075–0.15 mg/kg IV over 2 min	3–5 min	NA	Hypotension, heart block, HF	I†
Digoxin	0.25 mg IV each 2 h, up to 1.5 mg	2 h	0.125–0.25 mg daily	Digitalis toxicity, heart block, bradycardia	IIb**

HF indicates heart failure.
*Drugs are listed alphabetically within each class of recommendation.
**Type I in congestive HF.
†Type IIb in congestive HF.
‡Only representative members of the type of beta-adrenergic antagonist drugs are included in the table, but other, similar agents could be used for this indication in appropriate doses.

persistent AF is control of the ventricular rate. In a recent randomized trial, the therapeutic strategies of rate vs. rhythm control yielded similar clinical results with respect to symptoms in patients with AF, but exercise tolerance was better with rhythm control (179). The results of other studies comparing these 2 strategies are not yet available (178,305).

A. CRITERIA FOR RATE CONTROL. The adequacy of rate control during AF may be judged from clinical symptoms and ECG recordings. Control of the heart rate at rest does not ensure that the rate is well regulated during exercise, and excessive rate acceleration may occur during even mild exercise in patients with AF whose heart rates are well controlled at rest (409,410).

Criteria for rate control vary with patient age. The rate is generally considered controlled when the ventricular response ranges between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise (410,411). Atwood et al. (412) proposed considering the circadian pattern and the mean rate over a 24-h period on Holter recording. Exercise testing can also be used to evaluate heart rate during submaximal or maximal exercise. Heart rate variability during AF provides additional information about the status of the autonomic nervous system, which may have independent prognostic implications (413–415).

B. HEMODYNAMIC AND CLINICAL CONSEQUENCES OF A RAPID VENTRICULAR RESPONSE TO AF. Patients who develop rapid ventricular rates during an episode of AF may be highly symptomatic. If a rapid ventricular response is associated with symptomatic hypotension, angina, or congestive HF, prompt medical management is required, and cardioversion should be considered. When sustained, an uncontrolled ventricular response may result in deterioration of ventricular function (tachycardia-related cardiomyopathy), which is reversible when the heart rate is brought under control (416,417).

C. PHARMACOLOGICAL INTERVENTIONS FOR RATE CONTROL. Negative chronotropic therapy of AF is based mainly on depression of conduction across the AV node. The effective refractory period of the AV node is closely correlated with ventricular rates during AF, and drugs that prolong the effective refractory period of the AV node are generally effective. Another pharmacological determinant of the ventricular response is cholinergic activity (410). Sinus bradycardia and heart block may occur in some patients with paroxysmal AF, particularly the elderly, as an unwanted effect of pharmacological intervention with beta-blockers, digitalis glycosides, or calcium channel antagonists.

D. PHARMACOLOGICAL AGENTS TO CONTROL HEART RATE IN PATIENTS WITH ACUTE AF. The following agents may be administered to achieve control of the ventricular response to AF in an emergency setting (Table 14).

Digoxin. Although intravenous digoxin may effectively slow the ventricular rate at rest, there is a delay of at least 60 minutes before onset of a therapeutic effect in most patients, and a peak effect does not develop for up to 6 h. Digoxin is no more effective than placebo in converting AF to sinus rhythm (255,257,258) and may prolong the duration of AF (255,418). The efficacy of digoxin is reduced in states of high sympathetic tone, a common precipitant of paroxysmal AF. In a review of 139 episodes of paroxysmal AF recorded on Holter monitoring, there was no difference in the ventricular rates of patients taking digoxin and those not taking this medication (418). Other investigators, however, have found that digoxin reduces the frequency and severity of AF recurrence (22). Furthermore, the combination of digoxin and atenolol has been shown to be effective for ventricular rate control (419). Given the availability of more effective agents, digoxin is no longer first-line therapy for management of acute AF, except in patients with HF or LV dysfunction. In an uncontrolled study, parenteral magnesium sulfate in combination with digoxin appeared useful

Table 15. Orally Administered Pharmacological Agents for Heart Rate Control in Patients With Atrial Fibrillation

Drug*	Loading Dose	Onset	Usual Maintenance Dose**	Major Side Effects	Recommendation
Digoxin	0.25 mg PO each 2 h; up to 1.5 mg	2 h	0.125–0.375 mg daily	Digitalis toxicity, heart block, bradycardia	I
Diltiazem	NA	2–4 h	120–360 mg daily in divided doses; slow release available	Hypotension, heart block, HF	I
Metoprolol†	NA	4–6 h	25–100 mg BID	Hypotension, heart block, bradycardia, asthma, HF	I
Propranolol†	NA	60–90 min	80–240 mg daily in divided doses	Hypotension, heart block, bradycardia, asthma, HF	I
Verapamil	NA	1–2 h	120–360 mg daily in divided doses; slow release available	Hypotension, heart block, HF, digoxin interaction	I
Amiodarone	800 mg daily for 1 wk 600 mg daily for 1 wk 400 mg daily for 4–6 wk	1–3 wk	200 mg daily	Pulmonary toxicity, skin discoloration, hypothyroidism, corneal deposits, optic neuropathy, warfarin interaction, proarrhythmia	IIb

HF indicates heart failure; PO, by mouth; NA, not applicable; HF, heart failure; and BID, twice a day.
*Drugs are listed alphabetically within each class of recommendation.
**Recommended maintenance dosages are the usual ones necessary, but higher doses may be appropriate in some patients.
†The table includes representative members of the type of beta-blocker drugs, but other, similar agents could be used for this indication in appropriate doses.

for the acute management of rapid ventricular rates in patients with AF (420).

Nondihydropyridine Calcium Antagonists. The most commonly used calcium channel antagonist agents for treatment of AF are verapamil and diltiazem. Intravenously, each drug is effective in emergency settings (421,422), but the response is transient, and repeated doses or a continuous intravenous infusion may be required to maintain heart rate control. These agents, particularly verapamil, generally should not be used in patients with HF due to systolic dysfunction.

Management of Patients With WPW Syndrome. Intravenous agents such as digitalis and most especially calcium antagonists that slow AV nodal conduction are contraindicated in patients with WPW syndrome. Anterograde conduction along the accessory pathway during AF is facilitated when these agents are given (423,424), and this may result in acceleration of the ventricular rate, hypotension, or degeneration to ventricular fibrillation. When antiarrhythmic medication is needed in hemodynamically stable patients, intravenous type I or type III agents may generally be used. When the arrhythmia is associated with hemodynamic compromise, however, early direct-current cardioversion should be performed.

Beta-Blockers. Intravenous beta-blockade with propranolol, atenolol, metoprolol, or esmolol may help to control the rate of ventricular response to AF in specific settings. Beta-blockers may be particularly useful in states of high adrenergic tone (e.g., postoperative AF). Among patients with AF after noncardiac surgery, intravenous esmolol given in an intensive care unit produced a more rapid conversion to sinus rhythm than did intravenous diltiazem, but rates after 2 and 12 h were similar with each treatment (425).

Other Antiarrhythmic Agents. Amiodarone has both sympatholytic and calcium antagonistic properties, depresses AV conduction, and is effective in controlling the ventricular rate in patients with AF. Intravenous amiodarone is effective and well tolerated in critically ill patients who develop rapid atrial tachyarrhythmias refractory to conventional treatment but has not been sufficiently evaluated in this indication. Amiodarone is considered a suitable alternative agent for heart rate control when conventional measures are ineffective (426). New antiarrhythmic drugs (e.g., dofetilide and ibutilide) are effective for acute conversion of atrial flutter and AF but are not effective for controlling the ventricular rate.

E. PHARMACOLOGICAL AGENTS TO CONTROL HEART RATE IN PATIENTS WITH PERSISTENT AF. When restoration of sinus rhythm is not possible or is not attempted in patients with AF, control of the ventricular rate is essential. Drugs that block AV nodal conduction can be used to achieve rate control both at rest and during exercise or other types of cardiovascular stress (Table 15). Specific agents, listed alphabetically, are discussed below.

Beta-Blockers. For long-term use, beta-blockade is a safe therapy to control heart rate in AF patients and antagonizes the effects of increased sympathetic tone. In 7 of 12 comparisons with placebo, beta-blockers were effective at controlling resting heart rate. The effect was drug specific, with nadolol and atenolol being most efficacious. All 9 comparisons demonstrated good rate control with beta-blockers, but exercise tolerance was compromised in 3 of 9 studies (427). Sotalol, a nonselective beta-blocking drug with type III antiarrhythmic activity, provides excellent rate control during AF recurrence (428). Atenolol provided better control of exercise-induced tachycardia than digoxin alone (429). Patients taking beta-blockers may experience excessively slow rates at rest. Beta-blockers should be initiated gradually in patients with HF (430).

Digoxin. In contrast with its lack of rate control effect in acute AF, digoxin is generally effective for rate control in persistent AF, particularly when congestive HF is present

(416). According to a recent meta-analysis (427), digoxin administered alone slows the resting heart rate more than placebo, but it has been known for several generations that digitalis does not slow heart rate during exercise in patients with AF (431). Recent data indicate that digoxin lowers the ventricular rate in patients with recent-onset AF without overt HF as well (257), but the effect is modest, perhaps resulting from a vagotonic effect on the AV node.

Nondihydropyridine Calcium Antagonists. The negative inotropic effect of oral calcium antagonists requires that they be used cautiously in patients with HF. Calcium antagonists are preferred over beta-blockers for long-term use in patients with chronic obstructive pulmonary disease. Verapamil and diltiazem reduced heart rate both at rest and during exercise significantly better than placebo in several trials, with preserved or improved exercise tolerance in most patients (427). Investigational data also show that calcium channel antagonists prevent electrical remodeling of atrial tissue (421).

Combination Therapy. Combinations of these agents may often be required to achieve adequate rate control, but care should be taken to avoid excessive slowing. Addition of other drugs to digoxin is commonly required to control AV nodal conduction during exercise and to achieve consistent, adequate heart rate control. The combination of digoxin and atenolol produces a synergistic effect on the AV node (419), and pindolol combined with digoxin offered better rate protection than digoxin alone or combined with verapamil during exercise, with less effect on resting heart rate (424). In general, the combination of digoxin and beta-blockers appears to be more effective than the combination of digoxin and diltiazem (419).

Other Agents. Clonidine reduces standing ventricular response by 15% to 20% and may have value in hypertensive patients with AF (432). The antiarrhythmic agent propafenone exerts mild beta-blocking effects and may slow conduction across the AV node, but this is seldom sufficient to control heart rate in patients with AF. Should the atrial rhythm become slower and more regular, AV conduction may accelerate, and another agent is generally recommended in addition to propafenone to slow AV node conduction. Drug interaction may result in a rise in serum digoxin level when propafenone is given concurrently. Oral amiodarone has not been investigated properly in this indication and should not be used as a first-line agent because of the side effects associated with its chronic administration. Oral amiodarone also interacts with digoxin, raising serum concentrations of the latter.

