

ACC/AHA/ESC Guidelines

ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text

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 (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) *Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society*

Writing Committee Members, Valentin Fuster, MD, PhD, FACC, FAHA, FESC, Co-Chair, Lars E. Rydén, MD, PhD, FACC, FESC, FAHA, Co-Chair, David S. Cannom, MD, FACC, Harry J. Crijns, MD, FACC, FESC^{*}, Anne B. Curtis, MD, FACC, FAHA, Kenneth A. Ellenbogen, MD, FACC[†], Jonathan L. Halperin, MD, FACC, FAHA, Jean-Yves Le Heuzey, MD, FESC, G. Neal Kay, MD, FACC, James E. Lowe, MD, FACC, S. Bertil Olsson, MD, PhD, FESC, Eric N. Prystowsky, MD, FACC, Juan Luis Tamargo, MD, FESC, Samuel Wann, MD, FACC, FESC

ACC/AHA Task Force Members, Sidney C. Smith, Jr, MD, FACC, FAHA, FESC, Chair, Alice K. Jacobs, MD, FACC, FAHA, Vice-Chair, Cynthia D. Adams, MSN, APRN-BC, FAHA, Jeffery L. Anderson, MD, FACC, FAHA, Elliott M. Antman, MD, FACC, FAHA[‡], Jonathan L. Halperin, MD, FACC, FAHA, Sharon Ann Hunt, MD, FACC, FAHA, Rick Nishimura, MD, FACC, FAHA, Joseph P. Ornato, MD, FACC, FAHA, Richard L. Page, MD, FACC, FAHA, Barbara Riegel, DNSc, RN, FAHA

ESC Committee for Practice Guidelines, Silvia G. Priori, MD, PhD, FESC, Chair, Jean-Jacques Blanc, MD, FESC, France, Andrzej Budaj, MD, FESC, Poland, A. John Camm, MD, FESC, FACC, FAHA, United Kingdom, Veronica Dean, France, Jaap W. Deckers, MD, FESC, The Netherlands, Catherine Despres, France, Kenneth Dickstein, MD, PhD, FESC, Norway, John Lekakis, MD, FESC, Greece, Keith McGregor, PhD, France, Marco Metra, MD, Italy, Joao Morais, MD, FESC, Portugal, Ady Osterspey, MD, Germany, Juan Luis Tamargo, MD, FESC, Spain, José Luis Zamorano, MD, FESC, Spain

*European Heart Rhythm Association Official Representative.

[†]Heart Rhythm Society Official Representative.

[‡]Immediate Past Chair.

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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 as they are introduced and tested in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology Foundation (ACCF) 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, update, or revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. The Task Force is pleased to have this guideline developed in conjunction with the European Society of Cardiology (ESC). Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop or update written recommendations for clinical practice.

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 when appropriate. Writing committees 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. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines make every effort to avoid any actual, potential, or perceived conflict of interest that might arise as a result of an outside relationship or personal interest of the writing committee. Specifically, all members of the Writing Committee and peer reviewers of the document are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Writing committee members are also strongly encouraged to declare a previous relationship with industry that might be perceived as relevant to guideline development. If a writing committee member develops a new relationship with industry during their tenure, they are required to notify guideline staff in writing. The continued participation of the writing committee member will be reviewed. These statements are reviewed by the parent Task Force, reported orally to all members of the writing committee at each meeting, and updated and reviewed by the writing committee as changes occur. Please refer to the methodology manuals for further description of the policies used in guideline development, including relationships with industry, available online at the ACC, AHA, and ESC World Wide Web sites (http://www.acc.org/clinical/manual/manual_introltr.htm, <http://circ.ahajournals.org/manual/>, and <http://www.escardio.org/knowledge/guidelines/Rules/>). Please see Appendix I for author relationships with industry and Appendix II for peer reviewer relationships with industry that are pertinent to these guidelines.

These practice guidelines are intended to assist health-care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases and conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines and will be considered current

unless they are updated, revised, or sunsetted and withdrawn from distribution. The executive summary and recommendations are published in the August 15, 2006, issues of the *Journal of the American College of Cardiology and Circulation* and the August 16, 2006, issue of the *European Heart Journal*. The full-text guidelines are published in the August 15, 2006, issues of the *Journal of the American College of Cardiology and Circulation* and the September 2006 issue of *Europace*, as well as posted on the ACC (www.acc.org), AHA (www.americanheart.org), and ESC (www.escardio.org) World Wide Web sites. Copies of the full-text guidelines and the executive summary are available from all 3 organizations.

Sidney C. Smith Jr, MD, FACC, FAHA, FESC, Chair, ACC/AHA Task Force on Practice Guidelines.

Silvia G. Priori, MD, PhD, FESC, Chair, ESC Committee for Practice Guidelines.

1. Introduction

1.1. Organization of committee and evidence review

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is often associated with structural heart disease, although 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 optimum management of this frequent and complex arrhythmia.

The committee was composed of members representing the ACC, AHA, and ESC, as well as the European Heart Rhythm Association (EHRA) and the Heart Rhythm Society (HRS). This document was reviewed by 2 official reviewers nominated by the ACC, 2 official reviewers nominated by the AHA, and 2 official reviewers nominated by the ESC, as well as by the ACCF Clinical Electrophysiology Committee, the AHA ECG and Arrhythmias Committee, the AHA Stroke Review Committee, EHRA, HRS, and numerous additional content 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 the EHRA and the HRS.

The ACC/AHA/ESC Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation conducted a comprehensive review of the relevant literature from 2001 to 2006. Literature searches were conducted in the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Searches focused on English-language sources and studies in human subjects. Articles related to animal experimentation were cited when the information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Major search terms included atrial fibrillation, age, atrial remodeling, atrioventricular conduction, atrioventricular node, cardioversion, classification, clinical trial,

complications, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, experimental, heart failure (HF), hemodynamics, human, hyperthyroidism, hypothyroidism, meta-analysis, myocardial infarction, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, rhythm control, risks, sinus rhythm, symptoms, and tachycardia-mediated cardiomyopathy. The complete list of search terms is beyond the scope of this section.

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA/ESC format as follows and described in *Table 1*. Recommendations are evidence based and derived primarily from published data.

Classification of recommendations

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.
- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful.

Level of evidence

The weight of evidence was ranked from highest (A) to lowest (C), as follows:

- Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

1.2. Contents of these guidelines

These guidelines first present a comprehensive review of the latest information about the definition, classification, epidemiology, pathophysiological mechanisms, and clinical characteristics of AF. The management of this complex and potentially dangerous arrhythmia is then reviewed. This includes prevention of AF, control of heart rate, prevention of thromboembolism, and conversion to and maintenance of sinus rhythm. The treatment algorithms include pharmacological and nonpharmacological antiarrhythmic approaches, as well as antithrombotic strategies most appropriate for particular clinical conditions. 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 may include some drugs and devices that do not have the approval of all government regulatory agencies. Additional information may be obtained from the package inserts when the drug or device has been approved for the stated indication.

Because atrial flutter can precede or coexist with AF, special consideration is given to this arrhythmia in each section. There are important differences in the mechanisms

Size of Treatment Effect

	Class I Benefit >>> Risk Procedure/treatment SHOULD be performed/administered	Class IIa Benefit >> Risk Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment	Class IIb Benefit \approx Risk Additional studies with broad objectives needed; additional registry data would be helpful Procedure/treatment MAY BE CONSIDERED	Class III Risk \approx Benefit No additional studies needed Procedure/treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
Level A Multiple (3 to 5) population risk strata evaluated ^b General consistency of direction and magnitude of effect	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
Level B Limited (2 to 3) population risk strata evaluated ^b	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Limited evidence from single randomized trial or nonrandomized studies
Level C Very limited (1 to 2) population risk strata evaluated ^b	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

Estimate of Certainty (Precision) of Treatment Effect

^aIn 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought; such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

^bData available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

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 is addressed in the ACC/AHA/ESC Guidelines on the Management of Patients with Supraventricular Arrhythmias.¹

1.3. Changes since the initial publication of these guidelines in 2001

In developing this revision of the guidelines, the Writing Committee considered evidence published since 2001 and drafted revised recommendations where appropriate to incorporate results from major clinical trials such as those that compared rhythm-control and rate-control approaches to long-term management. The text has been reorganized to reflect the implications for patient care, beginning with recognition of AF and its pathogenesis and the general priorities of rate control, prevention of thromboembolism, and methods available for use in selected patients to correct the arrhythmia and maintain normal sinus rhythm. Advances in catheter-based ablation technologies have been incorporated into expanded sections and recommendations, with the recognition that such vital details as patient selection, optimum catheter positioning, absolute rates of treatment success, and the frequency of complications remain incompletely defined. Sections on drug therapy have been condensed and confined to human studies with compounds that have been approved for clinical use in North America and/or Europe. Accumulating evidence from clinical studies on the emerging role of angiotensin inhibition to reduce the occurrence and complications of AF and information on approaches to the primary prevention of AF are addressed comprehensively in the text, as these

may evolve further in the years ahead to form the basis for recommendations affecting patient care. Finally, data on specific aspects of management of patients who are prone to develop AF in special circumstances have become more robust, allowing formulation of recommendations based on a higher level of evidence than in the first edition of these guidelines. An example is the completion of a relatively large randomized trial addressing prophylactic administration of antiarrhythmic medication for patients undergoing cardiac surgery. In developing the updated recommendations, every effort was made to maintain consistency with other ACC/AHA and ESC practice guidelines addressing, for example, the management of patients undergoing myocardial revascularization procedures.

2. Definition

2.1. Atrial fibrillation

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact² (Figure 1). The ventricular response to AF depends on electrophysiological (EP) properties of the AV node and other conducting tissues, the level of vagal and sympathetic tone, the presence or absence of accessory conduction pathways, and the action of drugs.³ Regular cardiac cycles (R-R intervals) are possible in the presence of AV block or ventricular or AV junctional tachycardia. In patients with implanted pacemakers,

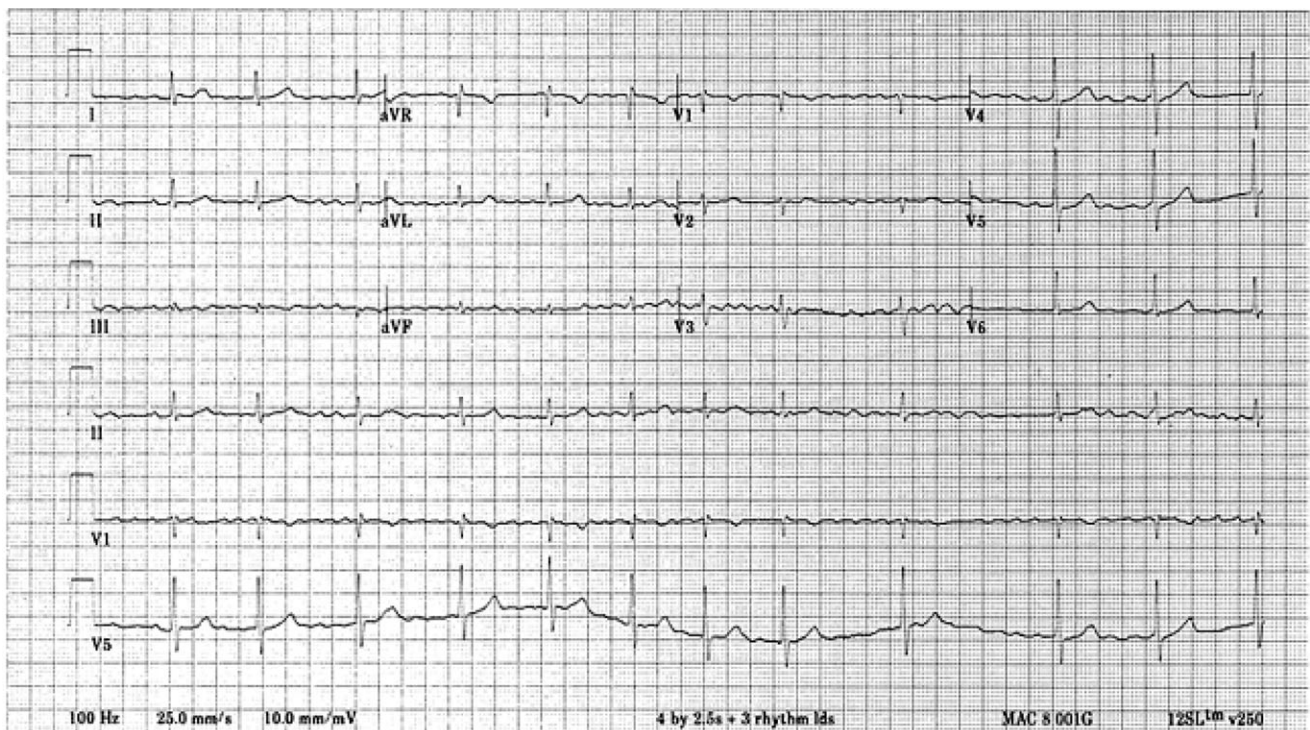


Figure 1 Electrocardiogram showing atrial fibrillation with a controlled rate of ventricular response. P waves are replaced by fibrillatory waves and the ventricular response is completely irregular.

diagnosis of AF may require temporary inhibition of the pacemaker to expose atrial fibrillatory activity.⁴ 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 beats per minute) suggest the presence of an accessory pathway or ventricular tachycardia.

2.2. Related arrhythmias

AF 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 in the typical form is characterized by a saw-tooth pattern of regular atrial activation called flutter (*f*) waves on the ECG, particularly visible in leads II, III, aVF, and V1 (Figure 2). In the untreated state, the atrial rate in atrial flutter typically ranges from 240 to 320 beats per minute, with *f* waves inverted in ECG leads II, III, and aVF and upright in lead V1. The direction 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 V1. Atrial flutter commonly occurs with 2:1 AV block, resulting in a regular or irregular ventricular rate of 120 to 160 beats per minute (most characteristically about 150 beats per minute). Atrial flutter may degenerate into AF and AF may convert to atrial flutter. The ECG pattern may fluctuate between atrial flutter and AF, reflecting changing activation of the atria. Atrial flutter is usually readily distinguished from AF, but when atrial

activity is prominent on the ECG in more than 1 lead, AF may be misdiagnosed as atrial flutter.⁵

Focal atrial tachycardias, AV reentrant tachycardias, and AV nodal reentrant tachycardias may also trigger AF. In other atrial tachycardias, P waves may be readily identified and are 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.

3. Classification

Various classification systems have been proposed for AF. One is based on the ECG presentation.²⁻⁴ Another is based on epicardial⁶ 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.⁷⁻¹⁰ To be clinically useful, a classification system must be based on a sufficient number of features and carry specific therapeutic implications.

Assorted labels have been used to describe the pattern of AF, including acute, chronic, paroxysmal, intermittent, constant, persistent, and permanent, but the vagaries of definitions make it difficult to compare studies of AF or the effectiveness of therapeutic strategies based on these designations. Although the pattern of the arrhythmia can change over time, it may be of clinical value to characterize the arrhythmia at a given moment. The classification scheme recommended in this document represents a consensus driven by a desire for simplicity and clinical relevance.



Figure 2 Electrocardiogram showing typical atrial flutter with variable atrioventricular conduction. Note the saw-tooth pattern, F waves, particularly visible in leads II, III, and aVF, without an isoelectric baseline between deflections.

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 (Figure 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 beyond 7 d, AF is designated persistent. Termination with pharmacological therapy or direct-current cardioversion does not change the designation. First-detected AF may be either paroxysmal or persistent AF. The category of persistent AF also includes cases of long-standing AF (e.g., greater than 1 y), usually leading to permanent AF, in which cardioversion has failed or has not been attempted.

These categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal AF and occasional persistent AF, or the reverse. Regarding paroxysmal and persistent AF, it is practical to categorize a given patient by the most frequent presentation. The definition of permanent AF is often arbitrary. The duration of AF refers both to individual episodes and to how long the patient has been affected by the arrhythmia. Thus, a patient with paroxysmal AF may have episodes that last seconds to hours occurring repeatedly for years.

Episodes of AF briefer than 30 s may be important in certain clinical situations involving symptomatic patients, pre-excitation or in assessing the effectiveness of therapeutic interventions. This terminology applies to episodes of AF that last more than 30 s without a reversible cause. Secondary AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease is considered separately. In these settings, AF is not the primary problem, and treatment of the underlying disorder concurrently with management of the episode of AF usually terminates the arrhythmia without recurrence. Conversely, because AF is common, it may occur independently of a concurrent disorder like well-controlled hypothyroidism, and then the general principles for management of the arrhythmia apply.

The term 'lone AF' has been variously defined but generally applies to young individuals (under 60 y of age) without

clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.¹¹ These patients have a favorable prognosis with respect to thromboembolism and mortality. Over time, patients may move out of the lone AF category due to aging or development of cardiac abnormalities such as enlargement of the left atrium (LA). Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term 'nonvalvular AF' is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

4. Epidemiology and prognosis

AF is the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. Most data regarding the epidemiology, prognosis, and quality of life in AF have been obtained in the United States and western Europe. It has been estimated that 2.2 million people in America and 4.5 million in the European Union have paroxysmal or persistent AF.¹² During the past 20 y, there has been a 66% increase in hospital admissions for AF¹³⁻¹⁵ due to a combination of factors including the aging of the population, a rising prevalence of chronic heart disease, and more frequent diagnosis through use of ambulatory monitoring devices. AF is an extremely costly public health problem,^{16,17} with hospitalizations as the primary cost driver (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%). Globally, the annual cost per patient is close to €3000 (approximately U.S. \$3600).¹⁶ Considering the prevalence of AF, the total societal burden is huge, for example, about €13.5 billion (approximately U.S. \$15.7 billion) in the European Union.

4.1. Prevalence

The estimated prevalence of AF is 0.4% to 1% in the general population, increasing with age.^{18,19} Cross-sectional studies have found a lower prevalence in those below the age of 60 y, increasing to 8% in those older than 80 y (Figure 4).²⁰⁻²² The age-adjusted prevalence of AF is higher

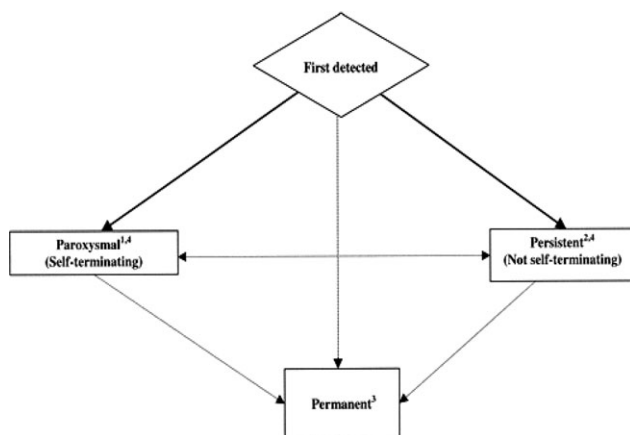


Figure 3 Patterns of atrial fibrillation (AF). 1, Episodes that generally last 7 d or less (most less than 24 h); 2, episodes that usually last longer than 7 d; 3, cardioversion failed or not attempted; and 4, both paroxysmal and persistent AF may be recurrent.

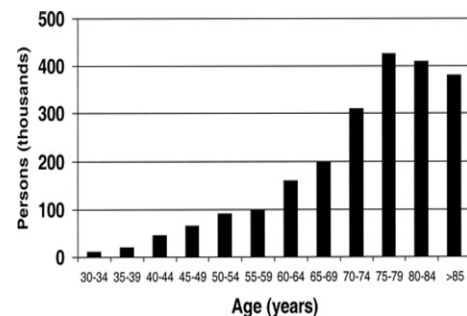


Figure 4 Estimated age-specific prevalence of atrial fibrillation (AF) based on 4 population-based surveys. Prevalence, age, distribution, and gender of patients with AF analysis and implications. Modified with permission from Feinberg WM, Blackshear JL, Laupacis A, *et al.* Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;155:469-73. Copyright © 1995, American Medical Association. All rights reserved.

in men,^{22,23} in whom the prevalence has more than doubled from the 1970s to the 1990s, while the prevalence in women has remained unchanged.²⁴ The median age of AF patients is about 75 y. Approximately 70% are between 65 and 85 y old. The overall number of men and women with AF is about equal, but approximately 60% of AF patients over 75 y are female. Based on limited data, the age-adjusted risk of developing AF in blacks seems less than half that in whites.^{18,25,26} AF is less common among African-American than Caucasian patients with heart failure (HF).