2. Nonpharmacological Regulation of AV Nodal Conduction and Pacing. Pacing at a rate that approximates the mean ventricular rate during spontaneous AV conduction can regulate the ventricular rhythm during AF (433). Because ventricular pacing prolongs the AV nodal refractory period as a result of concealed retrograde penetration, it eliminates ventricular cycles longer than the pacing cycle length and may reduce the number of short ventricular cycles related to rapid AV conduction during AF. As a result, ventricular pacing may be used as a strategy to reduce the irregularity of the ventricular rhythm (102). This modality may be useful for patients with marked variability in ventricular rates and for those who develop resting bradycardia during treatment with medications prescribed to control rapid ventricular rates with exertion. The precise role of pacemaker therapy to regulate the ventricular rate in patients with AF, however, remains controversial.

Table 16. Summary of Recommendations for Use of Pharmacological Agents to Control the Rate of Ventricular Response to Atrial Fibrillation

Drug*	Route of Administration	Type of Recommendation	Level of Evidence
Diltiazem	Intravenous	I	A
Esmolol	Intravenous	I	A
Verapamil	Intravenous or oral	I	A
Other beta-blockers	Intravenous or oral	I	B
Digoxin	Intravenous or oral	IIa	B

*The doses of medications used in these studies may not be the same as those recommended by the manufacturers.

A. CONCLUSIONS. A summary of recommendations for use of pharmacological agents to control the rate of ventricular response to AF is given in Table 16. A combination of drugs is often necessary to achieve rate control in AF patients in the acute and chronic settings. Therapy may require careful dose titration, and some patients may develop symptomatic bradycardia requiring permanent pacing. When pharmacological intervention fails to prevent recurrences of AF or to control heart rate, nonpharmacological therapy may be considered.

3. Nonpharmacological/AV Nodal Ablation. AV nodal ablation and permanent pacemaker implantation provide a highly effective means of improving symptoms in selected patients with AF (182,183,185,187). In general, patients most likely to benefit from this strategy are those who experience symptoms related to a rapid ventricular rate during AF that cannot be controlled adequately with antiarrhythmic or negative chronotropic medications. AV nodal ablation may be especially useful for patients with an excessive ventricular rate that induces a tachycardia-mediated decline in ventricular systolic function despite appropriate medical therapy. A meta-analysis of 21 studies published between 1989 and 1998 that included a total of 1,181 patients concluded that AV nodal ablation and permanent pacemaker implantation significantly improved cardiac symptom scores, quality-of-life measures, and healthcare utilization for patients with highly symptomatic AF that was refractory to medical treatment (187). In the Ablate and Pace Trial, 156 patients with medically refractory AF were prospectively enrolled in a registry to determine the effects of this strategy on quality of life, exercise capacity, and ventricular function over a period of 1 year after ablation (183). Significant improvement in quality of life was measured after AV nodal ablation and permanent

pacemaker implantation. For patients with impaired LV function before ablation, this treatment significantly improved LV ejection fraction. Two small randomized trials compared the effects of AV nodal ablation with antiarrhythmic medications on quality of life and symptoms in patients with paroxysmal (185) and persistent (182) AF. Significantly more patients with both forms of AF experienced improvement in symptoms and quality of life after AV nodal ablation than with antiarrhythmic medication therapy.

The use of catheter ablation to modify AV nodal conduction by eliminating posterior atrial inputs to the AV node has been reported to decrease the ventricular rate during AF and to improve cardiac symptoms without requiring pacemaker implantation (434,435). This technique has several limitations, including the inadvertent induction of complete AV block and a relatively high risk of increasing ventricular rate over the first 6 months after ablation. Two small randomized trials comparing the strategies of complete AV nodal ablation and permanent pacemaker implantation with AV nodal modification have demonstrated improved symptom relief with complete interruption of AV nodal conduction. Thus, AV nodal modification without pacemaker implantation is only rarely used for patients with rapid ventricular rates during AF. Complications of AV nodal ablation include those of pacemaker implantation, as well as ventricular arrhythmias, relatively rare instances of worsened LV function, thromboembolism associated with interruption of anticoagulation, and a greater rate of progression from paroxysmal to persistent AF. The 1-year mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3% (95% confidence interval [CI] 5.5% to 7.2%), with a risk of sudden death of approximately 2.0% (95% CI 1.5% to 2.6%). Although the relation of sudden death to this procedure remains controversial, it has been suggested that programming the pacemaker to a higher nominal rate (80 to 90 bpm) for the first month after ablation may reduce the risk.

Although the symptomatic benefits of AV nodal ablation have been clearly demonstrated, the limitations of this technique include the persistent need for anticoagulation, loss of AV synchrony, and lifelong pacemaker dependency. There is a small but real risk of sudden death due largely to torsade de pointes (436). In addition, ablation of the AV conduction system may preclude or limit the later use of newer nonpharmacological treatments. Patients with impaired diastolic ventricular compliance who are most dependent on AV synchrony for maintenance of cardiac output (such as those with HCM or restrictive cardiomyopathies) may experience persistent symptoms after AV nodal ablation and permanent pacemaker implantation. Thus, patients must be counseled regarding each of these considerations before proceeding with this irreversible treatment.

Recommendations for Heart Rate Control in Patients With AF

Class I

1. **Measure heart rate response both at rest and during exercise in patients with persistent or permanent AF and control the rate with pharmacological agents (using a beta-blocker or calcium channel antagonist in most cases) to the physiological range. (*Level of Evidence: C*)**
2. **Administer intravenous beta-blockers or calcium channel antagonists (verapamil, diltiazem) in the acute setting to slow the ventricular response to AF in the absence of conduction over an accessory pathway, exercising caution in patients with hypotension or HF. (*Level of Evidence: B*)**
3. **Perform immediate electrical cardioversion in patients with acute paroxysmal AF and a rapid ventricular response associated with acute MI, symptomatic hypotension, angina, or cardiac failure that does not respond promptly to pharmacological measures. (*Level of Evidence: C*) (See Section VIII-D, Recommendations for Pharmacological or Electrical Cardioversion of AF.)**

Class IIa

1. **Administer a combination of digoxin and a beta-blocker or calcium channel antagonist to control the heart rate at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia. (*Level of Evidence: C*)**
2. **Employ nonpharmacological therapy to control heart rate when pharmacological therapy is insufficient. (*Level of Evidence: C*)**

Class IIb

1. **Administer digoxin as the sole agent to control heart rate at rest in patients with persistent AF. (*Level of Evidence: B*)**
2. **Administer intravenous quinidine, procainamide, disopyramide, ibutilide, or amiodarone to hemodynamically stable patients with AF involving conduction over an accessory pathway. (*Level of Evidence: B*)**
3. **Immediate cardioversion is required when very rapid tachycardias or hemodynamic instability occurs in patients with AF involving conduction over an accessory pathway. (*Level of Evidence: B*)**

Class III

1. **Administer digitalis as the sole agent to control a rapid rate of ventricular response to AF in patients with paroxysmal AF. (*Level of Evidence: B*)**
2. **Catheter ablation without prior medical therapy to control AF. (*Level of Evidence: C*)**

Table 17. Risk Factors for Ischemic Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Risk Factors (Control Groups)	Relative Risk
Previous stroke or TIA	2.5
History of hypertension	1.6
Congestive heart failure	1.4
Advanced age (continuous, per decade)	1.4
Diabetes mellitus	1.7
Coronary artery disease	1.5

TIA indicates transient ischemic attack. Data derived from collaborative analysis of 5 primary prevention trials (28). As a group, patients with nonvalvular atrial fibrillation carry about a 6-fold increased risk of thromboembolism compared with patients in sinus rhythm.

Relative risk refers to comparison with atrial fibrillation patients without these risk factors.

G. Preventing Thromboembolism

1. Risk Stratification.

A. EPIDEMIOLOGICAL DATA. The rate of stroke in patients with AF is related to coexistent cardiovascular disease (10,28,165,166). In a small, retrospective, population-based study in Olmsted County, Minnesota, over 3 decades, the 15-year cumulative stroke rate in people with lone AF (defined as those younger than 60 years of age with no clinical history or echocardiographic signs of cardiopulmonary disease) was 1.3% (10). Conversely, in the Framingham Study (20), the age-adjusted stroke rate over a mean follow-up period of 11 years was 28.2% in those with lone AF, more liberally defined to include patients with a history of hypertension or cardiomegaly on chest roentgenography, compared with 6.8% in normal controls (20). In the Stroke Prevention in Atrial Fibrillation (SPAF) study, the annualized rate of ischemic stroke was similar in those with recurrent (3.2%) and permanent (3.3%) AF (437). Those with prior stroke or transient ischemic attack have a rate of subsequent stroke of 10% to 12% per year despite aspirin use, and these patients benefit substantially from treatment with adjusted-dose oral anticoagulation (438,439). In addition to prior thromboembolism, HF, hypertension, increasing age, and diabetes mellitus have consistently emerged as independent risk factors for ischemic stroke in nonvalvular AF (28,163,165,440,441). Others, such as female gender, systolic blood pressure greater than 160 mmHg, and LV dysfunction, have been variably linked to stroke (163,167,442). The relative risk for ischemic stroke associated with specific clinical features, derived from a collaborative analysis of participants given no antithrombotic therapy in the control groups of 5 randomized trials, is given in Table 17. Nearly half of AF-associated strokes occur in patients over age 75 years (Fig. 15), and AF is the most frequent cause of disabling stroke in elderly women (14,440,442). Older people are widely thought to be at increased risk for anticoagulant-related bleeding (443), and they are less likely to be treated with oral anticoagulation, even in situations for which it has been proven efficacious, in part because of concern about the risk of bleeding (444). Special consideration of these older patients is therefore a critical aspect of effective stroke prophylaxis (440).

Several reports suggest that patients with AF in the setting of thyrotoxicosis, which is often associated with decompensated congestive HF, are also at high risk (445–447), although the mechanism underlying this enhanced embolic potential is not clear (121,448,449). The notion of increased thromboembolic risk in thyrotoxic AF has been challenged on the basis of comparison of patients with thyrotoxicosis in AF with those in sinus rhythm; logistic regression analysis found only age to be an independent predictor of cerebral ischemic events (199). Although 13% of patients with AF had ischemic cerebrovascular events (6.4% per year) compared with 3% of those in normal sinus rhythm (1.7% per year) (121,169,200), there was no adjustment for duration of observation or time to event. When transient ischemic attacks are discounted, the increased risk of stroke in patients with AF reached statistical significance ($p = 0.03$) (199). Although it remains controversial whether patients with AF associated with thyrotoxicosis are at increased risk of thromboembolic cerebrovascular events

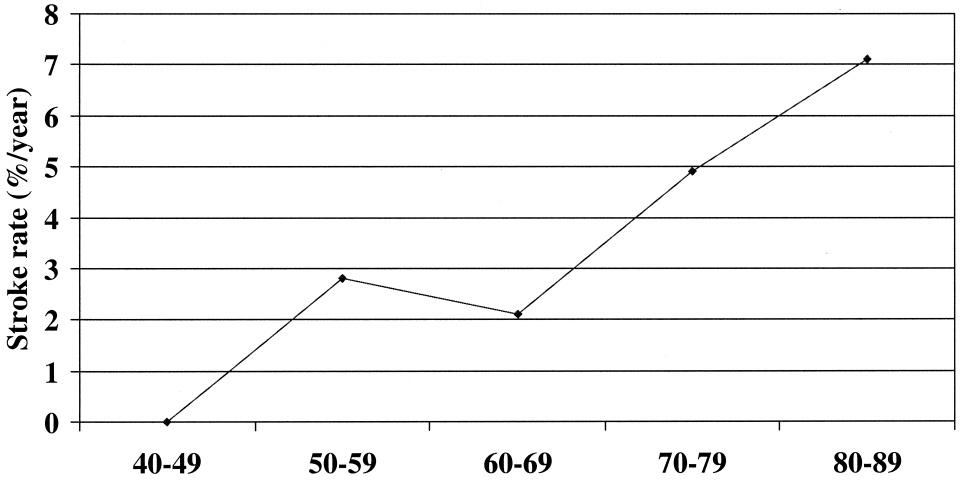

Figure 15. Stroke rates in relation to age among patients with atrial fibrillation in the Framingham Heart Study. Data are from Wolf et al. (23).

(450), the authors of these guidelines favor treatment with anticoagulant medication in the absence of a specific contraindication, at least until a euthyroid state has been restored and congestive HF has been corrected.

Atrial fibrillation is a frequent complication of HCM. Studies of patients with HCM and AF (451) have consistently reported a high incidence of stroke and systemic embolism (452–455). These retrospective longitudinal studies report stroke or systemic embolism in 20% to 40% of patients with HCM and AF followed up for a mean of 4 to 11 years, for a thromboembolism rate of 2.4% to 7.1% per year. In addition to AF, other factors associated with systemic embolism in patients with HCM include advanced age (455), hypertension (453), mitral annular calcification, and LA enlargement (453). On multivariate analysis, age and AF were independent predictors of thromboembolism (455). Although no randomized studies of anticoagulant therapy have been reported, the incidence of thromboembolism in patients with HCM and AF is high, warranting consideration of anticoagulant therapy.

B. ROLE OF ECHOCARDIOGRAPHY IN RISK STRATIFICATION. Transthoracic Echocardiography In patients with nonvalvular AF, correlations in placebo-assigned participants in randomized clinical trials of antithrombotic therapy determined the independent predictive value of transthoracic echocardiography for thromboembolic events (166,456). Fibrocalcific disease in the mitral annulus was a predictor of thromboembolism in the BATAF trial (Boston Area Anticoagulation Trial for Atrial Fibrillation) (456) but not in the SPAF study, in which the predictive values of LA size and LV function were independent of clinical features (166). Meta-analysis of 3 randomized trials of antithrombotic therapy found moderate to severe LV dysfunction to be the only independent echocardiographic predictor of stroke in patients with AF when clinical features were also considered (457). The diameter of the LA was a less useful predictor of ischemic events (457).

Secondary analyses of aspirin-assigned patients in multicenter trials of antithrombotic therapy in nonvalvular AF have yielded variable results regarding the role of transthoracic echocardiography in predicting thromboembolic risk (29,121). Secondary analysis of aspirin-assigned patients (receiving 325 mg per day) in the SPAF I and II studies detected several independent clinical and transthoracic echocardiographic features for thromboembolism. The only independent echocardiographic feature, however, was LV fractional shortening less than 25% by M-mode echocardiography when combined with recent (less than 100 days) congestive HF. Independent clinical risk factors were prior thromboembolism, age (over 75 years in women), and systolic hypertension (greater than 160 mmHg on 2 consecutive measurements). The risk-stratification scheme derived from this analysis was the basis for the SPAF-III study. Although risk stratification included an echocardiographic criterion, clinical features were clearly the dominant factors. Among the 2,012 aspirin-assigned patients from all 3 SPAF trials, including 290 in SPAF-III assigned to a relatively ineffective, fixed-dose combination of aspirin plus warfarin (1 to 3 mg per day; initial international normalized ratio [INR] of 1.2 to 1.5), no transthoracic echocardiographic parameter was independently predictive of thromboembolism. The Embolism in Left Atrial Thrombi (ELAT) study group evaluated 409 outpatients with nonvalvular AF treated with aspirin (160 mg per day) by both transthoracic echocardiography and TEE at study entry. Although LV fractional shortening was associated with thromboembolic events by univariate analysis, no independent echocardiographic predictors of thromboembolism were identified (169).

Transesophageal Echocardiography. TEE is the most sensitive and specific imaging technique for detection of LA and LAA thrombus, far surpassing transthoracic echocardiography (121). This modality also permits superior evaluation for other causes of cardiogenic embolism (200), as well as a means of measuring LAA function (199). Several TEE features have been associated with thromboembolism (including such LA/LAA abnormalities as thrombus, reduced flow velocity, and spontaneous echo contrast) and atheromatous disease of the aorta (156,458).

Detection of LA/LAA thrombus stands as a contraindication to elective cardioversion of AF. The absence of detectable thrombus, however, does not preclude thromboembolism after cardioversion if patients do not receive anticoagulation therapy (205,459). A TEE-guided strategy for elective cardioversion of AF has been reported to result in comparable outcomes for thromboembolism and death compared with conventional anticoagulation for 3 weeks before and 4 weeks after cardioversion (201) (see Section VIII-G-3, Conversion to Sinus Rhythm and Thromboembolism). Hence, transthoracic echocardiography is valuable for defining the origin of AF (e.g., detecting rheumatic mitral valve disease or HCM), and TEE may provide additional information for stratifying thromboembolic risk.

Among high-risk AF patients, the following echocardiographic findings have been associated with thromboembolism: impaired LV systolic function on transthoracic echocardiography, thrombus, dense spontaneous echo contrast or reduced velocity of blood flow in the LAA, and complex atheromatous plaque in the thoracic aorta on TEE. Other echocardiographic signs, such as the diameter of the LA and fibrocalcific endocardial abnormalities, have been variably associated with thromboembolism and may interact with other factors. Oral anticoagulation effectively lowers the risk of stroke in AF patients with these features. Whether the absence of these abnormalities identifies a low-risk group of patients with other clinical risk factors who could safely avoid anticoagulation has not been established.

C. THERAPEUTIC IMPLICATIONS. The efficacy and safety of oral anticoagulation and aspirin for prevention of stroke in patients with AF have been well characterized (460). The

Table 18. Published Risk-Stratification Schemes for Primary* Prevention of Thromboembolism in Patients With Nonvalvular Atrial Fibrillation

Source	High Risk	Intermediate Risk	Low Risk
Atrial Fibrillation Investigators (185)†	Age greater than or equal to 65 years History of hypertension Coronary artery disease Diabetes		Age less than 65 years No high-risk features
American College of Chest Physicians (473)	Age greater than 75 years History of hypertension Left ventricular dysfunction‡ More than 1 intermediate risk factor	Age 65–75 years Diabetes Coronary artery disease Thyrotoxicosis	Age less than 65 years No risk factors
Stroke Prevention in Atrial Fibrillation (468)	Women greater than 75 years Systolic BP greater than 160 mm Hg Left ventricular dysfunction†	History of hypertension No high-risk features	No high-risk features No history of hypertension

BP indicates blood pressure. Patients are classified on the basis of the presence or absence of any risk factor.

Adapted with permission from Am J Med, Vol. 109, Pearce et al., Assessment of these schemes for stratifying stroke risk in patients with nonvalvular atrial fibrillation, pp. 45–51, © 2000, with permission, from Excerpta Medica, Inc.

*Patients with AF and prior thromboembolism are at high risk of stroke, and anticoagulation is indicated for secondary prevention in such cases.

†Did not distinguish high-risk from intermediate-risk patients.

‡Left ventricular dysfunction refers to moderate to severe wall motion abnormality assessed globally by 2-dimensional echocardiography, reduced ejection fraction, fractional shortening less than 0.25 by M-mode echocardiography, or clinical heart failure.

selection of appropriate antithrombotic therapy is discussed below in the context of thromboembolic risk (Tables 18 and 19). Atrial fibrillation patients with low rates of stroke when treated with aspirin may not gain sufficient benefit from anticoagulation to outweigh the attendant risks and the need for close medical monitoring required during oral anticoagulation therapy (457,461). Estimating the risk of stroke for individual AF patients is a crucial factor in the decision to provide anticoagulation therapy to individual patients with AF (29), and accurate prediction of stroke risk to individualize antithrombotic management has become the salient clinical issue. The threshold risk of stroke that warrants anticoagulation of AF patients is controversial. Those whose stroke risk is less than or equal to 2% per year when taking aspirin do not benefit substantially from alternative treatment with oral anticoagulation, with anticoagulation of more than 100 patients for 1 year required to prevent 1 stroke (460). For high-risk AF patients with stroke rates greater than or equal to 6% per year with aspirin therapy, the comparable number needed to treat is 25 or fewer, which strongly favors the use of adjusted-dose oral anticoagulation. Opinion remains divided about routine use of oral anticoagulation for those with intermediate levels of stroke risk (greater than 2% or less than 6% per year).

Three clinical schemes have been proposed recently to stratify the risk of ischemic stroke in AF patients that are directly or indirectly based on analyses of prospectively monitored cohorts of participants in clinical trials in which antithrombotic therapy was controlled (441,457,462). One set of criteria is based on multivariate pooled analysis of

Table 19. Risk-Based Approach to Antithrombotic Therapy in Patients With Atrial Fibrillation

Patient Features	Antithrombotic Therapy	Grade of Recommendation
Age less than 60 years, no heart disease (lone AF)	Aspirin (325 mg per day) or no therapy	I
Age less than 60 years, heart disease but no risk factors*	Aspirin (325 mg per day)	I
Age greater than or equal to 60 years, no risk factors*	Aspirin (325 mg per day)	I
Age greater than or equal to 60 years with diabetes mellitus or CAD	Oral anticoagulation (INR 2.0–3.0) Addition of aspirin, 81–162 mg per day is optional	I IIb
Age greater than or equal to 75 years, especially women	Oral anticoagulation (INR ≈2.0)	I
HF LV ejection fraction less than or equal to 0.35, thyrotoxicosis, and hypertension	Oral anticoagulation (INR 2.0–3.0)	I
Rheumatic heart disease (mitral stenosis) Prosthetic heart valves Prior thromboembolism Persistent atrial thrombus on TEE	Oral anticoagulation (INR 2.5–3.5 or higher may be appropriate)	I

AF indicates atrial fibrillation; HF, heart failure; INR, international normalized ratio; LV, left ventricular; CAD, coronary artery disease; and TEE, transesophageal echocardiography.

*Risk factors for thromboembolism include HF, LV ejection fraction less than 0.35, and history of hypertension.

1,593 participants assigned to the control or placebo groups of 5 randomized primary prevention trials in which 106 ischemic strokes occurred over a mean follow-up of 1.4 years (28). This scheme divides patients into 2 strata, distinguishing low-risk patients from those at intermediate or high risk. Echocardiographic features were not considered initially, but subsequent analysis of 3 of these trials identified abnormal LV systolic function as an independent predictor of stroke (457). The SPAF study criteria were based on multivariate analysis of 854 participants assigned aspirin in the SPAF-I and -II clinical trials who were followed up for a mean of 2.3 years, during which 68 ischemic strokes were observed. A third set of criteria was developed by expert consensus (462) based on consideration of the 2 foregoing schemes and other available data to classify patients into low-, intermediate-, and high-risk groups (Table 18).