In population-based studies, patients with no history of cardiopulmonary disease account for fewer than 12% of all cases of AF.^{11,22,27,28} In some series, however, the observed proportion of lone AF was over 30%.^{29,30}

These differences may depend on selection bias when recruiting patients seen in clinical practice compared with population-based observations. In the Euro Heart Survey on AF,³¹ the prevalence of idiopathic AF amounted to 10%, with an expected highest value of 15% in paroxysmal AF, 14% in first-detected AF, 10% in persistent AF, and only 4% in permanent AF. Essential hypertension, ischemic heart disease, HF (Table 2), valvular heart disease, and diabetes are the most prominent conditions associated with AF.¹⁴

4.2. Incidence

In prospective studies, the incidence of AF increases from less than 0.1% per year in those under 40 y old to exceed 1.5% per year in women and 2% in men older than 80 (Figure 5).^{25,32,33} The age-adjusted incidence increased over a 30-y period in the Framingham Study,³² and this may have implications for the future impact of AF.³⁴ During 38 y of follow-up in the Framingham Study, 20.6% of men who developed AF had HF at inclusion versus 3.2% of those without AF; the corresponding incidences in women were 26.0% and 2.9%.³⁵ In patients referred for treatment of HF, the 2- to 3-y incidence of AF was 5% to 10%.^{25,36,37} The incidence of AF may be lower in HF patients treated with angiotensin inhibitors.³⁸⁻⁴⁰

Table 2 Prevalence of AF in patients with heart failure as reflected in several heart failure trials

Predominant NYHA Class	Prevalence of AF (%)	Study
I	4	SOLVD-prevention (1992) ^{14a}
II-III	10 to 26	SOLVD-treatment (1991) ^{14b} CHF-STAT (1995) ^{14c} MERIT-HF (1999) ^{14d} DIAMOND-CHF (1999) ⁵⁰¹
II-IV	12 to 27	CHARM (2003) Val-HeFT (2003) ⁸⁴⁸
III-IV	20 to 29	Middlekauff (1991) ^{14e} Stevenson (1996) GESICA (1994) ^{14f}
IV	50	CONSENSUS (1987) ^{14g}

AF indicates atrial fibrillation; NYHA, New York Heart Association; 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; DIAMOND-CHF, Danish Investigations of Arrhythmia and Mortality on Dofetilide-Congestive Heart Failure; CHARM, Candesartan in Heart failure, Assessment of Reduction in Mortality and morbidity; Val-HeFT, Valsartan Heart Failure Trial; GESICA, Grupo Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (V); CONSENSUS, Co-operative North Scandinavian Enalapril Survival Study.

Similarly, angiotensin inhibition may be associated with a reduced incidence of AF in patients with hypertension,^{41,42} although this may be confined to those with left ventricular hypertrophy (LVH).⁴³⁻⁴⁵

4.3. Prognosis

AF is associated with an increased long-term risk of stroke,⁴⁷ HF, and all-cause mortality, especially in women.⁴⁸ The mortality rate of patients with AF is about double that of patients in normal sinus rhythm and linked to the severity of underlying heart disease^{20,23,33} (Figure 6). About two-thirds of the 3.7% mortality over 8.6 mo in the Etude en Activité Libérale sur la Fibrillation Auriculaire Study (ALFA) was attributed to cardiovascular causes.²⁹ Table 3 shows a list of associated heart diseases in the population of the ALFA study.²⁹

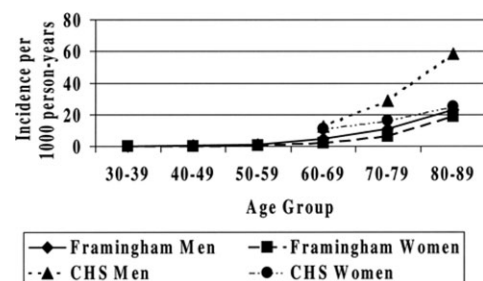


Figure 5 Incidence of atrial fibrillation in 2 American epidemiological studies. Framingham indicates the Framingham Heart Study. Data are from Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147:1561-4.³² CHS indicates the Cardiovascular Health Study. Data are from Psaty BM, Manolio TA, Kuller LH, *et al.* Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96:2455-6125; and Furberg CD, Psaty BM, Manolio TA, *et al.* Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;74:236-41,22 and Farrell B, Godwin J, Richards S, *et al.* The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;54:1044-54.⁴⁶

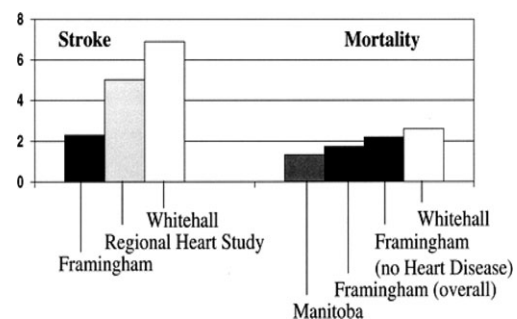


Figure 6 Relative risk of stroke and mortality in patients with atrial fibrillation (AF) compared with patients without AF. Source data from the Framingham Heart Study (Kannel WB, Abbott RD, Savage DD, *et al.* Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983;106:389-96),²³ the Regional Heart Study and the Whitehall study (Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation), and the Manitoba study (Krahn AD, Manfreda J, Tate RB, *et al.* The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. *Am J Med* 1995;98:476-84).³³

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	69	66	70	68
Male/female ratio	1	1	2	1
Time from first episode of AF (mo)	47	39	66	NA
Underlying heart disease (%)				
Coronary artery disease	17	12	18	19
Hypertensive heart disease	21	17	22	25
Valvular (rheumatic)	15	10	20	12
Dilated cardiomyopathy	9	2	13	9
Hypertrophic cardiomyopathy	5	3	4	9
Other	9	14	9	7
None	29	46	23	28
Other predisposing or associated factors (%)				
Hyperthyroidism	3	4	2	5
Hypertension	39	35	38	46
Bronchopulmonary disease	11	10	13	10
Diabetes	11	7	13	9
Congestive HF	30	14	43	18
Prior embolic events	8	8	11	4
Left atrial size (mm)	44	40	47	42
Left ventricular ejection fraction (%)	59	63	57	58

Persistent atrial fibrillation (AF) includes both recent-onset and chronic AF. Recent-onset AF was defined as persistent AF lasting greater than or equal to 7 and less than 30 d. Chronic AF was defined as persistent AF of more than 30-d duration. Patients in whom the diagnosis was definite and those in whom it was probable were included. Modified with permission from Levy S, Maarek M, Coumel P, *et al.* Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA Study, The College of French Cardiologists. *Circulation* 1999;99:3028–35.²⁹ © 1999 American Heart Association.

ALFA indicates Etude en Activité Libérale sur la Fibrillation Auriculaire, HF, heart failure; NA, not applicable or unavailable.

Mortality in the Veterans Administration Heart Failure Trials (V-HeFT) was not increased among patients with concomitant AF,⁴⁹ whereas in the Studies of Left Ventricular Dysfunction (SOLVD), mortality was 34% for those with AF versus 23% for patients in sinus rhythm (*p* less than 0.001).⁵⁰ The difference was attributed mainly to deaths due to HF rather than to thromboembolism. AF was a strong independent risk factor for mortality and major morbidity in large HF trials. In the Carvedilol Or Metoprolol European Trial (COMET), there was no difference in all-cause mortality in those with AF at entry, but mortality increased in those who developed AF during follow-up.⁵¹ In the Val-HeFT cohort of patients with chronic HF, development of AF was associated with significantly worse outcomes.⁴⁰ HF promotes AF, AF aggravates HF, and individuals with either condition who develop the alternate condition share a poor prognosis.⁵² Thus, managing the association is a major challenge⁵³ and the need for randomized trials to investigate the impact of AF on the prognosis in HF is apparent.

The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of people without AF^{20,21,29,32,33,47} (Figure 6). One of every 6 strokes occurs in a patient with AF.⁵⁴ Additionally, when transient ischemic attacks (TIAs) and clinically 'silent' strokes detected by brain imaging are considered, the rate of brain ischemia accompanying nonvalvular AF exceeds 7% per year.^{35,55–58} In patients with rheumatic heart disease and AF in the Framingham Heart Study, stroke risk was increased 17-fold compared with age-matched controls,⁵⁹ and attributable risk was 5 times greater than that in those with nonrheumatic AF.²¹ In the Manitoba Follow-up

Study, AF doubled the risk of stroke independently of other risk factors,³³ and the relative risks for stroke in non-rheumatic 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 Etude en Activité Libérale sur le Fibrillation Auriculaire (ALFA) study found a 2.4% incidence of thromboembolism over a mean of 8.6 mo of follow-up.²⁹ The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF was 1.5% in participants 50 to 59 y old and 23.5% in those aged 80 to 89 y.²¹

5. Pathophysiological mechanisms

5.1. Atrial factors

5.1.1. Atrial pathology as a cause of atrial fibrillation

The most frequent pathoanatomic changes in AF are atrial fibrosis and loss of atrial muscle mass. Histological examination of atrial tissue of patients with AF has shown patchy fibrosis juxtaposed with normal atrial fibers, which may account for nonhomogeneity of conduction.^{60–62} The sinoatrial (SA) and AV nodes may also be involved, accounting for the sick sinus syndrome and AV block. It is difficult to distinguish between changes due to AF and those due to associated heart disease, but fibrosis may precede the onset of AF.⁶³

Biopsy of the LA posterior wall during mitral valve surgery revealed mild to moderate fibrosis in specimens obtained from patients with sinus rhythm or AF of relatively short duration, compared with severe fibrosis and substantial loss of muscle mass in those from patients with long-standing AF.

Patients with mild or moderate fibrosis responded more successfully to cardioversion than did those with severe fibrosis, which was thought to contribute to persistent AF in cases of valvular heart disease.⁶⁴ In atrial tissue specimens from 53 explanted hearts from transplantation recipients with dilated cardiomyopathy, 19 of whom had permanent, 18 persistent, and 16 no documented AF, extracellular matrix remodeling including selective downregulation of atrial insulin-like growth factor II mRNA-binding protein 2 (IMP-2) and upregulation of matrix metalloproteinase 2 (MMP-2) and type 1 collagen volume fraction (CVF-1) were associated with sustained AF.⁶⁵

Atrial biopsies from patients undergoing cardiac surgery revealed apoptosis⁶⁶ that may lead to replacement of atrial myocytes by interstitial fibrosis, loss of myofibrils, accumulation of glycogen granules, disruption of cell coupling at gap junctions,⁶⁷ and organelle aggregates.⁶⁸ The concentration of membrane-bound glycoproteins that regulate cell-cell and cell-matrix interactions (disintegrin and metalloproteinases) in human atrial myocardium has been reported to double during AF. Increased disintegrin and metalloproteinase activity may contribute to atrial dilation in patients with long-standing AF.

Atrial fibrosis may be caused by genetic defects like lamin AC gene mutations.⁶⁹ Other triggers of fibrosis include inflammation⁷⁰ as seen in cardiac sarcoidosis⁷¹ and autoimmune disorders.⁷² In one study, histological changes consistent with myocarditis were reported in 66% of atrial biopsy specimens from patients with lone AF,⁶² but it is uncertain whether these inflammatory changes were a cause or consequence of AF. Autoimmune activity is suggested by high serum levels of antibodies against myosin heavy chains in patients with paroxysmal AF who have no identified heart disease.⁷² Apart from fibrosis, atrial pathological findings in patients with AF include amyloidosis,^{73,74} hemochromatosis,⁷⁵ and endomyocardial fibrosis.^{75,76} Fibrosis is also triggered by atrial dilation in any type of heart disease associated with AF, including valvular disease, hypertension, HF, or coronary atherosclerosis.⁷⁷ Stretch activates several molecular pathways, including the renin-angiotensin-aldosterone system (RAAS). Both angiotensin II and transforming growth factor-beta1 (TGF-beta1) are upregulated in response to stretch, and these molecules induce production of connective tissue growth factor (CTGF).⁷⁰ Atrial tissue from patients with persistent AF undergoing open-heart surgery demonstrated increased amounts of extracellular signal-regulated kinase messenger RNA (ERK-2-mRNA), and expression of angiotensin-converting enzyme (ACE) was increased 3-fold during persistent AF.⁷⁸ A study of 250 patients with AF and an equal number of controls demonstrated the association of RAAS gene polymorphisms with this type of AF.⁷⁹

Several RAAS pathways are activated in experimental^{78,80-84} as well as human AF,^{78,85} and ACE inhibition and angiotensin II receptor blockade had the potential to prevent AF by reducing fibrosis.^{84,86}

In experimental studies of HF, atrial dilation and interstitial fibrosis facilitates sustained AF.⁸⁶⁻⁹² The regional electrical silence (suggesting scar), voltage reduction, and conduction slowing described in patients with HF⁹³ are similar to changes in the atria that occur as a consequence of aging.

AF is associated with delayed interatrial conduction and dispersion of the atrial refractory period.⁹⁴ Thus, AF seems

to cause a variety of alterations in the atrial architecture and function that contribute to remodeling and perpetuation of the arrhythmia. Despite these pathological changes in the atria, however, isolation of the pulmonary veins (PVs) will prevent AF in many such patients with paroxysmal AF.

5.1.1.1. Pathological changes caused by atrial fibrillation. Just as atrial stretch may cause AF, AF can cause atrial dilation through loss of contractility and increased compliance.⁶¹ Stretch-related growth mechanisms and fibrosis increase the extracellular matrix, especially during prolonged periods of AF. Fibrosis is not the primary feature of AF-induced structural remodeling,^{95,96} although accumulation of extracellular matrix and fibrosis are associated with more pronounced myocytic changes once dilation occurs due to AF or associated heart disease.^{90,97} These changes closely resemble those in ventricular myocytes in the hibernating myocardium associated with chronic ischemia.⁹⁸ Among these features are an increase in cell size, perinuclear glycogen accumulation, loss of sarcoplasmic reticulum and sarcomeres (myolysis). Changes in gap junction distribution and expression are inconsistent,^{61,99} and may be less important than fibrosis or shortened refractoriness in promoting AF. Loss of sarcomeres and contractility seems to protect myocytes against the high metabolic stress associated with rapid rates. In fact, in the absence of other pathophysiological factors, the high atrial rate typical of AF may cause ischemia that affects myocytes more than the extracellular matrix and interstitial tissues.

Aside from changes in atrial dimensions that occur over time, data on human atrial structural remodeling are limited^{96,100} and difficult to distinguish from degenerative changes related to aging and associated heart disease.⁹⁶ One study that compared atrial tissue specimens from patients with paroxysmal and persistent lone AF found degenerative contraction bands in patients with either pattern of AF, while myolysis and mitochondria hibernation were limited to those with persistent AF. The activity of calpain I, a proteolytic enzyme activated in response to cytosolic calcium overload, was upregulated in both groups and correlated with ion channel protein and structural and electrical remodeling. Hence, calpain activation may link calcium overload to cellular adaptation in patients with AF.³⁴¹

5.1.2. Mechanisms of atrial fibrillation

The onset and maintenance of a tachyarrhythmia require both an initiating event and an anatomical substrate. With respect to AF, the situation is often complex, and available data support a 'focal' mechanism involving automaticity or multiple reentrant wavelets. These mechanisms are not mutually exclusive and may at various times coexist in the same patient (*Figure 7*).

5.1.2.1. Automatic focus theory. A focal origin of AF is supported by experimental models of aconitine and pacing-induced AF^{102,103} in which the arrhythmia persists only in isolated regions of atrial myocardium. This theory received minimal attention until the important observation that a focal source for AF could be identified in humans and ablation of this source could extinguish AF.¹⁰⁴ While PVs are the most frequent source of these rapidly atrial impulses, foci have also been found in the superior vena cava, ligament of Marshall, left posterior free wall, crista terminalis, and coronary sinus.^{79,104-110}

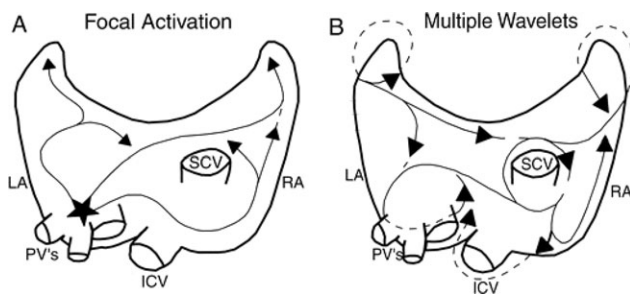


Figure 7 Posterior view of principal electrophysiological mechanisms of atrial fibrillation. (A), Focal activation. The initiating focus (indicated by the star) often lies within the region of the pulmonary veins. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. (B), Multiple-wavelet reentry. Wavelets (indicated by arrows) randomly reenter tissue previously activated by the same or another wavelet. The routes the wavelets travel vary. Reproduced with permission from Konings KT, Kirchhof CJ, Smeets JR, *et al*. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation* 1994;**89**:1665–80.¹⁰¹ LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium.

In histological studies, cardiac muscle with preserved electrical properties extends into the PV,^{106,111–116} and the primacy of PVs as triggers of AF has prompted substantial research into the anatomical and EP properties of these structures. Atrial tissue on the PV of patients with AF has shorter refractory periods than in control patients or other parts of the atria in patients with AF.^{117,118} The refractory period is shorter in atrial tissue in the distal PV than at the PV-LA junction. Decremental conduction in PV is more frequent in AF patients than in controls, and AF is more readily induced during pacing in the PV than in the LA. This heterogeneity of conduction may promote reentry and form a substrate for sustained AF.¹¹⁹ Programmed electrical stimulation in PV isolated by catheter ablation initiated sustained pulmonary venous tachycardia, probably as a consequence of reentry.¹²⁰ Rapidly firing atrial automatic foci may be responsible for these PV triggers, with an anatomical substrate for reentry vested within the PV.

Whether the source for AF is an automatic focus or a microreentrant circuit, rapid local activation in the LA cannot extend to the RA in an organized way. Experiments involving acetylcholine-induced AF in Langendorf-perfused sheep hearts demonstrated a dominant fibrillation frequency in the LA with decreasing frequency as activation progressed to the RA. A similar phenomenon has been shown in patients with paroxysmal AF.¹²¹ Such variation in conduction leads to disorganized atrial activation, which could explain the ECG appearance of a chaotic atrial rhythm.¹²² The existence of triggers for AF does not negate the role of substrate modification. In some patients with persistent AF, disruption of the muscular connections between the PV and the LA may terminate the arrhythmia. In others, AF persists following isolation of the supposed trigger but does not recur after cardioversion. Thus, in some patients with abnormal triggers, sustained AF may depend on an appropriate anatomical substrate.

5.1.2.2. Multiple-wavelet hypothesis. The multiple-wavelet hypothesis as the mechanism of reentrant AF was advanced by Moe and colleagues,¹²³ who proposed that fractionation

of wavefronts propagating through the atria results in self-perpetuating 'daughter wavelets'. In this model, the number of wavelets 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 increases the number of wavelets, favoring sustained AF. Simultaneous recordings from multiple electrodes supported the multiple-wavelet hypothesis in human subjects.¹²⁷

For many years, the multiple-wavelet hypothesis was the dominant theory explaining the mechanism of AF, but the data presented above and from experimental^{127a} and clinical^{127b,127c} mapping studies challenge this notion. Even so, a number of other observations support the importance of an abnormal atrial substrate in the maintenance of AF. For over 25 y, EP studies in humans have implicated atrial vulnerability in the pathogenesis of AF.^{128–132} In one study of 43 patients without structural heart disease, 18 of whom had paroxysmal AF, the coefficient of dispersion of atrial refractoriness was significantly greater in the patients with AF.¹²⁸ Furthermore, in 16 of 18 patients with a history of AF, the arrhythmia was induced with a single extrastimulus, while a more aggressive pacing protocol was required in 23 of 25 control patients without previously documented AF. In patients with idiopathic paroxysmal AF, widespread distribution of abnormal electrograms in the RA predicted development of persistent AF, suggesting an abnormal substrate.¹³² In patients with persistent AF who had undergone conversion to sinus rhythm, there was significant prolongation of intra-atrial conduction compared with a control group, especially among those who developed recurrent AF after cardioversion.¹³⁰

Patients with a history of paroxysmal AF, even those with lone AF, have abnormal atrial refractoriness and conduction compared with patients without AF. An abnormal signal-averaged P-wave ECG reflects slowed intra-atrial conduction and shorter wavelengths of reentrant impulses. The resulting increase in wavelet density promotes the onset and maintenance of AF. Among patients with HF, prolongation of the P wave was more frequent in those prone to paroxysmal AF.¹³³ In specimens of RA appendage tissue obtained from patients undergoing open-heart surgery, P-wave duration was correlated with amyloid deposition.⁷³ Because many of these observations were made prior to the onset of clinical AF, the findings cannot be ascribed to atrial remodeling that occurs as a consequence of AF. Atrial refractoriness increases with age in both men and women, but concurrent age-related fibrosis lengthens effective intra-atrial conduction pathways. This, coupled with the shorter wavelengths of reentrant impulses, increases the likelihood that AF will develop.^{134,135} Nonuniform alterations of refractoriness and conduction throughout the atria may provide a milieu for the maintenance of AF. However, the degree to which changes in the atrial architecture contribute to the initiation and maintenance of AF is not known. Isolation of the PV may prevent recurrent AF even in patients with substantial abnormalities in atrial size and function. Finally, the duration of episodes of AF correlates with both a decrease in atrial refractoriness and shortening of the AF cycle length, attesting to the importance of electrical remodeling in the maintenance of AF.¹³⁶ The anatomical and electrophysiological substrates are detailed in *Table 4*.

Table 4 Anatomical and electrophysiological substrates promoting the initiation and/or maintenance of atrial fibrillation

Diseases	Anatomical	Substrates ^a	
		Cellular	Electrophysiological
<i>Part A. substrate develops during sinus rhythm (remodeling related to stretch and dilatation). The main pathways involve the RAAS, TGF-beta, and CTGF.</i>			
Hypertension	Atrial dilatation	Myolysis	Conduction abnormalities
Heart failure	PV dilatation	Apoptosis, necrosis	ERP dispersion
Coronary disease	Fibrosis	Channel expression change	Ectopic activity
Valvular disease			
<i>Part B. substrate develops due to tachycardia (tachycardia-related remodeling, downregulation of calcium channel and calcium handling).</i>			
Focal AF	None or ^b	None or ^b	Ectopic activity
Atrial flutter	Atrial dilatation	Calcium channel downregulation	Microreentry
	PV dilatation	Myolysis	Short ERP ^c
	Large PV sleeves	Connexin downregulation	ERP dispersion ^d
	Reduced contractility ^{&cjs0952} ; Fibrosis	Adrenergic supersensitivity Changed sympathetic innervation	Slowed conduction

CTGF indicates connective tissue growth factor; ERP, effective refractory period; PV, pulmonary vein; RAAS, renin-angiotensin-aldosterone system; TGF-beta, transforming growth factor-beta.

^aSubstrate develops either while in sinus rhythm, usually caused by ventricular remodeling, atrial pressure overload and subsequent atrial dilatation (Part A), or due to the rapid atrial rate during atrial fibrillation (AF), according to the principle that 'AF begets AF' (Part B).

^bThe listed changes may only occur with prolonged episodes of AF at high atrial rate.

^cShort ERP and slow conduction may produce short wavelength, thereby promoting further AF.

^dERP dispersion together with spontaneous or stretch-induced ectopic activity may initiate AF. Long ERPs occur in Bachmann's bundle among other tissues. ^{&cjs0952}The reduction of atrial contractility during AF may enhance atrial dilatation, leading to persistent AF.

5.1.3. Atrial electrical remodeling

Pharmacological or direct-current cardioversion of AF has a higher success rate when AF has been present for less than 24 h,¹³⁷ whereas more prolonged AF makes restoring and maintaining sinus rhythm less likely. These observations gave rise to the adage 'atrial fibrillation begets atrial fibrillation'. The notion that AF is self-perpetuating takes experimental support from a goat model using an automatic atrial fibrillator that detected spontaneous termination of AF and reinduced the arrhythmia by electrical stimulation.¹³⁸ 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.¹³⁸ The increasing propensity to AF was related to progressive shortening of effective refractory periods with increasing episode duration, a phenomenon known as EP remodeling. These measurements support clinical observations¹³⁹ that the short atrial effective refractory period in patients with paroxysmal AF fails to adapt to rate, particularly during bradycardia. Confirmation came from recordings of action potentials in isolated fibrillating atrial tissue and from patients after cardioversion.¹⁴⁰ The duration of atrial monophasic action potentials was shorter after cardioversion and correlated with the instability of sinus rhythm.¹⁴¹

Tachycardia-induced AF may result from AV node reentry, an accessory pathway, atrial tachycardia, or atrial flutter.¹⁴²⁻¹⁴⁴ After a period of rapid atrial rate, electrical remodeling stimulates progressive intracellular calcium loading that leads to inactivation of the calcium current.^{145,146} Reduction of the calcium current in turn shortens the action potential duration and atrial refractory period, which may promote sustained AF. The role of potassium currents in this situation is less clear.¹⁴⁵ Electrical remodeling has also been demonstrated in PV myocytes subjected to sustained rapid atrial pacing, resulting in shorter action potential durations and both early and delayed afterdepolarizations.¹⁴⁷

In addition to remodeling and changes in electrical refractoriness, prolonged AF disturbs atrial contractile function. With persistent AF, recovery of atrial contraction can be delayed for days or weeks following the restoration of sinus rhythm, which has important implications for the duration of anticoagulation after cardioversion. (See Section 8.1.4, Preventing Thromboembolism.) Both canine and preliminary human data suggest that prolonged AF may also lengthen sinus node recovery time.^{148,149} The implication is that AF may be partly responsible for sinus node dysfunction in some patients with the tachycardia-bradycardia syndrome.

Reversal of electrical remodeling in human atria may occur at different rates depending on the region of the atrium studied.¹⁵⁰ When tested at various times after cardioversion, the effective refractory period of the lateral RA increased within 1 h after cardioversion, while that in the coronary sinus was delayed for 1 wk. In another study, recovery of normal atrial refractoriness after cardioversion of persistent AF was complete within 3 to 4 d,¹⁵¹ after which there was no difference in refractoriness between the RA appendage and the distal coronary sinus. The disparities between studies may reflect patient factors or the duration or pattern of AF before cardioversion.

5.1.4. Counteracting atrial electrical remodeling

Data are accumulating on the importance of the RAAS in the genesis of AF.¹⁴⁵ Irbesartan plus amiodarone was associated with a lower incidence of recurrent AF after cardioversion than amiodarone alone,³⁹ and use of angiotensin inhibitors and diuretics significantly reduced the incidence of AF after catheter ablation of atrial flutter.¹⁵² Amiodarone may reverse electrical remodeling even when AF is ongoing,¹⁵³ and this explains how amiodarone can convert persistent AF to sinus rhythm. Inhibition of the RAAS, alone or in combination with other therapies, may therefore prevent the onset or maintenance of AF⁴³ through several

mechanisms. These include hemodynamic changes (lower atrial pressure and wall stress), prevention of structural remodeling (fibrosis, dilation, and hypertrophy) in both the LA and left ventricle (LV), inhibition of neurohumoral activation, reduced blood pressure, prevention or amelioration of HF, and avoidance of hypokalemia. Treatment withtrandolapril reduced the incidence of AF in patients with LV dysfunction following acute MI,³⁶ but it remains to be clarified whether the antiarrhythmic effect of these agents is related to reversal of structural or electrical remodeling in the atria or to these other mechanisms.

5.1.5. Other factors contributing to atrial fibrillation

Other factors potentially involved in the induction or maintenance of AF include inflammation, autonomic nervous system activity, atrial ischemia,¹⁵⁴ atrial dilation,¹⁵⁵ anisotropic conduction,¹⁵⁶ and structural changes associated with aging.³ It has been postulated that oxidative stress and inflammation may be involved in the genesis of AF.^{157–159} In a case-control study, levels of C-reactive protein (CRP), a marker of systemic inflammation, were higher in patients with atrial arrhythmias than in those without rhythm disturbances,¹⁵⁹ and those with persistent AF had higher CRP levels than those with paroxysmal AF. In a population-based cohort of nearly 6000 patients, AF was more prevalent among patients in the highest quartile for CRP than those in the lowest quartile. In patients without AF at baseline, CRP levels were associated with the future development of AF.¹⁵⁸

The effects of HMG CoA-reductase inhibitors ('statins'), which have both anti-inflammatory and antioxidant properties, on electrical remodeling have been evaluated in a canine model of atrial tachycardia¹⁶⁰ but have not been adequately studied in human subjects. In the experimental model, tachycardia-related electrical remodeling was suppressed by pretreatment with simvastatin but not by the antioxidant vitamins C and E. The mechanism responsible for the salutary effect of simvastatin requires further investigation, and the utility of drugs in the statin class to prevent clinical AF has not yet been established.

Increased sympathetic or parasympathetic tone has been implicated in the initiation of AF. Autonomic ganglia containing parasympathetic and sympathetic fibers are present on the epicardial surface of both the RA and LA, clustered on the posterior wall near the ostia of the PV, superior vena cava (SVC), and coronary sinus. In animal models, parasympathetic stimulation shortens atrial and PV refractory periods, potentiating initiation and maintenance of AF,^{161,162} and vagal denervation of the atria prevents induction of AF.¹⁶³ In 297 patients with paroxysmal AF, vagal denervation concomitant with extensive endocardial catheter ablation was associated with significant reduction in subsequent AF in a third of cases.¹⁶² Pure autonomic initiation of clinical AF is uncommon and seen only in situations of high sympathetic or high vagal tone, but recordings of heart rate variability (HRV) disclose autonomic perturbations in some patients that precede the onset of AF.^{164–169}

There is a strong association between obstructive sleep apnea, hypertension, and AF.¹⁷⁰ It is likely that LV diastolic dysfunction plays a role in the genesis of AF, either by increasing pressure that affects stretch receptors in PV triggers and other areas of the atria or by inducing direct structural changes in atrial myocardium.^{171,172} Familial factors are discussed in Section 6.1.5.

5.2. Atrioventricular conduction

5.2.1. General aspects

In the absence of an accessory pathway or His-Purkinje dysfunction, the AV node limits conduction during AF.¹⁴⁴ Multiple atrial inputs to the AV node have been identified, 2 of which seem dominant: one directed posteriorly via the crista terminalis and the other aimed anteriorly via the interatrial septum. Other factors affecting AV conduction are the intrinsic refractoriness of the AV node, concealed conduction, and autonomic tone. Concealed conduction, which occurs when atrial impulses traverse part of the AV node but are not conducted to the ventricles, plays a prominent role in determining the ventricular response during AF.^{173,174} These impulses alter AV nodal refractoriness, slowing or blocking subsequent atrial impulses, and may explain the irregularity of ventricular response during AF.¹²⁵ When the atrial rate is relatively slow during AF, the ventricular rate tends to rise. Conversely, a higher atrial rate is associated with slower ventricular rate.

Increased parasympathetic and reduced sympathetic tone exert negative dromotropic effects on AV nodal conduction, while the opposite is true in states of decreased parasympathetic and increased sympathetic tone.^{173,175,176} Vagal tone also enhances the negative chronotropic effects of concealed conduction in the AV node.^{175,176} Fluctuations in autonomic tone can produce disparate ventricular responses to AF in a given patient as exemplified by a slow ventricular rate during sleep but accelerated ventricular response during exercise. Digitalis, which slows the ventricular rate during AF predominantly by increasing vagal tone, is more effective for controlling heart rate at rest in AF but less effective during activity. Wide swings in rate due to variations in autonomic tone may create a therapeutic challenge.

Conducted QRS complexes are narrow during AF unless there is fixed or rate-related bundle-branch block or accessory pathway. Aberrant conduction is common and facilitated by the irregularity of the ventricular response. When a long interval is followed by a relatively short interval, the QRS complex that closes the short interval is often aberrantly conducted (Ashman phenomenon).¹⁷⁷

5.2.2. Atrioventricular conduction in patients with preexcitation syndromes

Conduction across an accessory pathway during AF can result in a dangerously rapid ventricular rate.^{3,178,179} Whereas a substantial increase in sympathetic tone may increase the preexcited ventricular response, alterations in vagal tone have little effect on conduction over accessory pathways.

Transition of AV reentry into AF in patients with the Wolff-Parkinson-White (WPW) syndrome can produce a rapid ventricular response that degenerates into ventricular fibrillation, leading to death.^{178,180} Intravenous administration of drugs such as digitalis, verapamil, or diltiazem, which lengthen refractoriness and slow conduction across the AV node, does not block conduction over the accessory pathway and may accelerate the ventricular rate. Hence, these agents are contraindicated in this situation.¹⁸¹ Although the potential for beta blockers to potentiate conduction across the accessory pathway is controversial, caution should be exercised in the use of these agents as well as in patients with AF associated with preexcitation.

5.3. Myocardial and hemodynamic consequences of atrial fibrillation

Among factors that affect the hemodynamic function during AF are loss of synchronous atrial mechanical activity, irregular ventricular response, rapid heart rate, and impaired coronary arterial blood flow. Loss of atrial contraction may markedly decrease cardiac output, especially when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy. Hemodynamic impairment due to variation in R-R intervals during AF has been demonstrated in a canine model with complete heart block, in which cardiac output fell by approximately 9% during irregular ventricular pacing at the same mean cycle length as a regularly paced rhythm.¹⁸² In patients undergoing AV nodal ablation, irregular right ventricular (RV) pacing at the same rate as regular ventricular pacing resulted in a 15% reduction in cardiac output.¹⁸³ Myocardial contractility is not constant during AF because of force-interval relationships associated with variations in cycle length.¹⁸⁴ Although one might expect restoration of sinus rhythm to improve these hemodynamic characteristics, this is not always the case.^{185,186}

Myocardial blood flow is determined by the presence or absence of coronary obstructive disease, the difference between aortic diastolic pressure and LV end-diastolic pressure (myocardial perfusion pressure), coronary vascular resistance, and the duration of diastole. AF may adversely impact all of these factors. An irregular ventricular rhythm is associated with coronary blood flow compared with a regular rhythm at the same average rate.¹⁸⁶ Animal studies have consistently shown that the decrease in coronary flow caused by experimentally induced AF relates to an increase in coronary vascular resistance mediated by sympathetic activation of alpha-adrenergic receptors that is less pronounced than during regular atrial pacing at the same ventricular rate.¹⁸⁷ Similarly, coronary blood flow is lower during AF than during regular atrial pacing in patients with angiographically normal coronary arteries.¹⁸⁸ The reduced coronary flow reserve during AF may be particularly important in patients with coronary artery disease (CAD), in whom compensatory coronary vasodilation is limited. These findings may explain why patients without previous angina sometimes develop chest discomfort with the onset of AF.

In patients with persistent AF, mean LA volume increased over time from 45 to 64 cm³ while RA volume increased from 49 to 66 cm³.¹⁸⁹ Restoration and maintenance of sinus rhythm decreased atrial volumes.¹⁹⁰ Moreover, transesophageal echocardiography (TEE) has demonstrated that contractile function and blood flow velocity in the LA appendage (LAA) recover after cardioversion, consistent with a reversible atrial cardiomyopathy in patients with AF.^{191,192}

Beyond its effects on atrial function, a persistently elevated ventricular rate during AF—greater than or equal to 130 beats per minute in one study¹⁹³—can produce dilated ventricular cardiomyopathy (tachycardia-induced cardiomyopathy).^{3,193-196} It is critically important to recognize this cause of cardiomyopathy, in which HF is a consequence rather than the cause of AF. Control of the ventricular rate may lead to reversal of the myopathic process. In one study, the median LV ejection fraction increased with rate control from 25% to 52%.¹⁹⁴ This phenomenon also has

implications for timing measurements of ventricular performance in patients with AF. A reduced ejection fraction during or in the weeks following tachycardia may not reliably predict ventricular function once the rate has been consistently controlled. A variety of hypotheses have been proposed to explain tachycardia-mediated cardiomyopathy: myocardial energy depletion, ischemia, abnormal calcium regulation, and remodeling, but the actual mechanisms are still unclear.¹⁹⁷

Because of the relationship between LA and LV pressure, a rapid ventricular rate during AF may adversely impact mitral valve function, increasing mitral regurgitation. In addition, tachycardia may be associated with rate-related intraventricular conduction delay (including left bundle-branch block), which further compromises the synchrony of LV wall motion and reduces cardiac output. Such conduction disturbances may exacerbate mitral regurgitation and limit ventricular filling. Controlling the ventricular rate may reverse these effects.

5.4. 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.¹⁹⁸ Up to 25% of strokes in patients with AF may be due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or atheromatous pathology in the proximal aorta.^{199,200} In patients 80 to 89 y old, 36% of strokes occur in those with AF. The annual risk of stroke for octogenarians with AF is in the range of 3% to 8% per year, depending on associated stroke risk factors.²¹ About half of all elderly AF patients have hypertension (a major risk factor for cerebrovascular disease),⁴⁷ and approximately 12% harbor carotid artery stenosis.²⁰¹ Carotid atherosclerosis is not substantially more prevalent in AF patients with stroke than in patients without AF and is probably a relatively minor contributing epidemiological factor.²⁰²

5.4.1. Pathophysiology of thrombus formation

Thrombotic material associated with AF arises most frequently in the LAA, which cannot be regularly examined by precordial (transthoracic) echocardiography.²⁰³ Doppler TEE is a more sensitive and specific method to assess LAA function²⁰⁴ and to detect thrombus formation. Thrombi are more often encountered in AF patients with ischemic stroke than in those without stroke.²⁰⁵ Although 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.^{206,207} Thrombus formation begins with Virchow's triad of stasis, endothelial dysfunction, and a hypercoagulable state. Serial TEE studies of the LA²⁰⁸ and LAA²⁰⁹ during conversion of AF to sinus rhythm demonstrated reduced LAA flow velocities related to loss of organized mechanical contraction during AF. Stunning of the LAA²¹⁰ seems responsible for an increased risk of thromboembolic events after successful cardioversion, regardless of whether the method is electrical, pharmacological, or spontaneous.²¹⁰ Atrial stunning is at a maximum immediately after cardioversion, with progressive improvement of atrial transport function within a few days but sometimes as long as 3 to 4 wk, depending on the duration of AF.^{210,211}

This corroborates the observation that following cardioversion, more than 80% of thromboembolic events occur during the first 3 d and almost all occur within 10 d.²¹² Atrial stunning is more pronounced in patients with AF associated with ischemic heart disease than in those with hypertensive heart disease or lone AF.²¹⁰ Although stunning may be milder with certain associated conditions or a short duration of AF, anticoagulation is recommended during cardioversion in all patients with AF lasting longer than 48 h or of unknown duration, including lone AF except when anticoagulation is contraindicated.