Each of these schemes is predictive of stroke, but the differences between them are potentially important for patient management. Both the criteria derived by collaborative analysis of concurrent primary prevention trials (28) and those developed by expert consensus (462) identify a smaller proportion of patients with a lower risk of stroke than those classified as low risk on the basis of the SPAF study criteria (463). The SPAF study scheme also designates some male patients over age 75 years as low risk, whereas the other schemes classify all patients over age 75 years as high risk.

Although stratification of stroke risk identifies AF patients who benefit most and least from lifelong anticoagulation, the threshold for use of anticoagulation is controversial. Opinion is particularly divided about anticoagulation for those at intermediate risk for stroke (3% to 5% per year). Some advocate routinely providing anticoagulation to those with stroke rates in this range (464), whereas others favor selective anticoagulation of those at intermediate risk, with weight given to individual bleeding risks and patient preferences (29,463). The threshold of benefit at which AF patients choose anticoagulation varies; some at intermediate risk elect anticoagulation, whereas others do not (465).

The risk of thromboembolism for patients with chronic atrial flutter has been variably reported but is generally estimated as higher than for patients with sinus rhythm and less than for those with persistent or permanent AF. On the basis of multivariate analysis, Wood et al. (466) reported hypertension as the only significant correlate of previous thromboembolism for patients with chronic atrial flutter. Biblo et al. (467) recently reviewed 8 years of retrospective data on 749,988 hospitalized older patients, including 17,413 with atrial flutter and 337,428 with AF. The overall stroke risk ratio for patients with atrial flutter was 1.406 compared with the control group; for patients with AF, the relative risk was 1.642. Coexisting HF, rheumatic heart disease, and hypertension predicted an episode of AF in patients with atrial flutter. Risk ratios for patients with these comorbid conditions were 1.243, 1.464, and 1.333, respectively (467).

As a chronic arrhythmia, atrial flutter is uncommon, and the risk of thromboembolism is not as well established as it is for AF. Until more robust data become available, and although the overall thromboembolic risk associated with atrial flutter may be lower than with AF, it seems prudent to estimate risk by use of similar stratification criteria.

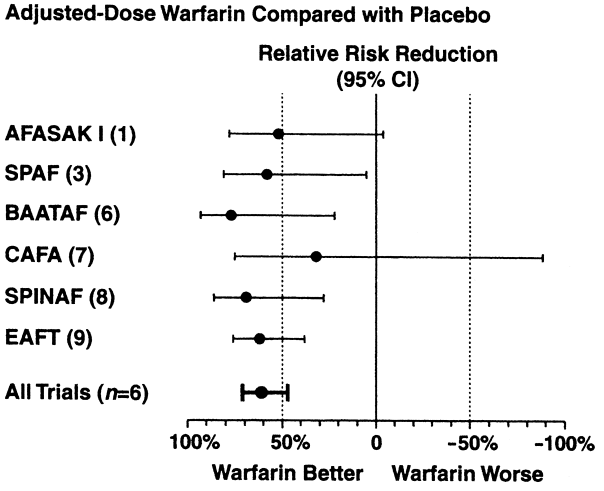

Figure 16. Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular AF: adjusted-dose warfarin compared with placebo. Adapted with permission from Hart et al. (163,460) Ann Intern Med 1999;131:492–501. (The American College of Physicians–American Society of Internal Medicine is not responsible for the accuracy of the translation.)

2. Antithrombotic Strategies for Prevention of Ischemic Stroke and Systemic Embolism. Before 1990, antithrombotic therapy for prevention of ischemic stroke and systemic embolism in patients with AF was limited mainly to those with rheumatic heart disease and prosthetic heart valves (14). Anticoagulation was also accepted therapy for patients who had sustained ischemic stroke to prevent recurrence but was often delayed to avoid hemorrhagic transformation. Some advocated anticoagulation of patients with thyrotoxicosis or other conditions associated with cardiomyopathy and AF. Five large randomized trials published between 1989 and 1992 evaluated oral anticoagulation, and 2 tested aspirin for primary prevention of thromboembolism in patients with nonvalvular AF (32,456,468,469) (Fig. 16 and Table 20). A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or transient cerebral ischemic attack (439). Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 61% (95% CI 47% to 71%) vs. placebo (460) (Fig. 17). This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. Excluding patients not undergoing oral anticoagulation at the time of stroke, the preventive efficacy of oral anticoagulation exceeded 80%. Four of these trials were placebo controlled; of the 2 that were double blinded with regard to anticoagulation (469), one was stopped early because of external evidence that oral anticoagulation was superior to placebo. In 3 of the trials, oral

Table 20. Randomized Trials of Antithrombotic Therapy in Patients With Nonvalvular Atrial Fibrillation

Trials	Reference	Year Published	No. of Patients	Interventions
Large Published Trials				
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I)	468	1989	1,007	OA, ASA, placebo
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II)	487	1998	677	OA, ASA, OA*+ASA, OA*
Stroke Prevention in Atrial Fibrillation I (SPAF I)	32	1991	1,330	OA, ASA, placebo
Stroke Prevention in Atrial Fibrillation II (SPAF II)	488	1994	1,100	OA, ASA
Stroke Prevention in Atrial Fibrillation III (SPAF III)	438	1996	1,044	OA, OA*+ASA
Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)	456	1990	420	OA, control
Canadian Atrial Fibrillation Anticoagulation (CAFA)	489	1991	378	OA, placebo
Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)	469	1992	571	OA, placebo
European Atrial Fibrillation Trial (EAFT)	439	1993	1,007	OA, ASA, placebo
Studio Italiano Fibrillazione Atriale (SIFA)	490	1997	916	OA, indobufen
Minidose Warfarin in Nonrheumatic Atrial Fibrillation	491	1998	303	OA, OA*
Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF)	461	1999	729	OA, OA*, ASA
Small or pilot trials				
Harenberg et al.	492	1993	75	LMW heparin, control
Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF)	493	1996	285	ASA, placebo
Subgroups with AF in other trials				
European Stroke Prevention Study II (ESPS II)	494	1997	429	ASA, dipyridamole, placebo
Ongoing or unpublished AF trials				
French Aspirin Coumarin Collaborative Study		. . .	. . .	OA, OA+ASA
Swedish Atrial Fibrillation Trial		. . .	. . .	. . .
Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF)		. . .	. . .	OA, thrombin inhibitor

AF indicates atrial fibrillation; OA, oral anticoagulation; OA*, low-dose oral anticoagulation; ASA, aspirin; LMW, low-molecular-weight.
Adapted with permission from Hart et al. (460) Ann Intern Med 1999;131:492–501. (The American College of Physicians–American Society of Internal Medicine is not responsible for the accuracy of the translation.)

anticoagulant dosing was regulated according to the prothrombin time ratio; 2 used the INR, with target ranges of 2.5 to 4.0 and 2 to 3, respectively. These trials are summarized in Table 20. The duration of follow-up in these trials was generally between 1 and 2 years; the longest was 2.2 years, whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods.

Anticoagulation increases the frequency and severity of major extracranial and intracranial hemorrhage, however, and all of these trials excluded patients considered at high risk of bleeding. Patient age and the intensity of anticoagulation are the most powerful predictors of major bleeding (470–473). Trial participants, at an average age of 69 years, were carefully selected and managed. It is thus unclear whether the relatively low rates of major hemorrhage also apply to AF patients in clinical practice, who have a mean age of about 75 years and whose anticoagulation therapy is less closely regulated (37,474).

The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications. Targeting the lowest adequate intensity of anticoagulation to minimize the risk of bleeding is particularly important for elderly AF patients. Maximum protection against ischemic stroke in AF is probably achieved with an INR range of 2.0 to 3.0 (438,475,476), whereas an INR range of 1.6 to 2.5 appears to be associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher-intensity anticoagulation (Fig. 17) (475,477). Two randomized trials with a target INR of 1.4 to 2.8 (estimated mean achieved INR 2.0 to 2.1) found the largest relative risk reductions for ischemic stroke. A trial in which AF patients with prior stroke or transient ischemic attack were randomly assigned to target INR ranges of 2.2 to 3.5 vs. 1.5 to 2.1 found a greater rate of major hemorrhage with the higher intensity (478). For patients with nonvalvular AF, an INR of 1.6 to 3.0 is efficacious and relatively safe. For primary prevention in most AF patients under age 75 years and for secondary prevention, an INR of 2.5 (target range 2.0 to 3.0) seems reasonable. A target INR of 2.0 (target range 1.6 to 2.5) is recommended for primary prevention in patients more than 75 years old. In clinical trials, INRs achieved during follow-up were more often below than above the target range. Low-intensity anticoagulation requires special efforts to minimize time spent below the target range, during which stroke protection is sharply reduced.

From time to time, it may be necessary to interrupt oral anticoagulant therapy in preparation for elective surgical procedures. In patients with mechanical prosthetic heart valves, it is generally appropriate to substitute unfractionated or low-molecular-weight heparin to prevent thrombo-

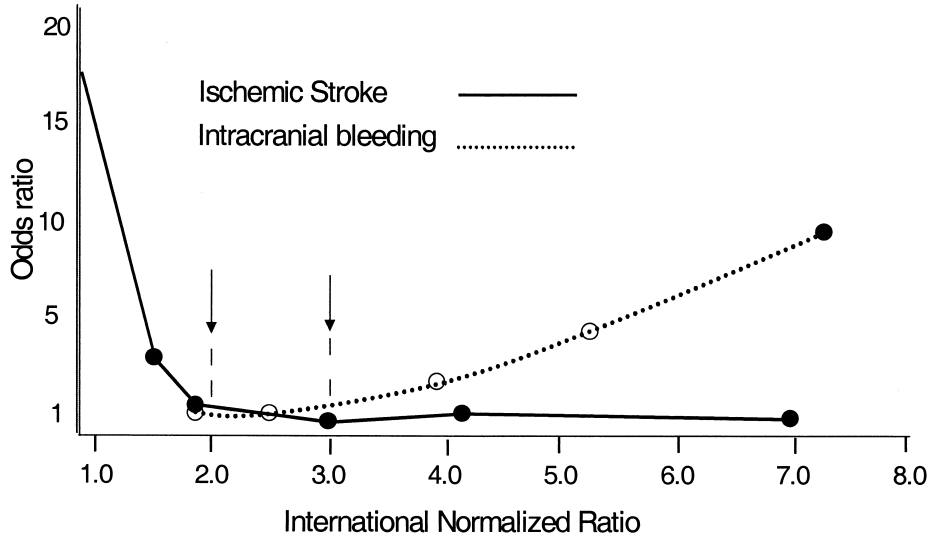

Figure 17. Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomized trials of antithrombotic therapy for patients with atrial fibrillation. Adapted with permission from Hylek et al. (472,475).

sis (479,480). In patients with AF who do not have mechanical valves, based on extrapolation from the annual rate of thromboembolism in patients with nonvalvular AF, it is the consensus of the writing group that anticoagulation may be interrupted for a period of up to 1 week for surgical or diagnostic procedures that carry a risk of bleeding, without substituting heparin. In high-risk patients, or when a series of procedures requires interruption of oral anticoagulant therapy for a period longer than 1 week, unfractionated or low-molecular-weight heparin may be administered intravenously or subcutaneously, respectively.