Decreased flow within the LA/LAA during AF has been associated with spontaneous echo contrast (SEC), thrombus formation, and embolic events.^{213–218} Specifically, SEC, or 'smoke,' a swirling haze of variable density, may be detected by transthoracic or transesophageal echocardiographic imaging of the cardiac chambers and great vessels under low-flow conditions.²¹⁹ This phenomenon relates to fibrinogen-mediated erythrocyte aggregation²²⁰ and is not resolved by anticoagulation.²²¹ There is evidence that SEC is a marker of stasis caused by AF.^{222–224} Independent predictors of SEC in patients with AF include LA enlargement, reduced LAA flow velocity,^{213,225} LV dysfunction, fibrinogen level,²¹⁸ and hematocrit.^{217,218} The utility of SEC for prospective thromboembolic risk stratification beyond that achieved by clinical assessment alone has, however, not been confirmed.

LAA flow velocities are lower in patients with atrial flutter than are usually seen during sinus rhythm but higher than in AF. Whether this accounts for any lower prevalence of LAA thrombus or thromboembolism associated with atrial flutter is uncertain. As in AF, atrial flutter is associated with low appendage emptying velocities following cardioversion with the potential for thromboembolism^{226,227} and anticoagulation is similarly recommended. (See Section 8.1.4.1.3, Therapeutic Implications.)

Although endothelial dysfunction has been difficult to demonstrate as distinctly contributing to thrombus formation in AF, it may, along with stasis, contribute to a hypercoagulable state. Systemic and/or atrial tissue levels of P-selectin and von Willebrand factor are elevated in some patients,^{228–233} and AF has been associated with biochemical markers of coagulation and platelet activation that reflect a systemic hypercoagulable state.^{228,234–236} Persistent and paroxysmal AF have been associated with increased systemic fibrinogen and fibrin D-dimer levels, indicating active intravascular thrombogenesis.^{228,236,237} Elevated thromboglobulin and platelet factor 4 levels in selected patients with AF indicate platelet activation,^{235,238,239} but these data are less robust, in line with the lower efficacy of platelet-inhibitor drugs for prevention of thromboembolism in clinical trials. Fibrin D-dimer levels are higher in patients with AF than in patients in sinus rhythm, irrespective of underlying heart disease.²⁴⁰ The levels of some markers of coagulation fall to normal during anticoagulation therapy,²³⁴ and some increase immediately after conversion to sinus rhythm and then normalize.²⁴¹ These biochemical markers do not, however, distinguish a secondary reaction to intravascular coagulation from a primary hypercoagulable state.

C-reactive protein (CRP) is increased in patients with AF compared with controls^{159,242} and correlates with clinical and echocardiographic stroke risk factors.²⁴³ Although these findings do not imply a causal relationship, the

association may indicate that a thromboembolic milieu in the LA may involve mechanisms linked to inflammation.²⁴³

In patients with rheumatic mitral stenosis undergoing trans-septal catheterization for balloon valvuloplasty, levels of fibrinopeptide A, thrombin-antithrombin III complex, and prothrombin fragment F1.2 are increased in the LA compared with the RA and femoral vein, indicating regional activation of the coagulation system.^{244,245} Whether such elevations are related to AF, for example, through atrial pressure overload or due to another mechanism has not been determined. Regional coagulopathy is associated with SEC in the LA and hence with atrial stasis.²⁴⁵

Contrary to the prevalent concept that systemic anticoagulation for 4 wk results in organization and endocardial adherence of LAA thrombus, TEE studies have verified resolution of thrombus in the majority of patients.²⁴⁶ Similar observations have defined the dynamic nature of LA/LAA dysfunction following conversion of AF, providing 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 SEC^{247,248} and fewer thromboembolic events, even in the presence of LA enlargement.²⁴⁹

5.4.2. Clinical implications

Because the pathophysiology of thromboembolism in patients with AF is uncertain, the mechanisms linking risk factors to ischemic stroke in patients with AF are incompletely defined. The strong association between hypertension and stroke in AF is probably mediated primarily by embolism originating in the LAA,²⁰⁰ but hypertension also increases the risk of noncardioembolic strokes in patients with AF.^{200,250} Hypertension in patients with AF is associated with reduced LAA flow velocity, SEC, and thrombus formation.^{225,251,252} Ventricular diastolic dysfunction might underlie the effect of hypertension on LA dynamics, but this relationship is still speculative.^{253,254} Whether control of hypertension lowers the risk for cardioembolic stroke in patients with AF is a vital question, because LV diastolic abnormalities associated with hypertension in the elderly are often multifactorial and difficult to reverse.^{254,255}

The increasing stroke risk in patients with AF with advancing age is also multifactorial. In patients with AF, aging is associated with LA enlargement, reduced LAA flow velocity, and SEC, all of which predispose to LA thrombus formation.^{225,251,256} Aging is a risk factor for atherosclerosis, and plaques in the aortic arch are associated with stroke independent of AF.²⁵⁷ Levels of prothrombin activation fragment F1.2, an index of thrombin generation, increase with age in the general population^{258–260} as well as in those with AF,^{12,261} suggesting 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,^{261,262} placing women over age 75 y with AF at particular risk for cardioembolic strokes.²⁶³

LV systolic dysfunction, as indicated by a history of HF or echocardiographic assessment, predicts ischemic stroke in patients with AF who receive no antithrombotic therapy^{264–267} but not in moderate-risk patients given aspirin.^{261,268} Mechanistic inferences are contradictory; LV systolic dysfunction has been associated both with LA

thrombus and with noncardioembolic strokes in patients with AF.^{200,269}

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

6. Causes, associated conditions, clinical manifestations, and quality of life

6.1. Causes and associated conditions

6.1.1. Reversible causes of atrial fibrillation

AF may be related to acute, temporary causes, including alcohol intake ('holiday heart syndrome'), surgery, electrocution, MI, pericarditis, myocarditis, pulmonary embolism or other pulmonary diseases, hyperthyroidism, and other metabolic disorders. In such cases, successful treatment of the underlying condition often eliminates AF. AF that develops in the setting of acute MI portends an adverse prognosis compared with preinfarct AF or sinus rhythm.^{270,271} AF may be associated with atrial flutter, the WPW syndrome, or AV nodal reentrant tachycardias, and treatment of the primary arrhythmias reduces or eliminates the incidence of recurrent AF.¹⁷² AF is a common early postoperative complication of cardiac or thoracic surgery.

6.1.2. Atrial fibrillation without associated heart disease

AF is often an electrical manifestation of underlying cardiac disease. Nonetheless, approximately 30% to 45% of cases of paroxysmal AF and 20% to 25% of cases of persistent AF occur in younger patients without demonstrable underlying disease ('lone AF').^{27,29} AF can present as an isolated¹⁰⁴ or familial arrhythmia, although a responsible underlying disease may appear over time.²⁷² Although AF may occur without underlying heart disease in the elderly, the changes in cardiac structure and function that accompany aging, such as an increase in myocardial stiffness, may be associated with AF, just as heart disease in older patients may be coincidental and unrelated to AF.

6.1.3. Medical conditions associated with atrial fibrillation

Obesity is an important risk factor for development of AF.²⁷³⁻²⁷⁵ After adjusting for clinical risk factors, the excess risk of AF appears mediated by LA dilation, because there is a graded increase in LA size as BMI increases from normal to the overweight and obese categories.²⁷³ Weight reduction has been linked to regression of LA enlargement.^{273,276} These findings suggest a physiological link between obesity, AF, and stroke and raise the intriguing possibility that weight reduction may decrease the risk of AF.

6.1.4. Atrial fibrillation with associated heart disease

Specific cardiovascular conditions associated with AF include valvular heart disease (most often, mitral valve disease), HF, CAD, and hypertension, particularly when LVH is present. In addition, AF may be associated with HCM, dilated cardiomyopathy, or congenital heart disease, especially atrial septal defect in adults. Potential etiologies also include restrictive cardiomyopathies (e.g., amyloidosis, hemochromatosis, and endomyocardial fibrosis), cardiac tumors, and

constrictive pericarditis. Other heart diseases, such as mitral valve prolapse with or 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. AF is commonly encountered in patients with sleep apnea syndrome, but whether the arrhythmia is provoked by hypoxia, another biochemical abnormality, changes in pulmonary dynamics or RA factors, changes in autonomic tone, or systemic hypertension has not been determined. *Table 5* lists etiologies and factors predisposing patients to AF. (For a list of associated heart diseases in the ALFA study, see *Table 3*.)

6.1.5. Familial (genetic) atrial fibrillation

Familial AF, defined as lone AF running in a family, is more common than previously recognized but should be distinguished from AF secondary to other genetic diseases like familial cardiomyopathies. The likelihood of developing AF is increased among those whose parents had AF, suggesting a familial susceptibility to the arrhythmia, but the mechanisms associated with transmission are not necessarily electrical, because the relationship has also been seen in patients who have a family history of hypertension, diabetes, or HF.²⁷⁷

The molecular defects responsible for familial AF are largely unknown. Specific chromosomal loci²⁷⁸ have been

Table 5 Etiologies and factors predisposing patients to AF

<i>Electrophysiological abnormalities</i>
Enhanced automaticity (focal AF)
Conduction abnormality (reentry)
<i>Atrial pressure elevation</i>
Mitral or tricuspid valve disease
Myocardial disease (primary or secondary, leading to systolic or diastolic dysfunction)
Semilunar valvular abnormalities (causing ventricular hypertrophy)
Systemic or pulmonary hypertension (pulmonary embolism)
Intracardiac tumors or thrombi
<i>Atrial ischemia</i>
Coronary artery disease
Inflammatory or infiltrative atrial disease
Pericarditis
Amyloidosis
Myocarditis
Age-induced atrial fibrotic changes
<i>Drugs</i>
Alcohol
Caffeine
<i>Endocrine disorders</i>
Hyperthyroidism
Pheochromocytoma
<i>Changes in autonomic tone</i>
Increased parasympathetic activity
Increased sympathetic activity
<i>Primary or metastatic disease in or adjacent to the atrial wall</i>
Postoperative
Cardiac, pulmonary, or esophageal
<i>Congenital heart disease Neurogenic</i>
Subarachnoid hemorrhage
Nonhemorrhagic, major stroke
Idiopathic (lone AF)
Familial AF

AF indicates atrial fibrillation.

linked to AF in some families, suggesting distinct genetic mutations.²⁷⁹ Two mutations associated with gain of function leading to short atrial refractoriness have been discovered in several Chinese families.^{280,281}

6.1.6. Autonomic influences in atrial fibrillation

Autonomic influences play an important role in the initiation of AF. The noninvasive measurement of autonomic tone in humans has been augmented by measures of HRV,²⁸² which reflect changes in the relative autonomic modulation of heart rate rather than the absolute level of sympathetic or parasympathetic tone. It appears that the balance between sympathetic and vagal influences is as important as absolute sympathetic or parasympathetic tone as a predictor of AF. Fluctuations in autonomic tone as measured by HRV occur prior to the development of AF. Vagal predominance in the minutes preceding the onset of AF has been observed in some patients with structurally normal hearts, while in others there is a shift toward sympathetic predominance.^{283,284} Although Coumel²⁸⁵ recognized that certain patients could be characterized in terms of a vagal or adrenergic form of AF, these cases likely represent the extremes of either influence. In general, vagally mediated AF occurs at night or after meals, while adrenergically induced AF typically occurs during the daytime in patients with organic heart disease.²⁸⁶ Vagally mediated AF is the more common form, and in such cases adrenergic blocking drugs or digitalis sometimes worsens symptoms and anticholinergic agents such as disopyramide are sometimes helpful to prevent recurrent AF. Classification of AF as of either the vagal or adrenergic form has only limited impact on management. For AF of the adrenergic type, beta blockers are the initial treatment of choice.

6.2. Clinical manifestations

AF has a heterogeneous clinical presentation, occurring in the presence or absence of detectable heart disease. 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, triggers, and response to therapy, but these features may be impossible to discern when AF is first encountered in an individual patient.

AF may be immediately recognized by sensation of palpitations or by its hemodynamic or thromboembolic consequences or follow an asymptomatic period of unknown duration. Ambulatory ECG recordings and device-based monitoring have revealed that an individual may experience periods of both symptomatic and asymptomatic AF.²⁸⁷⁻²⁹⁰ Patients in whom the arrhythmia has become permanent often notice that palpitation decreases with time and may become asymptomatic. This is particularly common among the elderly. Some patients experience symptoms only during paroxysmal AF or only intermittently during sustained AF. When present, symptoms of AF vary with the irregularity and rate of ventricular response,²⁹¹ underlying functional status, duration of AF, and individual patient factors.

The initial presentation of AF may be an embolic complication or exacerbation of HF, but most patients complain of palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope. Polyuria may be associated with the release of

atrial natriuretic peptide, particularly as episodes of AF begin or terminate. AF associated with a sustained, rapid ventricular response can lead to tachycardia-mediated cardiomyopathy, especially in patients unaware of the arrhythmia.

Syncope is an uncommon complication of AF that can occur upon conversion in patients with sinus node dysfunction or because of rapid ventricular rates in patients with HCM, in patients with valvular aortic stenosis, or when an accessory pathway is present.

6.3. Quality of life

Although stroke certainly accounts for much of the functional impairment associated with AF, available data suggest that quality of life is considerably impaired in patients with AF compared with age-matched controls. Sustained sinus rhythm is associated with improved quality of life and better exercise performance than AF in some studies but not others.²⁹²⁻²⁹⁶ In the SPAF study cohort, Ganiats *et al.*²⁹⁷ found the New York Heart Association functional classification, originally developed for HF, an insensitive index of quality of life in patients with AF. In another study,²⁹⁸ 47 of 69 patients (68%) with paroxysmal AF considered the arrhythmia disruptive of lifestyle, but this perception was not associated with either the frequency or duration of symptomatic episodes.

7. Clinical evaluation

7.1. Basic evaluation of the patient with atrial fibrillation

7.1.1. Clinical history and physical examination

The diagnosis of AF is based on history and clinical examination and confirmed by ECG recording, sometimes in the form of bedside telemetry or ambulatory Holter recordings. The initial evaluation of a patient with suspected or proved AF involves characterizing the pattern of the arrhythmia as paroxysmal or persistent, determining its cause, and defining associated cardiac and extracardiac factors pertinent to the etiology, tolerability, and history of prior management (*Table 6*). A thorough history will result in a well-planned, focused workup that serves as an effective guide to therapy.³ The workup of a patient with AF can usually take place and therapy initiated in a single outpatient encounter. Delay occurs when the rhythm has not been specifically documented and additional monitoring is necessary.

Typically, AF occurs in patients with underlying heart disease, such as hypertensive heart disease.^{33,299} (See Section 6, Causes, Associated Conditions, Clinical Manifestations, and Quality of Life.) Atherosclerotic or valvular heart diseases are also common substrates, whereas pulmonary pathology, preexcitation syndromes, and thyroid disease are less frequent causes.³⁰⁰ Because of reports of genetic transmission of AF, the family history is important as well.^{272,301} Although various environmental triggers can initiate episodes of AF, this aspect may not emerge from the 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 may occur during sleep or after a large meal and is more likely to

Table 6 Clinical evaluation in patients with AF

Minimum evaluation

1. *History and physical examination, to define*
 - Presence and nature of symptoms associated with AF
 - Clinical type of AF (first episode, paroxysmal, persistent, or permanent)
 - Onset of the first symptomatic attack or date of discovery of AF
 - Frequency, duration, precipitating factors, and modes of termination of AF
 - Response to any pharmacological agents that have been administered
 - 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 R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. *Transthoracic echocardiogram, to identify*
 - Valvular heart disease
 - LA and RA size
 - LV size and function
 - Peak RV pressure (pulmonary hypertension)
 - LV hypertrophy
 - LA thrombus (low sensitivity)
 - Pericardial disease
4. *Blood tests of thyroid, renal, and hepatic function*
 - For a first episode of AF, when the ventricular rate is difficult to control

Additional testing

One or several tests may be necessary.

1. *Six-minute walk test*
 - If the adequacy of rate control is in question
2. *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
3. *Holter monitoring or event recording*
 - If diagnosis of the type of arrhythmia is in question
 - As a means of evaluating rate control
4. *Transesophageal echocardiography*
 - To identify LA thrombus (in the LA appendage)
 - To guide cardioversion
5. *Electrophysiological study*
 - To clarify the mechanism of wide-QRS-complex tachycardia
 - To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
 - To seek sites for curative ablation or AV conduction block/modification
6. *Chest radiograph, to evaluate*
 - Lung parenchyma, when clinical findings suggest an abnormality
 - Pulmonary vasculature, when clinical findings suggest an abnormality

Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs (see Table 19).

AF indicates atrial fibrillation; AV, atrioventricular; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

arise during a period of rest succeeded by a period of stress. Stimulants such as caffeine or exercise may also precipitate AF.

The physical examination may suggest AF on the basis of irregular pulse, irregular jugular venous pulsations, and variation in the intensity of the first heart sound or absence of a fourth sound heard previously during sinus rhythm. Examination may also disclose associated valvular heart disease, myocardial abnormalities, or HF. The findings 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.

7.1.2. Investigations

The diagnosis of AF requires ECG documentation by at least a single-lead recording during the arrhythmia, which may be facilitated by review of emergency department records, Holter monitoring, or transtelephonic or telemetric recordings. A portable ECG recording tool may help establish the diagnosis in cases of paroxysmal AF and provide a permanent ECG record of the arrhythmia. In patients with implanted pacemakers or defibrillators, the diagnostic and memory functions may allow accurate and automatic detection of AF.³⁰² A chest radiograph may detect enlargement of the cardiac chambers and HF but is valuable mostly to detect

intrinsic pulmonary pathology and evaluate the pulmonary vasculature. It is less important than echocardiography for routine evaluation of patients with AF. As part of the initial evaluation, all patients with AF should have 2-dimensional, Doppler echocardiography to assess LA and LV dimensions and LV wall thickness and function and to exclude occult valvular or pericardial disease and HCM. LV systolic and diastolic performance helps guide decisions regarding antiarrhythmic and antithrombotic therapy. Thrombus should be sought in the LA but is seldom detected without TEE.^{203,303,304}

Blood tests are routine but can be abbreviated. It is important that thyroid, renal, and hepatic function, serum electrolytes, and the hemogram be measured at least once in the course of evaluating a patient with AF.³⁰⁵

7.2. Additional investigation of selected patients with atrial fibrillation

Abnormalities in P-wave duration detected by signal-averaged ECG during sinus rhythm that reflect slow intra-atrial conduction are associated with an increased risk of developing AF.^{133,306–308} The sensitivity and negative predictive value of signal-averaged P-wave ECG are high, but specificity and positive predictive value are low, limiting the usefulness of this technique.³⁰⁹ Measurement of HRV has failed to provide useful information for risk stratification.³⁰⁹

Both B-type natriuretic peptide (assessed by measuring BNP or N-terminal pro-BNP), which is produced mainly in the ventricles, and atrial natriuretic peptide (ANP), which is produced primarily in the atria, are associated with AF. Plasma levels of both peptides are elevated in patients with paroxysmal and persistent AF and decrease rapidly after restoration of sinus rhythm.^{310–313} Thus, the presence of AF should be considered when interpreting plasma levels of these peptides. In the absence of HF, there is an inverse correlation between LA volume and ANP/BNP levels;²⁵¹ spontaneous conversion to sinus rhythm is associated with higher ANP levels during AF and with smaller LA volumes.³¹¹ In long-standing persistent AF, lower plasma ANP levels may be related to degeneration of atrial myocytes.³¹⁴ High levels of BNP may be predictive of thromboembolism³¹⁵ and recurrent AF,^{40,316} but further studies are needed to evaluate the utility of BNP as a prognostic marker.

7.2.1. Electrocardiogram monitoring and exercise testing

Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF, which may be a cause of cryptogenic stroke. Ambulatory ECG (e.g., Holter) monitoring is also useful to judge the adequacy of rate control. This technology may provide valuable information to guide drug dosage for rate control or rhythm management.³¹⁷

Exercise testing should be performed if myocardial ischemia is suspected and prior to initiating type IC antiarrhythmic drug therapy. Another reason for exercise testing is to study the adequacy of rate control across a full spectrum of activity, not only at rest, in patients with persistent or permanent AF.

7.2.2. Transesophageal echocardiography

TEE is not part of the standard initial investigation of patients with AF. By placing a high-frequency ultrasound

transducer close to the heart, however, TEE provides high-quality images of cardiac structure³¹⁸ and function.³¹⁹ It is the most sensitive and specific technique to detect sources and potential mechanisms for cardiogenic embolism.³²⁰ The technology has been used to stratify stroke risk in patients with AF and to guide cardioversion. (See Section 8.1.4, Preventing Thromboembolism.) Several TEE features have been associated with thromboembolism in patients with nonvalvular AF, including LA/LAA thrombus, LA/LAA SEC, reduced LAA flow velocity, and aortic atheromatous abnormalities.²⁵² Although these features are associated with cardiogenic embolism,^{268,321} prospective investigations are needed to compare these TEE findings with clinical and transthoracic echocardiographic predictors of thromboembolism. Detection of LA/LAA thrombus in the setting of stroke or systemic embolism is convincing evidence of a cardiogenic mechanism.²⁰⁷

TEE of patients with AF before cardioversion has shown LA or LAA thrombus in 5% to 15%,^{304,321–323} but thromboembolism after conversion to sinus rhythm has been reported even when TEE did not show thrombus.³²⁴ These events typically occur relatively soon after cardioversion in patients who were not treated with anticoagulation, reinforcing the need to maintain continuous therapeutic anticoagulation in patients with AF undergoing cardioversion even when no thrombus is identified. For patients with AF of greater than 48-h duration, a TEE-guided strategy or the traditional strategy of anticoagulation for 4 wk before and 4 wk after elective cardioversion resulted in similar rates of thromboembolism (less than 1% during the 8 wk).³²⁵ Contrast-enhanced magnetic resonance imaging is an emerging technique for detection of intracardiac thrombi that appears more sensitive than precordial echocardiography and comparable to TEE.³²⁶

7.2.3. Electrophysiological study

An EP study can be helpful when AF is a consequence of reentrant tachycardia such as atrial flutter, intra-atrial reentry, or AV reentry involving an accessory pathway. Detection of a delta wave on the surface ECG in a patient with a history of AF or syncope is a firm indication for EP study and ablation of the bypass tract. Some patients with documented atrial flutter also have AF, and ablation of flutter can eliminate AF, although this is not common and successful ablation of flutter does not eliminate the possibility of developing AF in the future.³²⁷ AF associated with rapid ventricular rates and wide-complex QRS morphology may sometimes be mislabeled as ventricular tachycardia, and an EP study will differentiate the 2 arrhythmias. In short, EP testing is indicated when ablative therapy of arrhythmias that trigger AF or ablation of AF is planned.

In patients with AF who are candidates for ablation, an EP study is critical to define the targeted site or sites of ablation in the LA and/or right-sided structures. Evolving strategies in the ablation of AF are discussed in Section 8.0.

8. Management

Management of patients with AF involves 3 objectives—rate control, prevention of thromboembolism, and correction of the rhythm disturbance, and these are not mutually exclusive. The initial management decision involves primarily a rate-control or rhythm-control strategy. Under the

rate-control strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm. The rhythm-control strategy attempts restoration and/or maintenance of sinus rhythm. The latter strategy also requires attention to rate control. Depending on the patient's course, the strategy initially chosen may prove unsuccessful and the alternate strategy is then adopted. Regardless of whether the rate-control or rhythm-control strategy is pursued, attention must also be directed to antithrombotic therapy for prevention of thromboembolism.

At the initial encounter, an overall management strategy should be discussed with the patient, considering several factors: (1) type and duration of AF, (2) severity and type of symptoms, (3) associated cardiovascular disease, (4) patient age, (5) associated medical conditions, (6) short-term and long-term treatment goals, and (7) pharmacological and nonpharmacological therapeutic options. A patient with a first-documented episode of AF in whom rate control is achieved does not require hospitalization.

Duration and pattern of atrial fibrillation. As defined in Section 3, AF may be categorized as paroxysmal (self-terminating), persistent (requiring electrical or pharmacological termination), or permanent (cardioversion impossible or futile). The duration since onset may be known or unknown in an individual patient depending upon the presence or absence of specific symptoms or ECG documentation of the arrhythmia.

Type and severity of symptoms. As described in Section 6.2, few arrhythmias present with such protean manifestations, some of which are subtle. Some patients with AF become accommodated to a poor state of health and may feel markedly better once sinus rhythm is restored. In contrast, other patients have no or minimal symptoms during AF and restoration of sinus rhythm would not change their functional status. Before deciding on whether a patient is truly asymptomatic, it may be helpful to ask whether the patient has noticed a decline in activity over time, especially when there is no other obvious explanation.

Associated cardiovascular Disease. The likelihood that symptoms may progress is typically related to the presence of cardiovascular disease. The presence of ventricular hypertrophy could, for example, lead to symptoms as diastolic compliance worsens. Such a patient may not feel different in sinus rhythm when initially evaluated but may face difficulties in the future if left in AF until it becomes difficult to restore sinus rhythm because of atrial remodeling.

Potential for Changes in Cardiac Function Related to Age. Before choosing rate control as a long-term strategy, the clinician should consider how permanent AF is likely to affect the patient in the future. In a patient with asymptomatic persistent AF, attempts to restore sinus rhythm may not be needed. Prospective studies like Rate Control vs. Electrical cardioversion for persistent atrial fibrillation (RACE) and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) showed that patients who could tolerate rate-controlled AF had outcomes similar to those randomized to rhythm control. However, these studies enrolled predominantly older patients (average 70 y), most of whom had persistent AF and heart disease, and follow-up extended over just a few years. Thus, the trial data do not necessarily apply to younger patients without heart disease or to patients whose dependency upon sinus rhythm is likely to change appreciably over time. Among the latter may be

patients in HF, who are prone to deteriorate over time if left in AF. The problem with allowing AF to persist for years is that it may then be impossible to restore sinus rhythm as a consequence of electrical and structural remodeling, which preclude successful restoration or maintenance of sinus rhythm and favor permanent AF. This makes it important to ensure that a window of opportunity to maintain sinus rhythm is not overlooked early in the course of management of a patient with AF.

8.1. Pharmacological and nonpharmacological therapeutic options

Drugs and ablation are effective for both rate and rhythm control, and in special circumstances surgery may be the preferred option. Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is maintained. For rhythm control, drugs are typically the first choice and LA ablation is a second-line choice, especially in patients with symptomatic lone AF. In some patients, especially young ones with very symptomatic AF who need sinus rhythm, radiofrequency ablation may be preferred over years of drug therapy. Patients with preoperative AF undergoing cardiac surgery face a unique opportunity. While few patients are candidates for a stand-alone surgical procedure to cure AF using the maze or LA ablation techniques, these approaches can be an effective adjunct to coronary bypass or valve repair surgery to prevent recurrent postoperative AF. Applied in this way, AF may be eliminated without significant additional risk. Because the LAA is the site of over 95% of detected thrombi, this structure should be removed from the circulation when possible during cardiac surgery in patients at risk of developing postoperative AF, although this has not been proved to prevent stroke.³²⁸

Drugs are the primary treatment for rate control in most patients with AF. While ablation of the AV conduction system and permanent pacing (the 'ablate and pace' strategy) is an option that often yields remarkable symptomatic relief, growing concern about the negative effect of long-term RV pacing makes this a fallback rather than a primary treatment strategy. LV pacing, on the other hand, may overcome many of the adverse hemodynamic effects associated with RV pacing.

8.1.1. Pharmacological therapy

8.1.1.1. Drugs modulating the renin-angiotensin-aldosterone system. Experimental and clinical studies have demonstrated that ACE inhibitors and angiotensin receptor antagonists may decrease the incidence of AF³⁶ (see Section 8.5, Primary Prevention). ACE inhibitors decrease atrial pressure, reduce the frequency of atrial premature beats,³²⁹ reduce fibrosis,⁸⁶ and may lower the relapse rate after cardioversion^{39,330,331} in patients with AF. These drugs can reduce signal-averaged P-wave duration, the number of defibrillation attempts required to restore sinus rhythm, and the number of hospital readmissions for AF.³³² Withdrawal of ACE-inhibitor medication is associated with postoperative AF in patients undergoing coronary bypass surgery,³³³ and concurrent therapy with ACE-inhibitor and antiarrhythmic agents enhances maintenance of sinus rhythm.³³⁴

In patients with persistent AF and normal LV function, the combination of enalapril or irbesartan plus amiodarone resulted in lower rates of recurrent AF after electrical conversion than amiodarone alone.^{39,331} The role of treatment with inhibitors of the RAAS in long-term maintenance of sinus rhythm in patients at risk of developing recurrent AF requires clarification in randomized trials before this approach can be routinely recommended.

8.1.1.2. HMG CoA-reductase inhibitors (statins). Available evidence supports the efficacy of statin-type cholesterol-lowering agents in maintaining sinus rhythm in patients with persistent lone AF. Statins decrease the risk of recurrences after successful direct-current cardioversion without affecting the defibrillation threshold.³³⁵ The mechanisms by which these drugs prevent AF recurrence are poorly understood but include an inhibitory effect on the progression of CAD, pleiotropic (anti-inflammatory and antioxidant) effects,^{336,337} and direct antiarrhythmic effects involving alterations in transmembrane ion channels.³³⁸

8.1.2. Heart rate control versus rhythm control

8.1.2.1. Distinguishing short-term and long-term treatment goals. The initial and subsequent management of symptomatic AF may differ from one patient to another. For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control, while the long-term goal is to restore sinus rhythm. When cardioversion is contemplated and the duration of AF is unknown or exceeds 48 h, patients who do not require long-term anticoagulation may benefit from short-term anticoagulation. If rate control offers inadequate symptomatic relief, restoration of sinus rhythm becomes a clear long-term goal. Early cardioversion may be necessary if AF causes hypotension or worsening HF, making the establishment of sinus rhythm a combined short- and long-term therapeutic goal. In contrast, amelioration of symptoms by rate control in older patients may steer the clinician away from attempts to restore sinus rhythm. In some circumstances, when the initiating pathophysiology of AF is reversible, as for instance in the setting of thyrotoxicosis or after cardiac surgery, no long-term therapy may be necessary.

8.1.2.2. Clinical trials comparing rate control and rhythm control. Randomized trials comparing outcomes of rhythm-versus rate-control strategies in patients with AF are summarized in *Tables 7* and *8*. Among these, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) found no difference in mortality or stroke rate between patients assigned to one strategy or the other. The RACE (Rate Control vs. Electrical cardioversion for persistent atrial fibrillation) trial found rate control not inferior to rhythm control for prevention of death and morbidity. Clinically silent recurrences of AF in asymptomatic patients treated with antiarrhythmic drugs may be responsible for thromboembolic events after withdrawal of anticoagulation. Hence, patients at high risk for stroke may require anticoagulation regardless of whether the rate-control or rhythm-control strategy is chosen, but the AFFIRM trial was not designed to address this question. While secondary analyses support this notion,³³⁹ the stroke rate in patients assigned to rhythm

Table 7 Trials comparing rate control and rhythm control strategies in patients with AF

Trial	Reference	Patients (n)	AF Duration	Follow-up (y)	Age (mean y ± SD)	Patients in SR ^a	Clinical Events (n)			
							Stroke/embolism		Death	
							Rate	Rhythm	Rate	Rhythm
AFFIRM (2002)	296	4060	^b /NR	3.5	70 ± 9	35% vs. 63% (at 5 y)	88/2027	93/2033	310/2027	356/2033
RACE (2002)	293	522	1 to 399 d	2.3	68 ± 9	10% vs. 39% (at 2.3 y)	7/256	16/266	18/256	18/266
PIAF (2000)	294	252	7 to 360 d	1	61 ± 10	10% vs. 56% (at 1 y)	0/125	2/127	2/125	2/127
STAF (2003)	343	200	6 ± 3 mo	1.6	66 ± 8	11% vs. 26% (at 2 y)	2/100	5/100	8/100	4/100
HOT CAFÉ (2004)	344	205	7 to 730 d	1.7	61 ± 11	NR vs. 64%	1/101	3/104	1/101	3/104

AFFIRM indicates Atrial Fibrillation Follow-up Investigation of Rhythm Management; HOT CAFÉ, How to Treat Chronic Atrial Fibrillation; NR, not reported; PIAF, Pharmacological intervention in Atrial Fibrillation; RACE, Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation; SR, sinus rhythm; STAF, Strategies of Treatment of Atrial Fibrillation.

^aComparison between rate and rhythm control groups.

^bApproximately one third of patients were enrolled with first episode of atrial fibrillation (AF).

Table 8 General characteristics of rhythm control and rate control trials in patients with AF

Trial	Reference	Patients (n)	Mean Age (y)	Mean length of follow-up (y)	Inclusion criteria	Primary endpoint	Patients reaching primary endpoint (n)		P
							Rate control	Rhythm control	
PIAF (2000)	294	252	61.0	1.0	Persistent AF (7 to 360 d)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.317
RACE (2002)	293	522	68.0	2.3	Persistent AF or flutter for less than 1 y and 1 to 2 cardioversions over 2 y and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, PM implantation, thromboembolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (2002)	343	200	66.0	1.6	Persistent AF (longer than 4 wk and less than 2 y), left atrial size greater than 45 mm, CHF NYHA II-IV, LVEF less than 45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
AFFIRM (2002)	296	4060	69.7	3.5	Paroxysmal AF or persistent AF, age 65 y or older, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
HOT CAFÉ (2004)	344	205	60.8	1.7	First clinically overt episode of persistent AF (7 d or more and less than 2 y), 50 to 75 y old	Composite: death, thromboembolic complications; intracranial or other major hemorrhage	1/101 (1.0%)	4/104 (3.9%)	Greater than 0.71

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AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management, CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; HOT CAFÉ, How to Treat Chronic Atrial Fibrillation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PIAF, Pharmacological Intervention in Atrial Fibrillation; PM, pacemaker; RACE, Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation, STAF, Strategies of Treatment of Atrial Fibrillation.

control who stopped warfarin is uncertain, and additional research is needed to address this important question.

Depending upon symptoms, rate control may be reasonable initial therapy in older patients with persistent AF who have hypertension or heart disease. For younger individuals, especially those with paroxysmal lone AF, rhythm control may be a better initial approach. Often medications that exert both antiarrhythmic and rate-controlling effects are required. Catheter ablation should be considered to maintain sinus rhythm in selected patients who failed to respond to antiarrhythmic drug therapy.³⁴⁰

8.1.2.3. Effect on symptoms and quality of life. Information about the effects of antiarrhythmic and chronotropic therapies on quality of life is inconsistent.^{292,294,295} The AFFIRM,^{293,296} RACE,^{293,295} PIAF (Pharmacologic Intervention in Atrial Fibrillation),³⁴² and STAF (Strategies of Treatment of Atrial Fibrillation)³⁴³ studies found no differences in quality of life with rhythm control compared with rate control. Rhythm control in the PIAF and How to Treat Chronic Atrial Fibrillation (HOT CAFÉ)³⁴⁴ studies resulted in better exercise tolerance than rate control, but this did not translate into improved quality of life. In the Canadian Trial of Atrial Fibrillation (CTAF) study,³⁴⁷ there was no difference between amiodarone and sotalol or propafenone as assessed by responses to the Short Form-36 questionnaire, while a symptom severity scale showed benefit of amiodarone over the other drugs. In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T),²⁹² restoration and maintenance of sinus rhythm in patients with AF significantly improved quality of life in certain domains, but amiodarone was associated with a decrease in mental health function compared with sotalol or placebo.²⁹² Symptomatic improvement has also been reported after the maze procedure in patients with AF.³⁴⁸

In a substudy of AFFIRM, there was no significant association between achieved HR and quality-of-life measurements, New York Heart Association functional class, or 6-min walking distance in patients with AF compared with less well-controlled patients.³⁴⁵ On the whole, rate- and rhythm-control strategies do not affect quality of life significantly or differently. Even when sinus rhythm can be maintained, symptoms of associated cardiovascular conditions may obscure changes in quality of life related to AF. Clinicians must exercise judgment, however, in translating shifts in quality of life in these study populations to the sense of well-being experienced by individual patients. Patients with similar health status may experience entirely different quality of life, and treatment must be tailored to each individual, depending on the nature, intensity, and frequency of symptoms, patient preferences, comorbid conditions, and the ongoing response to treatment.

Long-term oral anticoagulant therapy with vitamin K antagonists involves multiple drug interactions and frequent blood testing, which influences quality of life in patients with AF. Gage *et al.*³⁴⁹ quantified this as a mean 1.3% decrease in utility, a measure of quality of life in quantitative decision analysis. Some patients (16%) thought that their quality of life would be greater with aspirin than with oral anticoagulants, despite its lesser efficacy. Other investigators, using decision analysis to assess patient preferences, found that 61% of 97 patients preferred anticoagulation to no treatment, a smaller proportion than that for which

published guidelines recommend treatment.³⁵⁰ In the future, these comparisons could be influenced by the development of more convenient approaches to antithrombotic therapy.

8.1.2.4. Effects on heart failure. HF may develop or deteriorate during either type of treatment for AF due to progression of underlying cardiac disease, inadequate control of the ventricular rate at the time of recurrent AF, or antiarrhythmic drug toxicity. Patients managed with rate compared with rhythm control did not, however, differ significantly in development or deterioration of HF. In the AFFIRM study, 2.1% of those in the rate-control group and 2.7% in the rhythm-control group developed AF after an average follow-up of 3.5 y. In the RACE study, the incidence of hospitalization for HF was 3.5% during a management strategy directed at rate control and 4.5% with rhythm control, during an average follow-up of 2.3 y. Similarly, there were no differences in the STAF or HOT CAFÉ studies. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study⁵³ is currently investigating this issue in a large number of patients.

8.1.2.5. Effects on thromboembolic complications. The majority of patients in the AFFIRM and RACE trials had 1 or more stroke risk factors in addition to AF, and the rhythm-control strategy did not lower the stroke rate more effectively than rate control and anticoagulation^{296,339,351} (see *Table 7*). One methodological concern is that the success of rhythm control at maintaining sinus rhythm was assessed by intermittent ECG recordings, whereas longer-term monitoring might have identified patients at lower thromboembolic risk. Most strokes were diagnosed after discontinuation of anticoagulation or at subtherapeutic intensity (International Normalized Ratio [INR] below 2.0). In addition, while recurrent AF was detected in only about one-third of those in the rhythm-control groups who developed stroke, at the time of ischemic stroke, patients in the rate-control groups typically had AF. Long-term oral anticoagulation therefore seems appropriate for most patients with AF who have risk factors for thromboembolism, regardless of treatment strategy and of whether AF is documented at any given time.

8.1.2.6. Effects on mortality and hospitalization. In the AFFIRM study, a trend toward increased overall mortality was observed in patients treated for rhythm control compared with rate control after an average of 3.5 y (26.7% vs. 25.9%, $p = 0.08$).²⁹⁶ The rhythm-control strategy was associated with excess mortality among older patients, those with HF, and those with CAD, but the tendency persisted after adjustment for these covariates. A substudy suggested that deleterious effects of antiarrhythmic drugs (mortality increase of 49%) may have offset the benefits of sinus rhythm (which was associated with a 53% reduction in mortality).³⁵² Hospitalization was more frequent in the rhythm-control arms in all trials, mainly due to admissions for cardioversion. A substudy of RACE compared anticoagulated patients in the rhythm-control group who sustained sinus rhythm with patients in the rate-control group who had permanent AF and found no benefit of rhythm control even in this selected subgroup.³⁵³ The implication that adverse drug effects in patients with underlying heart disease might exert an adverse effect on

morbidity and mortality that is not overcome by maintaining sinus rhythm must be interpreted cautiously because the comparisons of patient subgroups in these secondary analyses are not based on randomization (Table 9).