The use of low-molecular-weight heparins instead of unfractionated heparin in patients with AF is based largely on extrapolation from venous thromboembolic disease states. In general, low-molecular-weight heparins have several pharmacological advantages over unfractionated heparin. These include a longer half-life, more predictable bioavailability (greater than 90% after subcutaneous injection), predictable clearance (enabling once- or twice-daily subcutaneous administration), and predictable antithrombotic response based on body weight, which permits fixed-dose treatment without laboratory monitoring except under special circumstances such as obesity, renal insufficiency, or pregnancy (481). Treatment with low-molecular-weight heparins is associated with a lower risk of heparin-induced thrombocytopenia than unfractionated heparin (482). The favorable properties of low-molecular-weight heparins may simplify the treatment of AF in acute situations and shorten or eliminate the need for hospitalization to initiate anticoagulation. Self-administration of low-molecular-weight heparins out of hospital by patients with AF is a promising approach that may result in cost savings in conjunction with elective cardioversion (483).

Aspirin offers only modest protection against stroke for patients with AF (Fig. 18). Meta-analysis of 5 randomized trials showed a stroke reduction of 19% (95% CI 2% to 34%) (460). The effect of aspirin on stroke in these trials was less consistent than that of oral anticoagulation (460,484). Differences in patient features may have influenced aspirin efficacy. For example, aspirin reduced stroke occurrence by 33% in primary prevention studies (in which the stroke rate with placebo averaged 5% per year) vs. 11% for secondary prevention trials (in which the stroke rate with placebo averaged 14% per year) (460). Aspirin may be more efficacious for AF patients with hypertension or diabetes (484,485) and for reduction of noncardioembolic vs. cardioembolic ischemic strokes in AF patients (119). Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes (155). Aspirin appears to prevent nondisabling strokes more often than disabling strokes (460); thus, the greater the risk of disabling cardioembolic stroke in a population of AF patients, the less protection afforded by aspirin (155).

In summary, adjusted-dose oral anticoagulation is more efficacious than aspirin for prevention of stroke in patients with AF, as suggested by indirect comparisons and by a 33% risk reduction (95% CI 13% to 49%) in a meta-analysis of 5 randomized trials (460). Randomized trials involving high-risk AF patients (stroke rates greater than 6% per year) show larger relative risk reductions by adjusted-dose oral anticoagulation relative to aspirin (Fig. 18), whereas the relative risk reductions are consistently smaller in trials of AF patients with lower stroke rates. Accordingly, oral anticoagulation may be most beneficial for AF patients at higher intrinsic thromboembolic risk, offering only modest reductions over aspirin in both the relative risk and absolute rates of stroke for AF patients at low risk. Individual risk varies over time, so the need for anticoagulation must be reevaluated at regular intervals in all patients with AF.

The combination of low-dose oral anticoagulation (INR

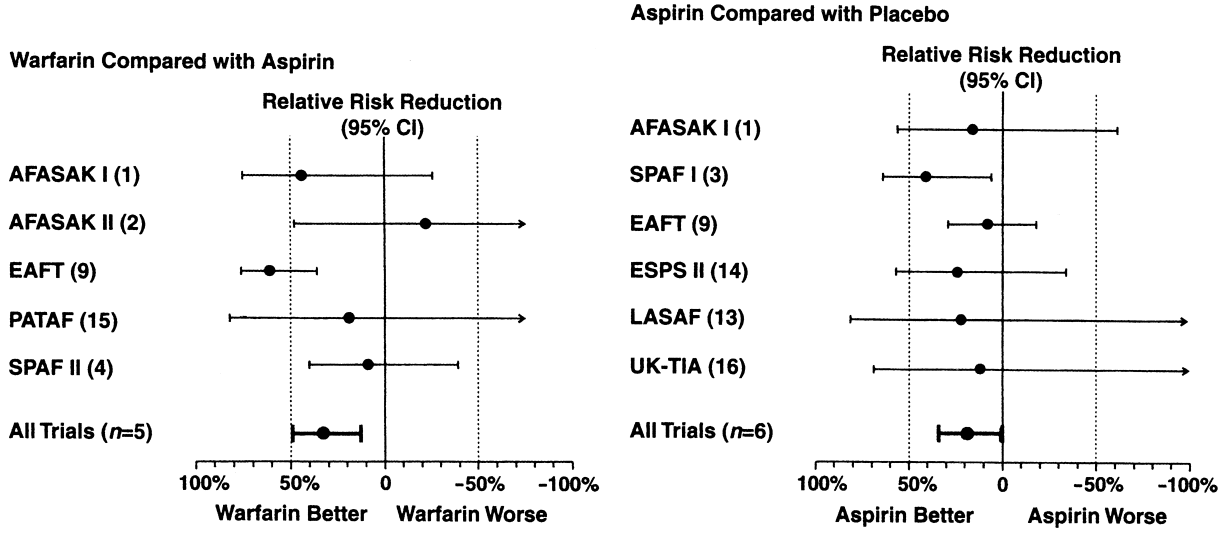

Figure 18. Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular AF: warfarin compared with aspirin and aspirin compared with placebo. Adapted with permission from Hart et al. (163,460) Ann Intern Med 1999;131:492–501. (The American College of Physicians–American Society of Internal Medicine is not responsible for the accuracy of the translation.)

less than 1.5) with aspirin adds little protection against stroke compared with aspirin alone in patients with AF (438). Combining aspirin with an oral anticoagulant at higher anticoagulation intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients (486). For AF patients who sustain cardioembolic events while receiving low-intensity anticoagulation, the anticoagulation intensity should be increased to a maximum target INR of 3 to 3.5 rather than routinely adding antiplatelet agents, pending further data.

An emerging surgical option, not yet sufficiently investigated to allow general clinical application, is obliteration of the LAA to remove a principal nidus of thrombus formation in patients with AF who cannot safely undergo anticoagulation. In addition to direct surgical amputation or truncation of appendage, several methods are under development to achieve this with intravascular catheters or transpericardial approaches. These must presently be considered investigational, and indications for this type of intervention have not been established convincingly.

Recommendations for Antithrombotic Therapy in Patients With AF

Class I

1. **Administer antithrombotic therapy (oral anticoagulation or aspirin) to all patients with AF, except those with lone AF, to prevent thromboembolism. (*Level of Evidence: A*)**
2. **Individualize the selection of the antithrombotic agent, based upon assessment of the absolute risks of stroke and bleeding and the relative risk and benefit for a particular patient. (*Level of Evidence: A*)**
3. **Chronic oral anticoagulant therapy in a dose adjusted to achieve a target intensity INR of 2 to 3 in patients at high risk of stroke, unless contraindicated. (*Level of Evidence: A*)**
   a. **The need for anticoagulation should be reevaluated at regular intervals. (*Level of Evidence: A*)**
   b. **INR should be determined at least weekly during the initiation of oral anticoagulation therapy and monthly when the patient is stable. (*Level of Evidence: A*)**
4. **Aspirin in a dose of 325 mg daily as an alternative in low-risk patients or in those with certain contraindications to oral anticoagulation. (*Level of Evidence: A*)**
5. **Oral anticoagulation for patients with AF who have rheumatic mitral valve disease or prosthetic heart valves (mechanical or tissue valves). (*Level of Evidence: B*)**
   a. **Base the target intensity of anticoagulation on the particular type of prosthesis, but not less than INR 2 to 3. (*Level of Evidence: B*)**

Class IIa

1. **Target a lower INR of 2 (range 1.6 to 2.5) for primary prevention of ischemic stroke and systemic embolism in patients over 75 years old considered at increased risk of bleeding complications but without frank contraindications to oral anticoagulant therapy. (*Level of Evidence: C*)**
2. **Manage antithrombotic therapy for patients with atrial flutter, in general, as for those with AF. (*Level of Evidence: C*)**
3. **Select antithrombotic therapy using the same criteria irrespective of the pattern of AF (i.e., for patients with paroxysmal, persistent, or permanent AF). (*Level of Evidence: B*)**

Class IIb

1. **Interrupt anticoagulation for a period of up to 1 week for surgical or diagnostic procedures that carry a risk of bleeding, without substituting heparin in patients with AF who do not have mechanical prosthetic heart valves. (*Level of Evidence: C*)**
2. **Administer unfractionated or low-molecular-weight heparin intravenously or subcutaneously, respectively in selected high-risk patients or when a series of procedures requires interruption of oral anticoagulant therapy for a period longer than 1 week. (*Level of Evidence: C*)**
3. **Manage patients with CAD with anticoagulation (INR 2 to 3) based on the same criteria used for patients without CAD. (*Level of Evidence: C*)**
   a. **A low dose of aspirin (less than 100 mg per day) or clopidogrel (75 mg per day) may be given concurrently with anticoagulation, but these strategies have not been evaluated sufficiently and may be associated with an increased risk of bleeding. (*Level of Evidence: C*)**
4. **Treatment with aspirin is optional for primary prevention of stroke in patients under 60 years of age without heart disease or risk factors for thromboembolism (lone AF). (*Level of Evidence: C*)**

Class III

Long-term anticoagulation for stroke prevention in patients under 60 years of age without heart disease (lone AF) and without risk factors for thromboembolism. (*Level of Evidence: C*)

3. Conversion to Sinus Rhythm and Thromboembolism. Randomized studies of antithrombotic therapy are lacking for patients undergoing cardioversion of AF or atrial flutter, but the risk of thromboembolism was between 1% and 5% in case-control series (292,495). Risk was nearer the lower end of this spectrum when anticoagulation pretreatment (INR 2 to 3) (29) was given for 3 to 4 weeks before and after conversion (100,297). It is now common practice to administer anticoagulant drugs to patients with AF of more than 2 days' duration when they are prepared for cardioversion. Manning et al. (195) suggested that TEE might be used to identify patients without LAA thrombi who do not require anticoagulation, but a subsequent investigation (205) and meta-analysis of several clinical studies found this approach to be unreliable (496).

If most AF-associated strokes result from embolism of stasis-induced thrombi from the LAA, then restoration and maintenance of atrial contraction should logically reduce thromboembolic risk. LV function can improve after cardioversion (497), potentially lowering embolic risk and improving cerebral hemodynamics (498). There is no solid clinical evidence that cardioversion followed by prolonged maintenance of sinus rhythm effectively reduces thromboembolism in AF patients. It is thus unclear at present whether efforts to restore and maintain sinus rhythm are justified for the specific purpose of preventing stroke.

Conversion of AF to sinus rhythm results in transient mechanical dysfunction of the LA and LAA (459) known as "stunning," which can occur after spontaneous, pharmacological (499,500), or electrical (500–502) conversion of AF or after radiofrequency catheter ablation of atrial flutter (503) and which may be associated with spontaneous echo contrast (459). Recovery of mechanical function may be delayed for several weeks, depending in part on the duration of AF before restoration of sinus rhythm (110,504,505). This could explain why some patients with no demonstrable LA thrombus on TEE before cardioversion subsequently experience thromboembolic events (205). Presumably, thrombus forms during the period of stunning and is expelled after the return of mechanical function, which explains the clustering of thromboembolic events in the first 10 days after cardioversion (506).

Patients in whom LAA thrombus is identified by TEE appear to be at high risk of thromboembolism after cardioversion of AF or atrial flutter, and they should be treated with anticoagulation for at least 3 to 4 weeks before and after either pharmacological or electrical cardioversion. In a multicenter study of 1,222 patients with either AF persisting longer than 2 days or atrial flutter and previous AF (201) who were randomized to a TEE-guided or conventional strategy, one group underwent anticoagulation with heparin briefly before and with warfarin for 4 weeks after cardioversion. Cardioversion was postponed when thrombus was identified, and warfarin was administered for 3 weeks before TEE was repeated. The other group received anticoagulation for 3 weeks before and 4 weeks after cardioversion. Both approaches were associated with a comparably low risk of stroke (0.81% with the TEE approach and 0.50% with the conventional approach) after 8 weeks of follow-up, and the risk of major bleeding did not differ significantly. There were no differences in the proportion of cardioverted subjects, and thus the clinical benefit of the TEE approach was limited to saving time before cardioversion.

In contrast to the perceived low rate of thromboembolism in patients with chronic atrial flutter, stroke or systemic embolism at the time of cardioversion to sinus rhythm has been reported often (507–509), and anticoagulation should be considered with either the conventional or TEE-guided strategy. TEE-guided cardioversion of atrial flutter has been performed with a low rate of systemic embolism, particularly when patients are stratified for other risk factors on the basis of clinical and/or TEE features (339,340).

Anticoagulation is recommended for 3 to 4 weeks before and after cardioversion for patients with AF of unknown duration or with AF for more than 48 h. Although LA thrombus and systemic embolism have been documented in patients with AF of shorter duration, the need for anticoagulation is less clear. When acute AF produces hemodynamic instability in the form of angina pectoris, MI, shock, or pulmonary edema, immediate cardioversion should not be delayed to achieve therapeutic anticoagulation. Nevertheless, intravenous heparin or low-molecular-weight hep-

arin should be initiated before cardioversion by synchronous direct-current countershock or intravenous antiarrhythmic medication.

Protection against late embolism may require continuation of anticoagulation for a more extended period after the procedure, and the duration of anticoagulation after cardioversion depends both on the likelihood that AF will recur in an individual patient and on the patient's intrinsic risk of thromboembolism. Late events are probably due to both the development of thrombus as a consequence of atrial stunning and the delayed recovery of atrial contraction after cardioversion. Berger and Schweitzer (506) pooled data from 32 studies on the timing of clinical thromboembolic events after cardioversion of AF or atrial flutter, 98% of which occurred within 10 days. These data support the use of anticoagulation for at least 2 weeks after cardioversion, but they have not been verified by prospective randomized studies.

Recommendations for Antithrombotic Therapy to Prevent Ischemic Stroke and Systemic Embolism in Patients With AF Undergoing Cardioversion

Class I

1. **Administer anticoagulation therapy regardless of the method (electrical or pharmacological) used to restore sinus rhythm. (*Level of Evidence: B*)**
2. **Anticoagulate patients with AF lasting more than 48 h or of unknown duration, for at least 3 to 4 weeks before and after cardioversion (INR 2 to 3). (*Level of Evidence: B*)**
3. **Perform immediate cardioversion in patients with acute (recent onset) AF accompanied by symptoms or signs of hemodynamic instability resulting in angina pectoris, MI, shock, or pulmonary edema, without waiting for prior anticoagulation. (*Level of Evidence: C*)**
   a. **If not contraindicated, administer heparin concurrently by an initial intravenous bolus injection followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time at 1.5 to 2 times the reference control value. (*Level of Evidence: C*)**
   b. **Next, provide oral anticoagulation (INR 2 to 3) for a period of at least 3 to 4 weeks, as for patients undergoing elective cardioversion. (*Level of Evidence: C*)**
   c. **Limited data from recent studies support subcutaneous administration of low-molecular-weight heparin in this indication. (*Level of Evidence: C*)**
4. **Screening for the presence of thrombus in the LA or LAA by TEE is an alternative for routine preanticoagulation in candidates for cardioversion of AF. (*Level of Evidence: B*)**
   a. **Anticoagulate patients in whom no thrombus is identified in the form of intravenous unfractionated heparin by an initial bolus injection before cardioversion, followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time at 1.5 to 2 times the reference control value. (*Level of Evidence: B*)**
   b. **Next, provide oral anticoagulation (INR 2 to 3) for a period of at least 3 to 4 weeks, as for patients undergoing elective cardioversion. (*Level of Evidence: B*)**
   c. **Limited data are available to support the subcutaneous administration of low-molecular-weight heparin in this indication. (*Level of Evidence: C*)**
   d. **Treat patients in whom thrombus is identified by TEE with oral anticoagulation (INR 2 to 3) for at least 3 to 4 weeks before and after restoration of sinus rhythm. (*Level of Evidence: B*)**

Class IIb

1. **Cardioversion without TEE guidance during the first 48 h after the onset of AF. (*Level of Evidence: C*)**
   a. **In these cases, anticoagulation before and after cardioversion is optional, depending on assessment of risk. (*Level of Evidence: C*)**
2. **Anticoagulate patients with atrial flutter undergoing cardioversion in the same way as for patients with AF. (*Level of Evidence: C*)**

H. Special Considerations

1. Postoperative AF. Although AF may occur after noncardiac surgery, the incidence of atrial arrhythmias including AF after open heart surgery is between 20% and 50% (510–512), depending on definitions and methods of detection. The incidence of postoperative AF is growing, perhaps more because of the age of surgical patients than because of technical factors, and this increases patient morbidity and hospital costs.

A. CLINICAL AND PATHOPHYSIOLOGICAL CORRELATES. Postoperative AF usually occurs within the first 5 days of cardiac surgery, with a peak incidence on day 2. The dysrhythmia usually runs a self-correcting course, and more than 90% of patients have resumed sinus rhythm by 6 to 8 weeks after surgery (513), a rate of spontaneous resolution higher than for other forms of AF. A number of studies have addressed clinical conditions that may predict postoperative AF with conflicting results, related in part to sample size (511,514–518). The most reproducible factor is age. Other independent predictors—most of which are clinically obvious—include valvular heart disease, chronic lung disease, atrial enlargement, and preoperative atrial arrhythmias (Table 21). In many cases, however, none of these features are present. It is likely that the collagen content of the atria of older patients is greater than in younger individuals (519). This may serve as a substrate on which various intraoperative and postoperative factors act to trigger AF after cardiac surgery (520) (Table 21). Among these factors are pericarditis (521) and increased sympathetic tone.

Table 21. Multivariate Predictors of Postoperative Atrial Arrhythmias in Patients Undergoing Myocardial Revascularization Surgery

Advanced age
Male gender
Digoxin
Peripheral arterial disease
Chronic lung disease
Valvular heart disease
Left atrial enlargement
Previous cardiac surgery
Discontinuation of beta-blocker medication
Preoperative atrial tachyarrhythmias
Pericarditis
Elevated postoperative adrenergic tone

Adapted with permission from the Society of Thoracic Surgeons (The Annals of Thoracic Surgery 1993;56:539–49) (511).

B. PREVENTION OF POSTOPERATIVE AF. It is important to consider prophylactic treatment of patients at greatest risk of developing postoperative AF. Over the past decade, pretreatment with beta-blockers decreased the incidence of AF in several clinical trials from 40% to 20% in patients undergoing coronary artery bypass graft (CABG) surgery and from 60% to 30% in those undergoing valvular procedures (512,513,522). In a meta-analysis of 24 trials (512) limited to CABG patients with ejection fraction greater than 30%, prophylactic beta-blockade protected against development of supraventricular tachycardia (summary odds ratio of 0.28, 95% CI 0.21 to 0.36).

Sotalol, which in its *dl*-racemic form has both beta-blocking and type III antiarrhythmic activity, is effective for prophylaxis against postoperative AF. In one study (523) comparing sotalol 120 mg per day with metoprolol 75 mg per day, AF developed in 16% of patients given sotalol vs. 32% of those treated with metoprolol ($p = 0.01$). This finding was confirmed in a smaller study (524) in which sotalol (80 or 120 mg twice a day) reduced postoperative AF compared with beta-blocker or placebo (12.5% vs. 38%), but not in another large study (208) that found little difference between sotalol and beta-blocker treatment.

When the prophylactic value of amiodarone 600 mg per day initiated at least 7 days preoperatively was evaluated in 124 patients undergoing cardiac surgery, the incidence of AF was 25% in the treated group compared with 53% with placebo ($p = 0.003$) (525). This approach is impractical unless patients are identified and treatment started at least a week before surgery. The Amiodarone Reduction in Coronary Heart (ARCH) trial found that postoperative administration of intravenous amiodarone (1 g per day for 2 days) reduced the incidence of postoperative AF from 47% to 35% vs. placebo in 300 patients ($p = 0.01$). The higher overall incidence of postoperative AF and more modest prophylactic effect than in other studies may have been related in part to less frequent use of beta-blockers (526).

Pretreatment with either digoxin or verapamil does not prevent postoperative AF (512,527,528). Results with procainamide have been inconsistent, and this drug is not widely used for prevention of postoperative AF (529). Other agents, such as disopyramide (526) or flecainide (529), have not been studied extensively because of concerns about the risks associated with type IC agents in patients with coronary disease.

Single-chamber and biatrial overdrive pacing have been used to prevent postoperative AF. In a recent randomized trial, postoperative biatrial pacing reduced the incidence of AF to 13% from 36% with LA pacing, 33% with RA pacing, and 42% without pacing in 132 patients undergoing CABG. Hospital length of stay was also abbreviated in the biatrial pacing group (530). Prophylactic atrial pacing to prevent postoperative AF requires further investigation before specific recommendations for its use can be made.

C. TREATMENT OF POSTOPERATIVE AF. Because of comorbidity including adrenergic stress, it may be difficult to control the ventricular rate in patients with postoperative AF. This can be accomplished with a beta-blocker, and short-acting agents are particularly useful when hemodynamic instability is a concern. Other AV nodal blocking agents, such as calcium channel antagonist agents, can be used as alternative therapy, but digoxin is less effective when adrenergic tone is high. Intravenous amiodarone has been associated with improved hemodynamics in this setting (426).

Given the self-limited course of postoperative AF, electrical cardioversion is usually unnecessary except when the dysrhythmia develops in the immediate postoperative (hypothermic) period. In the highly symptomatic or poorly controlled patient, cardioversion may be performed with the same precautions regarding anticoagulation as in nonsurgical cases. A variety of pharmacological agents, including amiodarone (531,532), procainamide (533,534), ibutilide, and sotalol, may be used to convert AF to sinus rhythm. Although a type III agent (e.g., ibutilide) was more effective than placebo in one study for treatment of postoperative AF (535), oral sotalol is appealing in this situation because its beta-blocking action slows the ventricular rate and proarrhythmic toxicity is relatively infrequent, but this agent appears to be less effective than the others for cardioversion.

A number of studies have shown an increased risk of stroke in post-CABG patients, so anticoagulation with heparin or an oral anticoagulant is appropriate when AF persists more than 48 h (536,537). However, this entails special challenges because of the greater potential for bleeding in surgical patients. The choice of drug, heparin and/or an oral anticoagulant, must be based on the individual clinical situation.

Atrial flutter is less common than AF after cardiac surgery (538). Pharmacological therapy for patients with atrial flutter is similar to that for patients with AF. Prevention of postoperative atrial flutter is as difficult as prevention of AF.