8.1.2.7. Implications of the rhythm-control versus rate-control studies. Theoretically, rhythm control should have advantages over rate control, yet a trend toward lower mortality was observed in the rate-control arm of the AFFIRM study and did not differ in the other trials from the outcome with the rhythm-control strategy. This might suggest that attempts to restore sinus rhythm with presently available antiarrhythmic drugs are obsolete. The RACE and AFFIRM trials did not address AF in younger, symptomatic patients with little underlying heart disease, in whom restoration of sinus rhythm by cardioversion antiarrhythmic drugs or nonpharmacological interventions still must be considered a useful therapeutic approach. One may conclude from these studies that rate control is a reasonable strategy in elderly patients with minimal symptoms related to AF. An effective method for maintaining sinus rhythm with fewer side effects would address a presently unmet need.

8.1.3. Rate control during atrial fibrillation

Criteria for rate control. In patients with AF, the ventricular rate may accelerate excessively during exercise even when it is well controlled at rest. In addition to allowing adequate time for ventricular filling and avoiding rate-related ischemia, enhancement of intraventricular conduction with rate reduction may result in improved hemodynamics. It may be useful to evaluate the heart rate response to submaximal or maximal exercise or to monitor the rate over an extended period (e.g., by 24-h Holter recording). In addition, rate variability during AF provides information about the status of the autonomic nervous system that may have independent prognostic implications.³⁵⁶⁻³⁵⁹

The definition of adequate rate control has been based primarily on short-term hemodynamic benefits and has not been well studied with respect to regularity or irregularity of the ventricular response to AF, quality of life, or symptoms or development of cardiomyopathy. No standard method for assessment of heart rate control has been established to guide management of patients with AF. Criteria for rate control vary with patient age but usually involve

achieving ventricular rates between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise. For the AFFIRM trial, adequate control was defined as an average heart rate up to 80 beats per minute at rest and either an average rate up to 100 beats per minute over at least 18-h ambulatory Holter monitoring with no rate above 100% of the maximum age-adjusted predicted exercise heart rate or a maximum heart rate of 110 beats per minute during a 6-min walk test.³⁶⁰ In the RACE trial, rate control was defined as less than 100 beats per minute at rest. Only about 5% of patients from these large clinical trials required AV ablation to achieve heart rate control within these limits.

Hemodynamic and clinical consequences of rapid rate. Patients who are symptomatic with rapid ventricular rates during AF require prompt medical management, and cardioversion should be considered if symptomatic hypotension, angina, or HF is present. A sustained, uncontrolled tachycardia may lead to deterioration of ventricular function (tachycardia-related cardiomyopathy)³⁶¹ and that improves with adequate rate control. In the Ablate and Pace Trial (APT), 25% of patients with AF who had an ejection fraction below 45% displayed a greater than 15% increase in ejection fraction after ablation.³⁶³ Tachycardia-induced cardiomyopathy tends to resolve within 6 mo of rate or rhythm control; when tachycardia recurs, LV ejection fraction declines and HF develops over a shorter period, and this is associated with a relatively poor prognosis.³⁶⁴

8.1.3.1. Pharmacological rate control during atrial fibrillation.

Recommendations

Class I

- (1) Measurement of the heart rate at rest and control of the rate using pharmacological agents (either a beta blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF. (Level of Evidence: B)
- (2) In the absence of preexcitation, intravenous administration of beta blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or HF. (Level of Evidence: B)

Table 9 Comparison of adverse outcomes in rhythm control and rate control trials in patients with AF

Trial	Reference	Deaths of all causes (n rate/rhythm)	Deaths from cardiovascular causes	Deaths from noncardiovascular causes	Stroke	Thromboembolic events	Bleeding
RACE (2002)	293	36	18/18	ND	ND	14/21	12/9
PIAF (2000)	294	4	1/1	1 ^a	ND	ND	ND
STAF (2003)	343	12 (8/4)	8/3	0/1	1/5	ND	8/11
AFFIRM (2002)	296	666 (310/356)	167/164	113/165	77/80	ND	107/96
HOT CAFÉ (2004)	344	4 (1/3)	0/2	1/1	0/3	ND	5/8

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AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; HOT CAFÉ, How to Treat Chronic Atrial Fibrillation; ND, not determined; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation; STAF, Strategies of Treatment of Atrial Fibrillation.

^aTotal number of patients not reported.

- (3) Intravenous administration of digoxin or amiodarone is recommended to control the heart rate in patients with AF and HF who do not have an accessory pathway. (Level of Evidence: B)
- (4) In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacological treatment as necessary to keep the rate in the physiological range. (Level of Evidence: C)
- (5) Digoxin is effective following oral administration to control the heart rate at rest in patients with AF and is indicated for patients with HF, LV dysfunction, or for sedentary individuals. (Level of Evidence: C)

Class IIa

- (1) A combination of digoxin and either a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both 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: B)
- (2) It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacological therapy is insufficient or associated with side effects. (Level of Evidence: B)
- (3) Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated. (Level of Evidence: C)
- (4) When electrical cardioversion is not necessary in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative. (Level of Evidence: C)

Class IIb

- (1) When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a beta blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate. (Level of Evidence: C)
- (2) Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway. (Level of Evidence: B)
- (3) When the rate cannot be controlled with pharmacological agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate. (Level of Evidence: C)

Class III

- (1) Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF. (Level of Evidence: B)
- (2) Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF. (Level of Evidence: C)
- (3) In patients with decompensated HF and AF, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended. (Level of Evidence: C)

- (4) Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended. (Level of Evidence: C)

The main determinants of ventricular rate during AF are the intrinsic conduction characteristics and refractoriness of the AV node and sympathetic and parasympathetic tone. The functional refractory period of the AV node correlates inversely with ventricular rate during AF, and drugs that prolong the refractory period are generally effective for rate control. The efficacy of pharmacological interventions designed to achieve rate control in patients with AF has been about 80% in clinical trials.³⁶⁵ There is no evidence that pharmacological rate control has any adverse influence on LV function, but bradycardia and heart block may occur as an unwanted effect of beta blockers, amiodarone, digitalis glycosides, or nondihydropyridine calcium channel antagonists, particularly in patients with paroxysmal AF, especially the elderly. When rapid control of the ventricular response to AF is required or oral administration of medication is not feasible, medication may be administered intravenously. Otherwise, in hemodynamically stable patients with a rapid ventricular response to AF, negative chronotropic medication may be administered orally (*Table 10*). Combinations may be necessary to achieve rate control in both acute and chronic situations, but proper therapy requires careful dose titration. Some patients develop symptomatic bradycardia that requires permanent pacing. Nonpharmacological therapy should be considered when pharmacological measures fail.

8.1.3.1.1. Beta blockers. Intravenous beta blockade with propranolol, atenolol, metoprolol, or esmolol is effective for control of the rate of ventricular response to AF. These agents may be particularly useful in states of high adrenergic tone (e.g., postoperative AF). After noncardiac surgery, intravenous esmolol produced more rapid conversion to sinus rhythm than diltiazem, but rates after 2 and 12 h were similar with both treatments.³⁶⁶

In 7 of 12 comparisons, beta-adrenergic blockade proved safe and effective for control of heart rate in patients with AF and superior to placebo. Nadolol and atenolol were the most efficacious of the drugs tested. Patients taking beta blockers may experience slow rates at rest, or exercise tolerance may be compromised when the rate response is blunted excessively.³⁶⁷ Sotalol, a nonselective beta-blocking drug with type III antiarrhythmic activity used for rhythm control, also provides excellent rate control in the event of AF recurrence³⁶⁸ and may achieve lower heart rate than metoprolol during exercise. Atenolol, metoprolol, and sotalol provide better control of exercise-induced tachycardia than digoxin.^{369,370} Carvedilol also lowers the ventricular rate at rest and during exercise in such patients and reduces ventricular ectopy.³⁷¹ With or without digoxin in the AFFIRM study, beta blockers were the most effective drug class for rate control, achieving the specified heart rate endpoints in 70% of patients compared with 54% with use of calcium channel blockers.³⁶⁰ Beta blockers should be initiated cautiously in patients with AF and HF who have reduced ejection fraction.³⁷²

Table 10 Intravenous and orally administered pharmacological agents for heart rate control in patients with atrial fibrillation

Drug	Class/LOE recommendation	Loading dose	Onset	Maintenance dose	Major side effects
Acute setting					
<i>Heart rate control in patients without accessory pathway</i>					
Esmolol ^{ab}	Class I, LOE C	500 mcg/kg IV over 1 min	5 min	60 to 200 mcg/kg/min IV	↓BP, HB, ↓HR, asthma, HF
Metoprolol ^b	Class I, LOE C	2.5 to 5 mg IV bolus over 2 min; up to 3 doses	5 min	NA	↓BP, HB, ↓HR, asthma, HF
Propranolol ^b	Class I, LOE C	0.15 mg/kg IV	5 min	NA	↓BP, HB, ↓HR, asthma, HF
Diltiazem	Class I, LOE B	0.25 mg/kg IV over 2 min	2 to 7 min	5 to 15 mg/h IV	↓BP, HB, HF
Verapamil	Class I, LOE B	0.075 to 0.15 mg/kg IV over 2 min	3 to 5 min	NA	↓BP, HB, HF
<i>Heart rate control in patients with accessory pathway^c</i>					
Amiodarone ^d &cjs0952;	Class IIa, LOE C	150 mg over 10 min	Days	0.5 to 1 mg/min IV	↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia
<i>Heart rate control in patients with heart failure and without accessory pathway</i>					
Digoxin	Class I, LOE B	0.25 mg IV each 2 h, up to 1.5 mg	60 min or more ^c	0.125 to 0.375 mg daily IV or orally	Digitalis toxicity, HB, ↓HR
Amiodarone ^d	Class IIa, LOE C	150 mg over 10 min	Days	0.5 to 1 mg/min IV	↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia
Non-acute setting and chronic maintenance therapy^e					
<i>Heart rate control</i>					
Metoprolol ^b	Class I, LOE C	Same as maintenance dose	4 to 6 h	25 to 100 mg twice a day, orally	↓BP, HB, ↓HR, asthma, HF
Propranolol ^b	Class I, LOE C	Same as maintenance dose	60 to 90 min	80 to 240 mg daily in divided doses, orally	↓BP, HB, ↓HR, asthma, HF
Diltiazem	Class I, LOE B	Same as maintenance dose	2 to 4 h	120 to 360 mg daily in divided doses; slow release available, orally	↓BP, HB, HF
Verapamil	Class I, LOE B	Same as maintenance dose	1 to 2 h	120 to 360 mg daily in divided doses; slow release available, orally	↓BP, HB, HF, digoxin interaction
<i>Heart rate control in patients with heart failure and without accessory pathway</i>					
Digoxin	Class I, LOE C	0.5 mg by mouth daily	2 days	0.125 to 0.375 mg daily, orally	Digitalis toxicity, HB, ↓HR
Amiodarone ^d	Class IIb, LOE C	800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 400 mg daily for 4 to 6 wk, orally	1 to 3 wk	200 mg daily, orally	↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia

^aOnset is variable and some effect occurs earlier.

^bOnly 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. Beta blockers are grouped in an order preceding the alphabetical listing of drugs.

^cConversion to sinus rhythm and catheter ablation of the accessory pathway are generally recommended; pharmacological therapy for rate control may be appropriate in certain patients.

^dAmiodarone can be useful to control the heart rate in patients with atrial fibrillation (AF) when other measures are unsuccessful or contraindicated.

^eAdequacy of heart rate control should be assessed during physical activity as well as at rest.

&cjs0952; If rhythm cannot be converted or ablated and rate control is needed, intravenous (IV) amiodarone is recommended.

↓BP indicates hypotension; ↓HR, bradycardia; HB, heart block; HF, heart failure; LOE, level of evidence; NA, not applicable.

8.1.3.1.2. Nondihydropyridine calcium channel antagonists. The nondihydropyridine calcium channel antagonist agents verapamil and diltiazem are commonly used for treatment of AF and are the only agents that have been associated with an improvement in quality of life and exercise tolerance. Intravenous bolus injection of either drug is effective to control the ventricular rate,^{367,373} although their short duration of action usually requires continuous intravenous infusion to maintain rate control. These agents should be used cautiously or avoided in patients with HF due to systolic dysfunction because of their negative inotropic effects. Eight randomized studies comparing calcium channel blockers to placebo³⁷⁰ found significant decrease in heart rate with diltiazem. Verapamil decreased heart rate both at rest (by 8 to 23 beats per minute) and during exercise (by 20 to 34 beats per minute). Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness,³⁷⁴ with preserved or improved exercise tolerance in most patients.³⁷⁴ These agents may be preferred for long-term use over beta blockers in patients with bronchospasm or chronic obstructive pulmonary disease.

8.1.3.1.3. Digoxin. Although intravenous digoxin may slow the ventricular response to AF at rest, there is a delay of at least 60 min before onset of a therapeutic effect in most patients, and the peak effect does not develop for up to 6 h. Digoxin is no more effective than placebo in converting AF to sinus rhythm and may perpetuate AF.^{375,376} Its efficacy is reduced in states of high sympathetic tone, a possible precipitant of paroxysmal AF. In a review of 139 episodes of paroxysmal AF detected by Holter monitoring, there was no difference in the ventricular rates of patients taking digoxin and those not taking this agent.³⁷⁶ Other investigators, however, have reported that digoxin reduces the frequency and severity of AF recurrences,³⁰ and the combination of digoxin and atenolol is effective for rate control.³⁷⁷ Given the availability of more effective agents, digoxin is no longer considered first-line therapy for rapid management of AF, except in patients with HF or LV dysfunction, or perhaps in patients who are so sedentary as to obviate the need for rate control during activity.

Digoxin exerts only a transient rate-slowing effect in patients with recent-onset AF,³⁷⁸ perhaps as a result of a vagotonic effect on the AV node. In contrast to its limited negative chronotropic effect in patients with paroxysmal AF, digoxin is moderately effective in those with persistent AF, particularly when HF is present.^{362,370} According to a systematic review, digoxin administered alone slows the heart rate more than placebo by an average of 4 to 21 beats per minute at rest, but it does not slow heart rate during exercise in patients with AF.^{367,370} The most frequent adverse effects of digoxin are ventricular arrhythmias, atrioventricular block, and sinus pauses, all of which are dose dependent. Because of drug interactions, the serum digoxin concentration may rise and toxic effects may be potentiated when verapamil or antiarrhythmic agents such as propafenone or amiodarone are administered concurrently.

8.1.3.1.4. Antiarrhythmic agents. Amiodarone has both sympatholytic and calcium antagonistic properties, depresses AV conduction, and is effective for controlling the ventricular rate in patients with AF. Intravenous amiodarone is generally well tolerated in critically ill patients who develop rapid atrial tachyarrhythmias refractory to

conventional treatment, but efficacy has not been sufficiently evaluated in this indication.³⁷⁹ Amiodarone is considered a suitable alternative agent for heart rate control when conventional measures are ineffective.³⁷⁹ When conventional measures are ineffective, amiodarone may be considered as an alternative agent for heart rate control in patients with AF,³⁷⁹ but this represents an off-label use in the United States and in some other countries and the potential benefit must be carefully weighed against the considerable potential toxicity of this drug. Patients given amiodarone who did not convert from AF to sinus rhythm experienced substantially lower ventricular rates than those treated with placebo,³⁷⁰ but important adverse effects make this agent a second-line therapy for rate control. In one study, oral amiodarone decreased the ventricular rate without affecting exercise capacity, quality of life, or AF symptoms.³⁸⁰ High-dose oral amiodarone loading can worsen hemodynamics in patients with recent decompensation of HF or hypotension.³⁸¹ Amiodarone may cause potentially fatal toxicity, including pulmonary fibrosis, hepatic injury, and proarrhythmia.

Dofetilide and ibutilide are effective for conversion of atrial flutter and AF but are not effective for control of the ventricular rate. Propafenone exerts mild beta-blocking effects that may slow conduction across the AV node, but this is seldom sufficient to control the rate in patients with AF, and AV conduction may accelerate when the atrial rhythm becomes slower and more regular, so other agents in addition to propafenone are generally required to maintain control of the heart rate when AF recurs.

8.1.3.1.5. Combination therapy. Combinations of drugs may be required to achieve adequate rate control in some patients with AF, but care should be taken to avoid bradycardia.³⁷⁰ The addition of other drugs to digoxin is commonly required to control the rate during exercise. The combination of digoxin and atenolol produces a synergistic effect on the AV node,³⁷⁷ and the combination of digoxin and pindolol provided better control during exercise than digoxin alone or in combination with verapamil.³⁸² In general, the combination of digoxin and a beta blocker appears more effective than the combination of digoxin with a calcium channel antagonist.³⁷⁷

8.1.3.1.6. Special considerations in patients with the Wolff-Parkinson-White (WPW) syndrome. Intravenous beta blockers, digitalis, adenosine, lidocaine, and nondihydropyridine calcium channel antagonists, all of which slow conduction across the AV node, are contraindicated in patients with the WPW syndrome and tachycardia associated with ventricular preexcitation, because they can facilitate antegrade conduction along the accessory pathway during AF,³ resulting in acceleration of the ventricular rate, hypotension, or ventricular fibrillation.¹⁸¹ When the arrhythmia is associated with hemodynamic compromise, however, early direct-current cardioversion is indicated. In hemodynamically stable patients with preexcitation, type I antiarrhythmic agents or amiodarone may be administered intravenously. Beta blockers and calcium channel blockers are reasonable for oral chronic use.³⁸³

8.1.3.2. Pharmacological therapy to control heart rate in patients with both atrial fibrillation and atrial flutter. A patient treated with AV nodal blocking drugs whose

ventricular rate is well controlled during AF may experience a rise or fall in rate if he or she develops atrial flutter. This is also true when antiarrhythmic agents such as propafenone or flecainide are used to prevent recurrent AF. These compounds may increase the likelihood of 1:1 AV conduction during atrial flutter, leading to a very rapid ventricular response. Thus, when these agents are given for prophylaxis against recurrent paroxysmal AF or atrial flutter, AV nodal blocking drugs should be routinely coadministered. An exception may be patients with paroxysmal AF who have undergone catheter ablation of the cavotricuspid isthmus to prevent atrial flutter.