Recommendations for Prevention and Management of Postoperative AF

Class I

1. **Treat patients undergoing cardiac surgery with an oral beta-blocker to prevent postoperative AF, unless contraindicated. (*Level of Evidence: A*)**
2. **In patients who develop postoperative AF, achieve rate control by administration of AV nodal blocking agents. (*Level of Evidence: B*)**

Class IIa

1. **Administer sotalol or amiodarone prophylactically to patients at increased risk of developing postoperative AF. (*Level of Evidence: B*)**
2. **Restore sinus rhythm in patients who develop postoperative AF by pharmacological cardioversion with ibutilide or direct-current cardioversion, as recommended for nonsurgical patients. (*Level of Evidence: B*)**
3. **In patients with recurrent or refractory postoperative AF, attempt maintenance of sinus rhythm by administration of antiarrhythmic medications, as recommended for patients with CAD who develop AF. (*Level of Evidence: B*)**
4. **Administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients. (*Level of Evidence: B*)**

2. Acute MI. Estimates of the incidence of AF in patients with acute MI vary depending on the population sampled. In the Cooperative Cardiovascular Project, 22% of Medicare patients aged greater than or equal to 65 years hospitalized for acute MI had AF (171). In the TRACE (Trandolapril Cardiac Evaluation) study of patients with LV dysfunction associated with acute MI, 21% had AF (539). Lower rates of AF were observed in patients selected for other prospective trials, such as GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), in which the incidence was 10.4% (540), but this may reflect the younger age of patients who present with acute MI associated with ST-segment elevation on the ECG. AF is more commonly associated with acute MI in those who are older, have higher Killip class, and have LV dysfunction.

Atrial fibrillation is an independent risk factor for increased in-hospital mortality in the setting of acute MI (25.3% with AF vs. 16.0% without AF), 30-day mortality (29.3% vs. 19.1%), and 1-year mortality (48.3% vs. 32.7%) (171); patients who developed AF during hospitalization had a worse prognosis than those with AF on admission (171). Stroke rates are also increased in patients with MI and AF compared with those without AF (540). Outcomes appear to have improved in the thrombolytic era for patients with AF and acute MI compared with experience between 1981 and 1983 (541), but a stroke rate of 3.1% in the setting of AF and acute MI (540) emphasizes the importance of this association even in the era of thrombolysis.

Specific recommendations for therapy of AF in the setting of acute MI are primarily based on consensus, because no adequate trials have tested alternate strategies. Urgent electrical cardioversion is appropriate for patients presenting with AF related to acute MI, intractable ischemia, or hemodynamic instability. Intravenous administration of a beta-blocker and digoxin is also indicated for rate control in patients with acute MI to reduce myocardial oxygen demands. Anticoagulants are indicated in those with large anterior infarcts and in survivors of acute MI with persistent AF. ACE inhibition appears to reduce the incidence of AF in patients with LV dysfunction after acute MI (539).

Management decisions have been summarized in the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction (542) and are reflected in the consensus recommendations as follows.

Recommendations for Management of Patients With AF and Acute MI

Class I

1. **Electrical cardioversion for patients with severe hemodynamic compromise or intractable ischemia. (*Level of Evidence: C*)**
2. **Intravenous administration of digitalis or amiodarone to slow a rapid ventricular response and improve LV function. (*Level of Evidence: C*)**
3. **Intravenous beta-blockers to slow a rapid ventricular response in patients without clinical LV dysfunction, bronchospastic disease, or AV block. (*Level of Evidence: C*)**
4. **Heparin for patients with AF and acute MI, unless contraindications to anticoagulation are present. (*Level of Evidence: C*)**

Class III

Administer type IC antiarrhythmic drugs in patients with AF in the setting of acute MI. (*Level of Evidence: C*)

There have been no controlled studies of cardioversion, antiarrhythmic drugs, or other interventions to maintain sinus rhythm for stable patients with AF in acute MI. Physicians should apply the guidelines for management outlined elsewhere in this document with emphasis on recognition of AF and risk stratification and should recognize the significance of the dysrhythmia as an independent predictor of poor long-term outcome in patients with acute MI (543,544).

3. WPW Preexcitation Syndromes. Atrial fibrillation may induce ventricular fibrillation and sudden death in patients with the WPW syndrome when atrial impulses are conducted antegrade across a bypass tract. This complication is feared but infrequent. The incidence of sudden death ranges from 0 to 0.6% per year in patients with WPW (370,485,510,545). In contrast, a large population-based study in Olmsted County, Minnesota, found 4 newly

diagnosed cases of WPW per 100,000 population per year; only 2 sudden deaths occurred over 1,338 patient-years of follow-up. Among 113 patients with WPW, 6 had documented AF and 3 had atrial flutter. Patients with WPW syndrome at high risk of sudden death are those with short antegrade bypass tract refractory periods (less than 250 ms) and short R-R intervals during preexcited AF (180 plus or minus 29 ms) (97,546). In patients prone to ventricular fibrillation, there is also a higher incidence of multiple pathways (97).

Catheter ablation of bypass tracts should be considered for most symptomatic patients with WPW (547), particularly those who have had documented AF or syncope (suggesting rapid heart rate) or those with a short bypass tract refractory period. Ablation of the bypass tract will not necessarily prevent the occurrence of AF, especially in older patients, and additional pharmacological therapy may be required.

Patients with WPW in whom AF occurs with a rapid ventricular response associated with hemodynamic instability should be cardioverted immediately because of the high risk of developing ventricular fibrillation. When a patient with a preexcited tachycardia is clinically stable, intravenous procainamide may be given to convert the atrial mechanism to sinus rhythm. It is critically important to avoid agents with the potential to increase the refractoriness of the AV node, which could encourage preferential conduction over the accessory pathway. Specifically, administration of AV nodal blocking agents such as digoxin, diltiazem, or verapamil is contraindicated. Beta-blockers are ineffective in this situation, and their administration by the intravenous route may have adverse hemodynamic effects. Intravenous adenosine may be used when the QRS complex is narrow (less than 120 ms duration) during the tachycardia, because this indicates that antegrade conduction is occurring through the AV node.

Recommendations for Management of AF and Ventricular Preexcitation

Class I

1. **Catheter ablation of the accessory pathway in symptomatic patients with AF who have WPW syndrome, particularly those with syncope due to rapid heart rate or those with a short bypass tract refractory period. (*Level of Evidence: B*)**
2. **Immediate electrical cardioversion to prevent ventricular fibrillation in patients with WPW in whom AF occurs with a rapid ventricular response associated with hemodynamic instability. (*Level of Evidence: B*)**
3. **Intravenous procainamide or ibutilide in an attempt to restore sinus rhythm in patients with WPW in whom AF occurs without hemodynamic instability in association with a wide QRS complex on the ECG (greater than or equal to 120 ms duration). (*Level of Evidence: C*)**

Class IIb

Administer intravenous quinidine, procainamide, disopyramide, ibutilide, or amiodarone to hemodynamically stable patients with AF involving conduction over an accessory pathway. (*Level of Evidence: B*)

- **a. Immediate cardioversion is required when very rapid tachycardias or hemodynamic instability occurs in patients with AF involving conduction over an accessory pathway. (*Level of Evidence: B*)**

Class III

Intravenous administration of beta-blocking agents, digitalis glycosides, diltiazem, or verapamil in patients with WPW syndrome who have preexcited ventricular activation in AF. (*Level of Evidence: B*)

4. Hyperthyroidism. AF occurs in 10% to 25% of patients with hyperthyroidism, more commonly in men and the elderly than in women or patients less than 75 years old (548,549). Treatment is primarily directed toward restoring a euthyroid state, which is usually associated with a spontaneous reversion to sinus rhythm. Antiarrhythmic drugs and electrical cardioversion are generally unsuccessful while the thyrotoxic condition persists (550,551). Beta-blockers are somewhat effective in controlling the ventricular rate in this situation, and aggressive treatment with intravenous beta-blockers is particularly important in cases of thyroid storm, for which high doses may be required. Calcium channel antagonists may also be useful (551). Although specific evidence is lacking in AF caused by hyperthyroidism, oral anticoagulation is recommended to prevent systemic embolism (552).

Recommendations for Management of AF in Patients With Hyperthyroidism

Class I

1. **Administer a beta-blocker as necessary to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated. (*Level of Evidence: B*)**
2. **In circumstances when a beta-blocker cannot be used, administer a calcium channel antagonist (diltiazem or verapamil) to control the ventricular rate. (*Level of Evidence: B*)**
3. **In patients with AF associated with thyrotoxicosis, use oral anticoagulation (INR 2 to 3) to prevent thromboembolism, as recommended for AF patients with other risk factors for stroke. (*Level of Evidence: C*)**
   - **a. Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism. (*Level of Evidence: C*)**

5. Pregnancy. Atrial fibrillation is rare during pregnancy (553) and is usually associated with another underlying cause, such as mitral stenosis (554), congenital heart disease

(555), or hyperthyroidism (556). A rapid ventricular response to AF can have serious hemodynamic consequences for both the mother and the fetus.

In a pregnant woman who develops AF, diagnosis and treatment of the underlying condition causing the dysrhythmia is the first priority. The ventricular rate should be controlled with digoxin, a beta-blocker, or a calcium channel antagonist (557–559). All currently available antiarrhythmic drugs have the potential to cross the placenta and to be excreted in breast milk and should be avoided if possible. Quinidine (558), mexiletine (560), sotalol (561), flecainide (561), and amiodarone (559,562–564) have all been used successfully during pregnancy in a relatively small number of cases. Quinidine has the longest record of safety in pregnant women and remains the agent of choice for pharmacological cardioversion of AF in this situation (308,558). In the event of hemodynamic embarrassment, electrical cardioversion can be performed without fetal damage (565).

The role of anticoagulation to prevent systemic arterial embolism has not been systematically studied in pregnant patients with AF, but the dysrhythmia is frequently associated with conditions that carry a high risk of thromboembolism, including congenital or valvular heart disease. Consideration should be given to avoiding warfarin because it crosses the placental barrier and is associated with teratogenic embryopathy in the first trimester and with fetal hemorrhage in the later stages of pregnancy (566–572). The preferred anticoagulant is heparin, which does not cross the placenta. The value of subcutaneous unfractionated heparin or low-molecular-weight heparin in preventing ischemic stroke in patients with AF has not been proven, however, and the use of these agents is based predominantly on experience in patients with prosthetic heart valves or venous thromboembolism.