8.1.3.3. Regulation of atrioventricular nodal conduction by pacing. Because ventricular pacing prolongs the AV nodal refractory period as a result of concealed retrograde penetration, it eliminates longer ventricular cycles and may reduce the number of short ventricular cycles related to rapid AV conduction during AF. Pacing at approximately the mean ventricular rate during spontaneous AV conduction can regulate the ventricular rhythm during AF.³⁸⁴ This may be useful for patients with marked variability in ventricular rates or for those who develop resting bradycardia during treatment with medication. In some patients, the hemodynamic benefit of revascularization may be offset by asynchronous ventricular activation during RV pacing. At least 2 multicenter studies examined a ventricular rate regularization algorithm. In one study, patients with paroxysmal AF indicated a preference for the paced regularization strategy, while patients with permanent AF showed no preference despite a 29% improvement of irregularity.³⁸⁵ In another study, ventricular rate regularization did not improve quality of life in patients with paroxysmal or permanent AF.³⁸⁶

8.1.3.4. AV nodal ablation. AV nodal ablation in conjunction with permanent pacemaker implantation provides highly effective control of the heart rate and improves symptoms in selected patients with AF.^{363,387-389} In general, patients most likely to benefit from this strategy are those with symptoms or tachycardia-mediated cardiomyopathy related to rapid ventricular rate during AF that cannot be controlled adequately with antiarrhythmic or negative chronotropic medications. Meta-analysis of 21 studies published between 1989 and 1998 that included a total of 1181 patients concluded that AV nodal ablation and permanent pacemaker implantation significantly improved cardiac symptoms, quality of life, and healthcare utilization for patients with symptomatic AF refractory to medical treatment.³⁸⁹ In the APT, 156 patients with refractory AF displayed improvements in quality of life, exercise capacity, and ventricular function over 1 y.³⁶³ In a study of 56 patients with impaired LV function (ejection fraction less than 40%), the mean ejection fraction improved from 26% plus or minus 8% to 34% plus or minus 13% after AV nodal ablation and pacemaker implantation and became normal in 16 patients (29%).³⁹⁰ Patients with persistent LV dysfunction after ablation were more likely to have structural heart disease associated with less than 60% survival at 5 y. In small randomized trials involving patients with paroxysmal³⁸⁸ and persistent³⁸⁷ AF, significantly greater proportions experienced improvement in symptoms and quality of life after AV nodal ablation than with antiarrhythmic medication therapy. Of 2027 patients randomized to make control in

the AFFIRM study, AV nodal ablation was performed in 5%³⁶⁰ after failure to achieve adequate rate control with a mean of 2.4 plus or minus 0.7 medications. Another 147 patients required pacemaker implantation because of symptomatic bradycardia. Catheter ablation of inferior atrial inputs to the AV node slows the ventricular rate during AF and improves symptoms without pacemaker implantation.^{391,392} This technique has several limitations, however, including inadvertent complete AV block and a tendency of ventricular rate to rise over the 6 mo following ablation. Two small, randomized trials comparing this type of AV nodal modification with complete AV nodal ablation and permanent pacemaker implantation demonstrated better symptom relief with the complete interruption procedure. Thus, AV nodal modification without pacemaker implantation is only rarely used.

Ablation of the AV inputs in the atrium may improve the reliability of the junctional escape mechanism.³⁹³ This involves selective ablation of fast and slow AV nodal pathways followed, if necessary, by ablation between these inputs to achieve complete AV block. Complications of AV nodal ablation include those associated with pacemaker implantation, ventricular arrhythmias, thromboembolism associated with interruption of anticoagulation, the rare occurrence of LV dysfunction, and progression from paroxysmal to persistent AF. The 1-y mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3% (95% confidence interval [CI] 5.5% to 7.2%), including a 2.0% risk of sudden death (95% CI 1.5% to 2.6%). Although a causal relationship between the procedure and sudden death remains controversial, it has been suggested that programming the pacemaker to a relatively high nominal rate (90 beats per minute) for the first month after ablation may reduce the risk.^{394,395}

Although the symptomatic benefits of AV nodal ablation are clear, limitations include the persistent need for anticoagulation, loss of AV synchrony, and lifelong pacemaker dependency. There is also a finite risk of sudden death due to torsades de pointes or ventricular fibrillation.³⁹⁶ Patients with abnormalities of diastolic ventricular compliance who depend on AV synchrony to maintain cardiac output, such as those with hypertrophic cardiomyopathy or hypertensive heart disease, may experience persistent symptoms after AV nodal ablation and pacemaker implantation. Hence, patients should be counseled regarding each of these considerations before proceeding with this irreversible measure.

The adverse hemodynamic effects of RV apical pacing following AV nodal ablation have been a source of concern. Compared with RV apical pacing, LV pacing significantly improves indices of both LV systolic function (pressure-volume loop, stroke work, ejection fraction, and dP/dt) and diastolic filling.³⁹⁷ Acutely, LV pacing was associated with a 6% increase in ejection fraction and a 17% decrease in mitral regurgitation.³⁹⁸ The Post AV Node Ablation Evaluation (PAVE) randomized 184 patients undergoing AV nodal ablation because of permanent AF to standard RV apical pacing or biventricular pacing.³⁹⁹ After 6 mo, the biventricular pacing group walked 25.6 meters farther in 6 min ($P=0.03$), had greater peak oxygen consumption, and had higher scores in 9 of 10 quality-of-life domains than the RV pacing group. While there was no difference in LV ejection fraction between the groups at

baseline, the LV ejection fraction remained stable in the biventricular pacing group while it declined in the RV pacing group (46% vs. 41%, respectively; $P = 0.03$). There was no significant difference in mortality. A subgroup analysis suggested that functional improvements were confined to patients with LV ejection fraction below 35% before ablation.

Patients with normal LV function or reversible LV dysfunction undergoing AV nodal ablation are most likely to benefit from standard AV nodal ablation and pacemaker implantation. For those with impaired LV function not due to tachycardia, a biventricular pacemaker with or without defibrillator capability should be considered. Upgrading to a biventricular device should be considered for patients with HF and an RV pacing system who have undergone AV node ablation.⁴⁰⁰

8.1.4. Preventing thromboembolism

For recommendations regarding antithrombotic therapy in patients with AF undergoing cardioversion, see Section 8.2.7.

Recommendations

Class I

- (1) Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications. (Level of Evidence: A)
- (2) The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient. (Level of Evidence: A)
- (3) For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis. (Level of Evidence: A)
- (4) Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. Such factors include age 75 y or greater, hypertension, HF, impaired LV systolic function (ejection fraction 35% or less or fractional shortening less than 25%), and diabetes mellitus. (Level of Evidence: A)
- (5) INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. (Level of Evidence: A)
- (6) Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation. (Level of Evidence: A)
- (7) For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5. (Level of Evidence: B)
- (8) Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. (Level of Evidence: C)

Class IIa

- (1) For primary prevention of thromboembolism in patients with nonvalvular AF who have just 1 of the following

validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences: age greater than or equal to 75 y (especially in female patients), hypertension, HF, impaired LV function, or diabetes mellitus. (Level of Evidence: A)

- (2) For patients with nonvalvular AF who have 1 or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 y, female gender, or CAD. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences. (Level of Evidence: B)
- (3) It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF. (Level of Evidence: B)
- (4) In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 wk without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding. (Level of Evidence: C)
- (5) It is reasonable to reevaluate the need for anticoagulation at regular intervals. (Level of Evidence: C)

Class IIb

- (1) In patients 75 y of age and older at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0 to 3.0, a lower INR target of 2.0 (range 1.6 to 2.5) may be considered for primary prevention of ischemic stroke and systemic embolism. (Level of Evidence: C)
- (2) When surgical procedures require interruption of oral anticoagulant therapy for longer than 1 wk in high-risk patients, unfractionated heparin may be administered or low-molecular-weight heparin given by subcutaneous injection, although the efficacy of these alternatives in this situation is uncertain. (Level of Evidence: C)
- (3) Following percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (less than 100 mg per d) and/or clopidogrel (75 mg per d) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. (Level of Evidence: C)
- (4) In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0). Clopidogrel should be given for a minimum of 1 mo after implantation of a bare metal

stent, at least 3 mo for a sirolimus-eluting stent, at least 6 mo for a paclitaxel-eluting stent, and 12 mo or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated. (Level of Evidence: C)

- (5) In patients with AF younger than 60 y without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established. (Level of Evidence: C)
- (6) In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity anticoagulation (INR 2.0 to 3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of anticoagulation to a maximum target INR of 3.0 to 3.5. (Level of Evidence: C)

Class III

Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease (lone AF) or any risk factors for thromboembolism. (Level of Evidence: C)

8.1.4.1. Risk stratification

8.1.4.1.1. Epidemiological data. In a small, retrospective, population-based study in Olmsted County, Minnesota, over 3 decades, the 15-y cumulative stroke rate in people with lone AF (defined as those younger than 60 y with no clinical history or echocardiographic signs of cardiopulmonary disease) was 1.3%.¹¹ Conversely, in the Framingham Study,²⁸ the age-adjusted stroke rate over a mean follow-up period of 11 y 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.²⁸ In the SPAF study, the annualized rate of ischemic stroke during aspirin treatment was similar in those with paroxysmal (3.2%) and permanent (3.3%) AF.⁴⁰¹ Those with prior stroke or TIA have a rate of subsequent stroke of 10% to 12% per year when treated with aspirin, and these patients benefit substantially from adjusted-dose oral anticoagulation.^{402,403} In addition to prior thromboembolism, HF, hypertension, increasing age, and diabetes mellitus have consistently emerged as independent risk factors for ischemic stroke associated with nonvalvular AF.^{47,261,264,382,405} Other factors, such as female gender, systolic blood pressure over 160 mm Hg, and LV dysfunction, have been variably linked to stroke.^{261,266,406} 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 displayed in *Table 11*.

In patients with nonvalvular AF, prior stroke or TIA is the strongest independent predictor of stroke, significantly associated with stroke in all 6 studies in which it was evaluated, with incremental relative risk between 1.9 and 3.7 (averaging approximately 3.0). Attempts to identify patients with prior stroke or TIA who have relatively low stroke risks by virtue of the absence of other risk factors did not identify any reliable predictors.^{261,407-409} The pathogenic constructs

Table 11 Risk factors for ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation

Risk factors	Relative risk
Previous stroke or TIA	2.5
Diabetes mellitus	1.7
History of hypertension	1.6
Heart failure	1.4
Advanced age (continuous, per decade)	1.4

Data derived from collaborative analysis of 5 untreated control groups in primary prevention trials.⁴⁷ As a group, patients with nonvalvular atrial fibrillation (AF) carry about a 6-fold increased risk of thromboembolism compared with patients in sinus rhythm. Relative risk refers to comparison of patients with AF to patients without these risk factors.

TIA indicates transient ischemic attack.

of stroke in AF are incomplete, but available data indicate that all patients with prior stroke or TIA are at high risk of recurrent thromboembolism and require anticoagulation unless there are firm contraindications in a given patient. Efforts to enhance risk stratification should remove such patients from consideration and focus instead on the predictive value of pertinent risk factors and absolute stroke rates for primary prevention. Patient age is a consistent independent predictor of stroke (*Figure 8*). In 7 studies in which the variable was assessed, hazard ratios averaged 1.5 per decade. Nearly half of AF-associated strokes occur in patients over 75 y, and AF is the most frequent cause of disabling stroke in elderly women.^{21,405,406} Older people are also at increased risk for anticoagulant-related bleeding⁴¹⁰ and are less likely to be treated with oral anticoagulation, even in situations for which it has been proved efficacious, in part because of concern about the risk of bleeding.⁴¹¹ Special consideration of these older patients is therefore a critical aspect of effective stroke prophylaxis.⁴⁰⁵

Female gender has emerged as an independent predictor of stroke in 3 cohort studies of patients with AF but not in several others.^{47,268,404} The relative increase was 1.6 in the largest study of the ATRIA cohort.²⁶² In the SPAF analyses of aspirin-treated patients, gender interacted with age such that women over 75 y old were at particularly high risk, but this interaction was not apparent in the Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) cohort.^{262,412}

Similarly, hypertension is a consistent, powerful predictor of stroke, with a history of hypertension independently predictive in 5 studies (median relative risk approximately 2.0) and systolic blood pressure significant in 2 others (mean relative risk approximately 2.0). A history of hypertension and systolic blood pressure over 160 mm Hg were independently predictive of stroke in the SPAF aspirin-treated cohorts.

Diabetes was a significant independent predictor in 4 studies, associated with an average relative risk of 1.8, but not in 2 other studies. The strength of diabetes as a predictor may be greater in lower-risk patients with AF, prompting speculation that it may be associated with noncardioembolic strokes. Diabetes is a less powerful independent predictor than prior stroke/TIA, hypertension, or age, but analysis of the type, duration, or control of diabetes has not been undertaken to refine its predictive value for thromboembolism in patients with AF. The reduction in stroke among warfarin-treated patients with diabetes was below average in 2 studies.^{413,414}

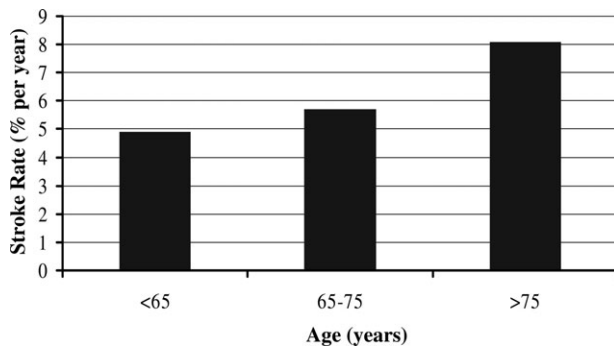


Figure 8 Stroke rates in relation to age among patients in untreated control groups of randomized trials of antithrombotic therapy. Data are from the Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–57.⁴⁷

In 2 studies, CAD was a univariate predictor of stroke in otherwise low-risk patients^{47,415}; it has not been shown to have independent predictive value for stroke in patients with AF.

Clinical HF has not been conclusively shown to have independent predictive value for stroke in any study of AF patients. In the SPAF I and II studies,⁴¹² recent (within 3 mo) HF or impaired LV systolic function (defined as M-mode echocardiographic fractional shortening less than 25%) was a significant independent predictor, as was LV systolic dysfunction by 2-dimensional echocardiography in placebo-treated patients in some studies²⁶⁶ but not in others.^{261,268} Clinical diagnosis of HF may be difficult in elderly patients with AF, and misclassification could blunt the power of association. In short, while it seems logical based on pathophysiological concepts and echocardiographic correlates that HF should be an independent predictor of stroke in patients with nonvalvular AF, available data do not provide strong support.

8.1.4.1.2. Echocardiography and risk stratification. Echocardiography is valuable to define the origin of AF (e.g., detecting rheumatic mitral valve disease or HCM) and may add information useful in stratifying thromboembolic risk. Among high-risk AF patients, impaired LV systolic function on transthoracic echocardiography, thrombus, dense SEC or reduced velocity of blood flow in the LAA, and complex atheromatous plaque in the thoracic aorta on TEE have been associated with thromboembolism, and oral anticoagulation effectively lowers the risk of stroke in AF patients with these features. LA diameter and fibrocalcific endocardial abnormalities have been less consistently associated with thromboembolism. Whether the absence of these echocardiographic abnormalities identifies a low-risk group of patients who could safely avoid anticoagulation has not been established, limiting the value of echocardiography as a prime determinant of the need for chronic anticoagulation in patients with AF.

Transthoracic echocardiography. Correlations in placebo-assigned participants in randomized trials of antithrombotic therapy provide information about the independent predictive value of transthoracic echocardiography for thromboembolic events in patients with nonvalvular AF.^{265,416}

Meta-analysis of 3 trials found moderate to severe LV dysfunction to be the only independent echocardiographic predictor of stroke in patients with AF after adjustment for clinical features; the diameter of the LA was less useful.²⁶⁶

Secondary analyses of aspirin-assigned patients in multicenter trials yield variable results regarding the role of transthoracic echocardiography for predicting thromboembolic risk.^{54,203} In the SPAF I and II studies, LV fractional shortening less than 25% (estimated by M-mode echocardiography) was the only independent echocardiographic predictor of stroke. Among 2012 aspirin-assigned patients in the SPAF trials (including 290 in SPAF-III assigned to a relatively ineffective fixed-dose combination of aspirin plus warfarin), no transthoracic echocardiographic parameter independently predicted thromboembolism when clinical risk factors were considered. Similarly, no independent predictors of thromboembolism were identified by transthoracic echocardiography and TEE at entry in the Embolism in the Left Atrial Thrombi (ELAT) study of 409 patients with nonvalvular AF taking aspirin, 160 mg daily.²⁶⁸

Transesophageal echocardiography. TEE is a sensitive and specific technique for detection of LA and LAA thrombus, far surpassing transthoracic echocardiography.²⁰³ This modality also permits superior evaluation for other causes of cardiogenic embolism,³²⁰ as well as a means of measuring LAA function.³¹⁹ Several TEE features have been associated with thromboembolism, including thrombus, reduced flow velocity, and SEC in the LA or LAA and atheromatous disease of the aorta.^{252,417}

Detection of LA/LAA thrombus stands as a contraindication to elective cardioversion of AF. Unfortunately, the absence of a detectable thrombus does not preclude stroke after cardioversion in the absence of anticoagulation therapy.^{324,418} A TEE-guided strategy for elective cardioversion of AF yielded comparable outcomes for thromboembolism and death compared with conventional anticoagulation for 3 wk before and 4 wk after cardioversion.³²⁰

8.1.4.1.3. Therapeutic implications. The efficacy and safety of oral anticoagulation and platelet inhibitor therapy with aspirin for prevention of stroke in patients with AF have been well characterized.⁴²⁰ The selection of appropriate antithrombotic therapy is discussed below in the context of thromboembolic risk (see Section 8.1.6, Pharmacological Agents to Maintain Sinus Rhythm, and Section 8.1.7, Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients With Atrial Fibrillation). Patients with AF who have 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.^{421,422} Estimating the risk of stroke for individual AF patients is crucial for the decision to provide anticoagulation therapy to individual patients with AF,⁵⁴ but the threshold risk that warrants anticoagulation is controversial. Patients with a stroke risk of 2% per year or less do not benefit substantially from oral anticoagulation, which would require treating 100 or more patients for 1 y to prevent a single stroke.⁴²⁰ For high-risk AF patients with stroke rates of 6% per year or greater, the comparable number needed-to-treat is 25 or fewer, strongly favoring anticoagulation. Opinion remains divided about routine anticoagulation for patients at intermediate stroke risk (annual rate 3% to 5%).

To stratify the risk of ischemic stroke in patients with AF, several clinical schemes have been proposed based on analyses of prospectively monitored cohorts of participants in clinical trials in which antithrombotic therapy was controlled.^{391,421,423} One set of criteria (Atrial Fibrillation Investigators [AFI]) is based on multivariate pooled analysis of 1593 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 y. 47 Patients were divided into 2 strata, distinguishing low-risk patients from those at intermediate or high risk. Although echocardiographic features were not considered initially, a subsequent analysis of 3 of the trials identified abnormal LV systolic function as an independent predictor of stroke.⁴²¹ The SPAF study criteria were based on multivariate analysis of 854 patients assigned to aspirin and followed for a mean of 2.3 y, during which 68 ischemic strokes were observed. These criteria were subsequently used to select a low-risk cohort for treatment with aspirin in the SPAF III study. Over a mean follow-up of 2 y, the rate of ischemic stroke was 2.0% per year (95% CI 1.5% to 2.8%) and the rate of disabling ischemic stroke was 0.8% per year (95% CI 0.5% to 1.3%). Patients with a history of hypertension had a higher rate of thromboembolism (3.6% per year) than those without hypertension (1.1% per year; *p* less than 0.001). Other criteria have been developed by expert consensus^{423,424} based on consideration of the foregoing schemes to classify patients into low-, intermediate-, and high-risk groups. Still others have employed recursive partitioning and other techniques to identify low-risk patients.

Nine schemes that included more than 30 stroke events have been promulgated based on multivariate analysis of clinical and/or echocardiographic predictors. Three were derived from overlapping patient cohorts, while 6 were derived from entirely independent cohorts.^{47,261,266,412,415} Of the 6 studies with distinct patient cohorts, 2 involved participants in randomized trials, 2 were based on clinical case series, one was a population-based epidemiological study, and the other was a hospital-based case-control study. The largest study²⁶² was limited to analysis of female gender as an independent predictor.