Recommendations for Management of AF During Pregnancy

Class I

1. **Control the rate of ventricular response with digoxin, a beta-blocker, or a calcium channel antagonist. (*Level of Evidence: C*)**
2. **Electrical cardioversion in patients who become hemodynamically unstable due to the dysrhythmia. (*Level of Evidence: C*)**
3. **Administer antithrombotic therapy (anticoagulant or aspirin) throughout pregnancy to all patients with AF (except those with lone AF). (*Level of Evidence: C*)**

Class IIb

1. **Attempt pharmacological cardioversion by administration of quinidine, procainamide, or sotalol in hemodynamically stable patients who develop AF during pregnancy. (*Level of Evidence: C*)**
2. **Administer heparin to patients with risk factors for thromboembolism during the first trimester and last month of pregnancy. Unfractionated heparin may be administered either by continuous intravenous infusion in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2 times the control (reference) value or by intermittent subcutaneous injection in a dose of 10,000 to 20,000 units every 12 h, adjusted to prolong the mid-interval (6 h after injection) activated partial thromboplastin time to 1.5 times control. (*Level of Evidence: B*)**
   a. **Limited data are available to support the subcutaneous administration of low-molecular-weight heparin for this indication. (*Level of Evidence: C*)**
3. **Administer an oral anticoagulant during the second trimester to patients at high thromboembolic risk. (*Level of Evidence: C*)**

6. Hypertrophic Cardiomyopathy. Opinions differ regarding the clinical significance of AF in the setting of HCM. In a retrospective series of 52 patients studied between 1960 and 1985, 89% of patients who developed AF experienced clinical deterioration that was ameliorated by restoration of sinus rhythm (164). In a multivariate analysis of a population-based cohort of 37 patients with HCM who experienced an annual cardiac mortality rate of 5%, AF was associated with decreased survival (445). A lower annual mortality rate (1.3%) was observed in a single-center retrospective study of 277 patients with HCM. The prevalence of AF was 18%; among the 50 cases with AF, 15 deaths were recorded, a third of which were attributed to stroke (446). The natural history of HCM is better defined in the combined experience of 3 large centers, which included 717 cases followed up for a mean of 8 plus or minus 7 years. Eighty-six deaths (12%) occurred, of which 51% were sudden death (mean age 45 plus or minus 20 years); death was attributable to HF in 36% of patients (mean age 56 plus or minus 19 years) and to stroke in 13% (mean age 73 plus or minus 14 years). Ten of the 11 fatal strokes were associated with AF. Although most of the sudden deaths were attributed to ventricular arrhythmias, cardiogenic stroke may have been underestimated as a contributory mechanism (573).

There have been no systematic studies of the treatment of AF in patients with HCM, but various antiarrhythmic agents, including disopyramide, propafenone, and amiodarone, have been used. Some authors advocate administration of amiodarone both to prevent episodes of AF and to modulate the rate of ventricular response (574). The use of electrical pacing to prevent AF has not been studied, but the high incidence of ischemic stroke in patients with HCM who develop AF justifies efforts to restore and maintain sinus rhythm and to use anticoagulant medication.

Recommendations for Management of AF in Patients With HCM

Class I

Treat patients with HCM who develop AF with oral anticoagulation (INR 2 to 3) as recommended for other high-risk patients for prevention of thromboembolism. (*Level of Evidence: B*)

Class IIa

Antiarrhythmic medications to prevent recurrences. Available data are insufficient to recommend one agent over another in this situation, but disopyramide and amiodarone are generally preferred. (*Level of Evidence: C*)

7. Pulmonary Diseases. Supraventricular arrhythmias, including AF, are common in patients with chronic obstructive lung disease (575,576) and have adverse prognostic implications in patients with acute exacerbations of chronic obstructive pulmonary disease (577). Treatment of the underlying lung disease and correction of hypoxia and acid-base imbalance are of primary importance. Theophylline and beta-adrenergic agonists, which are commonly used to relieve bronchospasm in these patients, can precipitate AF and make it difficult to control the rate of ventricular response. Beta-blockers, sotalol, propafenone, and adenosine are contraindicated in patients with bronchospasm and wheezing. Rate control can usually be achieved safely with calcium channel antagonists (578); digoxin offers no advantage over calcium channel antagonists in this situation. Pharmacological antiarrhythmic therapy and electrical cardioversion may be ineffective against AF until respiratory decompensation has been corrected. Intravenous flecainide may be efficacious in restoring sinus rhythm in some patients (232). Electrical cardioversion may be attempted in hemodynamically unstable patients. In resistant cases, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate. The role of anticoagulation in patients with AF due to chronic obstructive lung disease has not been studied specifically.

Recommendations for Management of AF in Patients With Pulmonary Diseases

Class I

1. **In patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease, correction of hypoxemia and acidosis are the primary therapeutic measures. (*Level of Evidence: C*)**
2. **In patients with obstructive pulmonary disease who develop AF, a calcium channel antagonist agent (diltiazem or verapamil) is preferred for ventricular rate control. (*Level of Evidence: C*)**
3. **Attempt electrical cardioversion in patients with pulmonary disease who become hemodynamically unstable owing to AF. (*Level of Evidence: C*)**

Class III

1. **Use of theophylline and beta-adrenergic agonist agents in patients with bronchospastic lung disease who develop AF. (*Level of Evidence: C*)**
2. **Use of beta-blockers, sotalol, propafenone, and adenosine in patients with obstructive lung disease who develop AF. (*Level of Evidence: C*)**

I. Primary Prevention

Although measures aimed at the primary prevention of AF have not been widely investigated, 2 randomized trials have demonstrated that atrial or AV synchronous pacing reduces the incidence of subsequent AF in patients with bradycardia compared with ventricular pacing (401,579,580). Whether this merely reflects avoidance of AF induced by ventricular pacing or actual prevention of AF by atrial or AV synchronous pacing is not known, because no difference emerged until 2 years after pacemaker implantation in the recently published Canadian Trial of Physiologic Pacing (580). Another potential avenue for primary prevention has been suggested by a secondary analysis of a placebo-controlled trial of the angiotensin converting enzyme inhibitor trandolapril in survivors of acute MI, which found a lower incidence of AF in treated patients (26). Given the association between hypertension and AF, it would be helpful to know whether some types of antihypertensive therapy are superior to others for prevention of AF and whether controlling blood pressure itself can reduce the incidence of AF. It may be that some of the benefit of treating hypertension with respect to lowering the incidence of stroke may be due to the prevention of AF. (See Section V, Pathophysiological Mechanisms). Insufficient data are available at this time to permit recommendations for primary prevention of AF in populations at risk.

IX. PROPOSED MANAGEMENT STRATEGIES

A. Overview of Algorithms for Management of Patients With AF

Management of patients with AF requires knowledge of its pattern of presentation (paroxysmal, persistent, or permanent) and decisions about restoration and maintenance of sinus rhythm, control of the ventricular rate, and anticoagulation. These issues are addressed in the various management algorithms for each presentation of AF (Figs. 9, 10, 11, and 12).

1. Newly Discovered AF (Fig. 9). It is not always clear whether the initial presentation of AF is actually the patient's first episode, particularly in those with minimal or no symptoms of the dysrhythmia, so both are considered together. In patients who have self-limited episodes of AF, antiarrhythmic drugs to prevent recurrence are usually unnecessary unless AF is associated with severe symptoms related to hypotension, myocardial ischemia, or HF. Whether these individuals require long-term or even short-term anticoagulation is not clear, and the decision must be individualized

for each patient based on the intrinsic risk of thromboembolism. When AF persists, one option is to accept progression to permanent AF, with attention to antithrombotic therapy and control of the ventricular rate. Although it may seem reasonable to make at least one attempt to restore sinus rhythm, this may not be in the best interest of all patients. An example is the older man without risk factors for thromboembolism in whom asymptomatic AF is discovered on routine examination and control of the ventricular rate is readily achieved. Here, the potential toxicity of antiarrhythmic drugs may outweigh the benefit of restoration of sinus rhythm. If the decision is made to attempt to restore and maintain sinus rhythm, anticoagulation and rate control are important before cardioversion. Although long-term antiarrhythmic therapy may not be needed to prevent recurrent AF after cardioversion, short-term therapy may be beneficial. In patients with AF of more than 3 months' duration, early recurrence is common after cardioversion. Antiarrhythmic medication may be initiated before cardioversion (after adequate anticoagulation) in such cases to reduce the likelihood of recurrence, and the duration of drug therapy would be brief (e.g., 1 month).

2. Recurrent Paroxysmal AF (Figs. 10, 11). In patients who experience brief or minimally symptomatic recurrences of paroxysmal AF, it is reasonable to avoid antiarrhythmic drugs, but troublesome symptoms generally call for suppressive antiarrhythmic therapy. Rate control and prevention of thromboembolism are appropriate in both situations. In any given patient, several different antiarrhythmic drugs may be effective, and thus the initial selection is based mainly on safety (Fig. 11). For individuals with no or minimal structural heart disease, flecainide, propafenone, and sotalol are recommended as initial antiarrhythmic therapy because they are generally well tolerated and are essentially devoid of extracardiac organ toxicity. When one or another of these drugs is ineffective or is associated with side effects, then second or third-line choices include amiodarone, dofetilide, disopyramide, procainamide, and quinidine, which have greater potential for adverse reactions. A nonpharmacological approach may be appropriate for some patients, and this should be considered before amiodarone therapy is instituted. Occasionally, a consistent initiating factor may be found, such as vagally mediated AF (in which case drugs such as disopyramide or flecainide are appropriate initial agents) or adrenergically induced AF (for which beta-blockers or sotalol is suggested).

Many patients with organic heart disease can be broadly categorized into those with HF, CAD, or hypertension. Other types of heart disease can be associated with AF, and the clinician must determine which of these categories best fits the individual patient. For patients with HF, safety data support the selection of amiodarone or dofetilide to maintain sinus rhythm. Patients with ischemic heart disease often require beta-blocker medication, and sotalol, a drug with both beta-blocking activity and primary antiarrhythmic efficacy, is considered first, unless the patient has HF. Amiodarone and dofetilide are considered secondary agents, and the clinician may consider disopyramide, procainamide, or quinidine on an individual basis. In patients with hypertension without LV hypertrophy, drugs such as flecainide and propafenone, which do not prolong repolarization and the QT interval, may offer a safety advantage and are recommended first. If these agents either prove ineffective or produce side effects, then amiodarone, dofetilide, or sotalol represent appropriate secondary choices. Disopyramide, procainamide, and quinidine are considered third-line agents in this situation. Hypertrophied myocardium may be prone to proarrhythmic toxicity and development of the torsade de pointes type of ventricular tachycardia. Amiodarone is suggested as first-line therapy in patients with LV hypertrophy (wall thickness greater than or equal to 1.4 cm) because of its relative safety compared with several other agents. Because neither ECG nor echocardiography invariably detects LV hypertrophy as defined by measurement of myocardial mass, clinicians may face a conundrum. The selection of antiarrhythmic drugs for patients with a history of hypertension is compounded by the dearth of prospective, controlled trials comparing the safety and efficacy of drug therapy for AF.

The scarcity of data from randomized trials of antiarrhythmic medications for treatment of patients with AF applies generally to all patient groups. Accordingly, the drug-selection algorithm presented here has been developed as a consensus of experts and is particularly subject to revision as additional evidence emerges in this field.

3. Recurrent Persistent AF (Figs. 11, 12). Patients with minimal or no symptoms referable to AF who have undergone at least 1 attempt to restore sinus rhythm may remain in AF after its second occurrence, with therapy for rate control and prevention of thromboembolism as needed. Alternatively, those with symptoms favoring sinus rhythm should be treated with an antiarrhythmic agent (in addition to medications for rate control and anticoagulation) before cardioversion. The selection of an antiarrhythmic drug should be based on the same algorithm used for patients with recurrent paroxysmal AF.

4. Permanent AF (Fig. 12). Permanent AF is the designation given to cases in which sinus rhythm cannot be sustained after cardioversion of AF or when the patient and physician have decided to allow AF to continue without further efforts to restore sinus rhythm. It is important to maintain control of the ventricular rate and to use antithrombotic therapy, as outlined elsewhere in this document, for all patients in this category.

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