A multivariate analysis from the Framingham Heart Study examined risk factors for stroke among 705 patients with recently detected AF, excluding those who had sustained ischemic stroke, TIA, or death within 30 d of diagnosis.⁴²⁵ The only significant predictors of ischemic stroke were age (RR = 1.3 per decade), female gender (RR = 1.9), prior stroke or TIA (RR = 1.9), and diabetes mellitus (RR = 1.8), consistent with earlier studies. Systolic blood pressure became a significant predictor of stroke when warfarin was included in a time-dependent Cox proportional hazards model. With a scoring system based on age, gender, systolic hypertension, diabetes, and prior stroke or TIA, the proportion of patients classified as low risk varied from 14.3% to 30.6% depending upon whether stroke rate thresholds were less than 1.5% per year or less than 2% per year. Observed stroke rates were 1.1% to 1.5% per year based on 88 validated events. In the future, it may be possible to consider other characteristics that may contribute to stroke risk, including genetic abnormalities of hemostatic factors and endothelial dysfunction, but none have yet been identified that have sufficient predictive value for clinical use in risk stratification.^{230,413}

Another stroke risk classification scheme, known as CHADS₂ (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) integrates elements from several of the foregoing schemes. The CHADS₂ risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age over 75 y, a history of hypertension, diabetes, or recent HF (Table 12).^{415,426} The predictive value of this scoring system was evaluated in 1733 Medicare beneficiaries with nonvalvular AF between the ages of 65 and 95 y who were not given warfarin at hospital discharge. Although high scores were associated with an increased stroke rate in this elderly cohort, few patients had a score of 5 or more or a score of 0. In the same cohort, the modified AFI scheme had high-risk (prior stroke or TIA, hypertension, or diabetes) and moderate-risk (age greater than 65 y without other high-risk features) categories, corresponding to stroke rates of 5.4% per year (95% CI 4.2% to 6.5% per year) for high-risk and 2.2% per year (95% CI 1.1% to 3.5% per year) for moderate-risk patients. Patients with high-risk features according to the SPAF criteria (prior stroke or TIA, women older than 75 y, or recent HF) had a stroke rate of 5.7% per year (95% CI 4.4% to 7.0% per year); moderate-risk patients (history of hypertension with no other high-risk features) had a rate of 3.3% per year (95% CI 1.7% to 5.2% per year); and low-risk patients (without risk factors) had a stroke rate of 1.5% per year (95% CI 0.5% to 2.8% per year).

Although the schemes for stratification of stroke risk identify patients who benefit most and least from anticoagulation, the threshold for use of anticoagulation is controversial. Opinion is particularly divided about anticoagulation for those at intermediate risk (stroke rate 3% to 5% per year).

Table 12 Stroke risk in patients with nonvalvular af not treated with anticoagulation according to the CHADS₂ index

CHADS ₂ risk criteria	Score	
Prior stroke or TIA	2	
Age >75 y	1	
Hypertension	1	
Diabetes mellitus	1	
Heart failure	1	
Patients (N = 1733)	Adjusted stroke rate (%/y) ^a (95% CI)	CHADS ₂ score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

Data are from van Walraven WC, Hart RG, Wells GA, *et al.* A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–43⁴¹⁵; and Gage BF, Waterman AD, Shannon W, *et al.* Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285:2864–70.⁴²⁶

AF indicates atrial fibrillation; CHADS₂, Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; TIA, transient ischemic attack.

^aThe adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage.

Some advocate the routine use of anticoagulation for those with stroke rates in this range,⁴²⁷ whereas others favor selective anticoagulation of patients at intermediate risk, with weight given to individual bleeding risks and patient preferences.^{54,428} The threshold of benefit at which AF patients choose anticoagulation varies; some at intermediate risk elect anticoagulation, whereas others do not.⁴²⁹ Our recommendations for antithrombotic therapy in patients with AF are summarized in *Table 13*.

Atrial flutter is uncommon as a chronic arrhythmia, and the risk of thromboembolism is not as well established as it is for AF but is generally estimated as higher than that for patients with sinus rhythm and less than that for those with persistent or permanent AF. On the basis of multivariate analysis, Wood *et al.*⁴³⁰ reported hypertension as the only significant correlate of previous thromboembolism for patients with chronic atrial flutter. From a review of 8 y of retrospective data from 749 988 hospitalized older patients, including 17 413 with atrial flutter and 337 428 with AF, 3 of 4 patients with atrial flutter also had or developed AF. The overall stroke risk ratio for patients with atrial flutter was 1.406, and for those with AF, it was 1.642 compared with the control group. 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.⁴³¹

Although the overall thromboembolic risk associated with atrial flutter may be somewhat lower than with AF, it seems prudent to estimate risk by the use of similar stratification criteria for both arrhythmias until more robust data become available (*Tables 13 and 14*).

8.1.4.2. 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 or prosthetic heart valves.²¹ 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. Since then, 24 randomized trials involving patients with nonvalvular AF have been published, including

20 012 participants with an average follow-up of 1.6 y, a total exposure of about 32 800 patient-y (*Table 15*). In these studies, patient age averaged 71 y; 36% were women. Most trials originated in Europe (14 trials, 7273 participants) or North America (7 trials, 8349 participants). Most studied oral vitamin K inhibitors or aspirin in varying dosages/intensities, but other anticoagulants (low-molecular-weight heparin, ximelagatran) and other antiplatelet agents (dipyridamole, indobufen, trifusal) have also been tested. Nine trials had double-blind designs for antiplatelet^{57,403,432–435} or anticoagulation^{436–438} comparisons.

8.1.4.2.1. Anticoagulation with vitamin K antagonist agents. Five large randomized trials published between 1989 and 1992 evaluated oral anticoagulation mainly for primary prevention of thromboembolism in patients with nonvalvular AF^{57,428,432,436,437} (*Figure 9, Table 15*). A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or TIA.⁴⁰³ 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 62% (95% CI 48% to 72%) versus placebo⁴²⁰ (*Figure 9*). This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. By on-treatment analysis (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,⁴³⁷ one was stopped early because of external evidence that oral anticoagulation was superior to placebo, and the other included no female subjects. In 3 of the trials, oral anticoagulant dosing was regulated according to the prothrombin time ratio; 2 used INR target ranges of 2.5 to 4.0 and 2.0 to 3.0. These trials are summarized in *Table 15*. The duration of follow-up was generally between 1 and 2 y; the longest was 2.2 y, whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods.

All reported trials excluded patients considered at high risk of bleeding. Patient age and the intensity of anticoagulation are the most powerful predictors of major bleeding.^{449–454} Trial participants, at an average age of 69 y, were

Table 13 Antithrombotic therapy for patients with atrial fibrillation

Risk Category	Recommended therapy	
No risk factors	Aspirin, 81 to 325 mg daily	
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)	
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5) ^a	
Less validated or weaker risk factors	Moderate-risk factors	High-risk factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve ^a
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

INR indicates international normalized ratio; LV, left ventricular; TIA, transient ischemic attack.

^aIf mechanical valve, target international normalized ratio (INR) greater than 2.5.

Table 14 Risk-based approach to antithrombotic therapy in patients with atrial fibrillation

Patient features	Antithrombotic therapy	Class of recommendation
Age less than 60 y, no heart disease (lone AF)	Aspirin (81 to 325 mg per day) or no therapy	I
Age less than 60 y, heart disease but no risk factors ^a	Aspirin (81 to 325 mg per day)	I
Age 60 to 74 y, no risk factors ^a	Aspirin (81 to 325 mg per day)	I
Age 65 to 74 y with diabetes mellitus or CAD	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, women	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, men, no other risk factors	Oral anticoagulation (INR 2.0 to 3.0) or aspirin (81 to 325 mg per day)	I
Age 65 or older, heart failure	Oral anticoagulation (INR 2.0 to 3.0)	I
LV ejection fraction less than 35% or fractional shortening less than 25%, and hypertension	Oral anticoagulation (INR 2.0 to 3.0)	I
Rheumatic heart disease (mitral stenosis)	Oral anticoagulation (INR 2.0 to 3.0)	I
Prosthetic heart valves	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Prior thromboembolism	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Persistent atrial thrombus on TEE	Oral anticoagulation (INR 2.0 to 3.0 or higher)	Ia

AF indicates atrial fibrillation; CAD, coronary artery disease; INR, international normalized ratio; TEE, transesophageal echocardiography.

^aRisk factors for thromboembolism include heart failure (HF), left ventricular (LV) ejection fraction less than 35%, and history of hypertension.

Table 15 Randomized trials of antithrombotic therapy in patients with nonvalvular AF

Trials	Reference	Year published	No. of patients	interventions
Large published trials				
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I)	432	1989	1007	VKA, ASA, placebo
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II)	439	1998	677	VKA, ASA, LDA + ASA, LDA
Stroke Prevention in Atrial Fibrillation I (SPAF I)	57	1991	1330	VKA, ASA, placebo
Stroke Prevention in Atrial Fibrillation II (SPAF II)	440	1994	1100	VKA, ASA
Stroke Prevention in Atrial Fibrillation III (SPAF III)	402	1996	1044	VKA, LDA + ASA
Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)	428	1990	420	VKA, control
Canadian Atrial Fibrillation Anticoagulation (CAFA)	436	1991	378	VKA, placebo
Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)	437	1992	571	VKA, placebo
European Atrial Fibrillation Trial (EAFT)	403	1993	1007	VKA, ASA, placebo
Studio Italiano Fibrillazione Atriale (SIFA)	441	1997	916	VKA, indobufen
Minidose Warfarin in Nonrheumatic Atrial Fibrillation	442	1998	303	VKA, LDA
Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF)	443	1999	729	VKA, LDA, ASA
Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients with Atrial Fibrillation (SPORTIF-III)	477	2003	3407	DTI, VKA
Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients With Atrial Fibrillation (SPORTIF-V)	438	2005	3922	DTI, VKA
National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF)	445	2004	1209	VKA, triflusal, VKA + triflusal
Small or pilot trials				
Harenberg <i>et al.</i>	446	1993	75	LMW heparin, control
Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF)	447	1996	285	ASA, placebo
Subgroups with AF in other trials				
European Stroke Prevention Study II (ESPS II)	404	1997	429	ASA, dipyridamole, placebo

Adapted with permission from Hart RG, Benavente O, McBride R, *et al.* Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492-501.⁴²⁰

AF, atrial fibrillation; ASA, aspirin; DTI, direct thrombin inhibitor; LDA, low-dose aspirin; LMW, low-molecular-weight; VKA, vitamin K antagonist.

carefully selected and managed, however, and it is unclear whether the relatively low observed rates of major hemorrhage also apply to patients with AF in clinical practice, who have a mean age of about 75 y and less closely regulated anticoagulation therapy.^{19,431,455}

The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications (*Figure 10*). Targeting the lowest adequate intensity of anticoagulation to minimize the risk of bleeding is particularly important for elderly AF

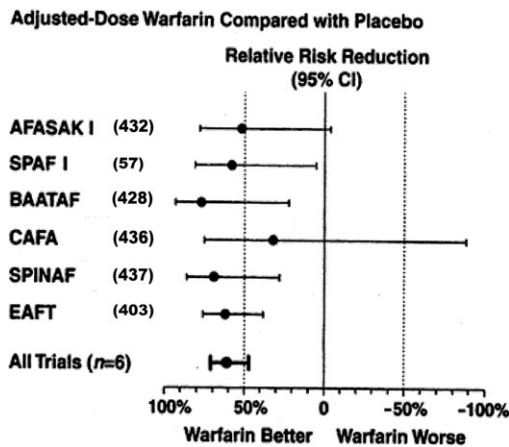


Figure 9 Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation. Adjusted-dose warfarin compared with placebo (six random trials). Adapted with permission from Hart RG, Benavente O, McBride R, *et al*. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.⁴²⁰ AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

patients. Maximum protection against ischemic stroke in AF is probably achieved at an INR range of 2.0 to 3.0,⁴⁵⁶ whereas an INR range of 1.6 to 2.5 is associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher-intensity anticoagulation.^{432,449} 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 TIA were randomly assigned to target INR ranges of 2.2 to 3.5 versus 1.5 to 2.1 found a greater rate of major hemorrhage with the higher intensity.⁴⁵⁰ 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 y and for secondary prevention, an INR of 2.5 (target range 2.0 to 3.0) is recommended. A target INR of 2.0 (target range 1.6 to 2.5) seems reasonable for primary prevention in patients older than 75 y who are considered at high risk of bleeding. 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. The major bleeding rate for 5 randomized clinical trials was 1.2% per year²⁰² (Figure 11).

Despite anticoagulation of more elderly patients with AF, rates of intracerebral hemorrhage are considerably lower than in the past, typically between 0.1% and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension.^{438,457} In 2 time-dependent INR analyses of anticoagulation in elderly AF cohorts, intracranial bleeding increased with INR values over 3.5 to 4.0, and there was no increment with values between 2.0 and 3.0 compared with lower INR levels.^{454,456} Pooled results of randomized

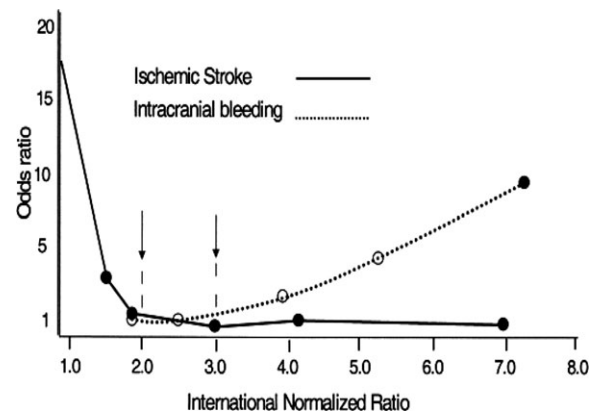


Figure 10 Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897–902.⁴⁵¹ Data from Odén A, Fahlén M and Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res* 2006;117:493–9.⁴⁵²

trials and a large cohort comparison, however, suggest a doubling of intracranial hemorrhages with mean INR values between 2.0 and 2.5.⁴⁵⁸ Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhage during anticoagulant therapy include associated cerebrovascular disease and possibly concomitant antiplatelet therapy, tobacco or alcohol consumption, ethnicity, genotype, and certain vascular abnormalities detected by brain imaging, such as amyloid angiopathy, leukoaraiosis, or microbleeds.⁴⁵⁷ No stratification scheme for prediction of intracerebral hemorrhage during anticoagulant therapy has been prospectively evaluated.

8.1.4.2.2. Aspirin for antithrombotic therapy in patients with atrial fibrillation. Aspirin offers only modest protection against stroke for patients with AF^{46,57,403,432,439,440,443,447,448} (Figure 12). Meta-analysis of 5 randomized trials showed a stroke reduction of 19% (95% CI 2% to 34%).⁴²⁰ The effect of aspirin on stroke in these trials was less consistent than that of oral anticoagulation,^{420,459} but 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) versus 11% for secondary prevention trials (in which the stroke rate with placebo averaged 14% per year).⁴²⁰ Aspirin may be more efficacious for AF patients with hypertension or diabetes⁴⁵⁹ and for reduction of noncardioembolic versus cardioembolic ischemic strokes in AF patients.²⁰⁰ Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes.²⁵⁰ Aspirin appears to prevent nondisabling strokes more than disabling strokes.⁴²⁰ Thus, the greater the risk of disabling cardioembolic stroke in a population of patients with AF, the less protection is afforded by aspirin.²⁵⁰

Additional information about event rates on aspirin or no antithrombotic therapy can be extracted from contemporary databases such as the ATRIA cohort of 13 428 ambulatory patients with AF enrolled in the Kaiser Permanente Medical Care Program in North Carolina during the period 1996 through 1999.^{262,456,458,461} In the 11 526 patients without

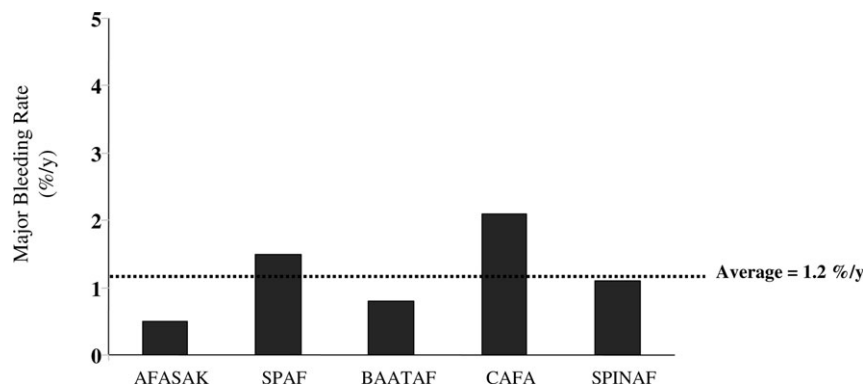


Figure 11 Annual rates of major hemorrhage during anticoagulation in primary prevention trials involving patients with nonvalvular atrial fibrillation. The mean age of participants was 69 years. Major hemorrhage was variously defined but typically involved bleeding severe enough to require hospitalization, transfusion or surgical intervention, involved a critical anatomical site, or was permanently disabling or fatal. Data adapted from Hart RG, Benavente O, McBride R, *et al.* Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.⁴²⁰ AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

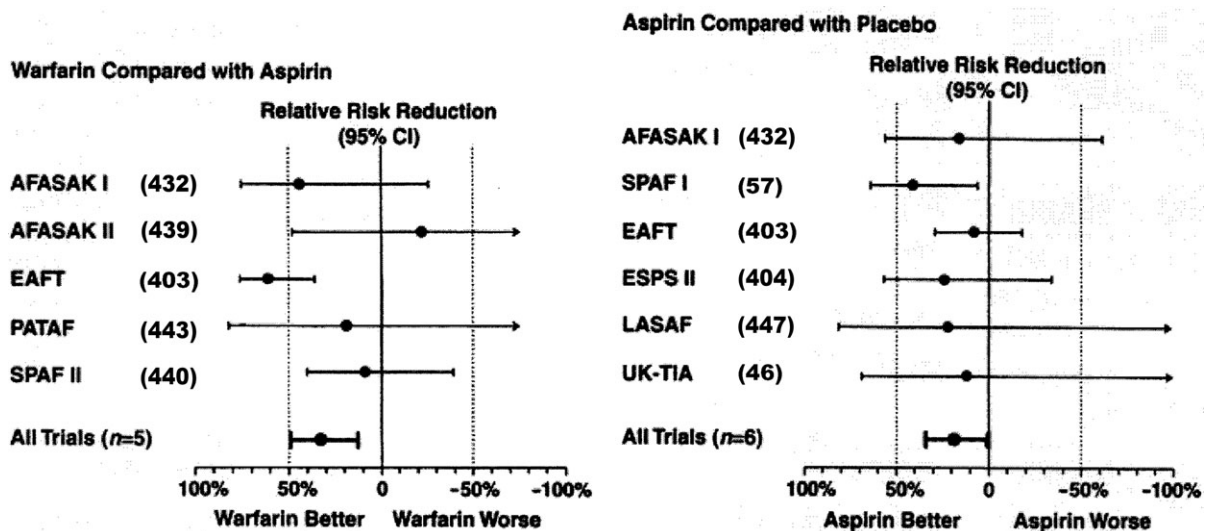


Figure 12 Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation: warfarin compared with aspirin and aspirin compared with placebo. Modified with permission from Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.⁴²⁰ AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, The United Kingdom transient ischaemic attack aspirin trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

apparent contraindications to anticoagulation,⁴⁵⁸ 6320 patients were treated with warfarin. Among the 5089 patients not treated with warfarin, the absolute rate of thromboembolism was 2.0% per year.⁴⁶¹ There was a history of stroke or TIA in only 4% of the patients not treated with anticoagulation, making this mainly a primary prevention cohort.⁴⁵⁸ During a mean follow-up of 2.2 y (median 2.35 y), 249 thromboembolic events (231 ischemic strokes and 18 systemic embolic events outside the central nervous system) occurred among the patients who were not anticoagulated (2.0% per year [95% CI 1.8% to 2.3%]). From a nested case-control study of 294 patients, it was estimated that about 45% were using aspirin. When those

from the larger cohort with contraindications to warfarin (who were older and more often had prior stroke or TIA) were included, the rate of thromboembolism was 2.5% per year.

While the use of administrative and claims-based data from a managed care organization may have been prone to underdetection of stroke events, these rates were not very different from those in other reported populations. By comparison, among 1853 patients without prior thromboembolic events assigned to aspirin in the SPAF I, II, and III trials, the rate of ischemic stroke was 2.7% per year.²⁶¹ In the AFI cohort of 2732 patients from 6 randomized trials (about half from the SPAF trials), without prior stroke or TIA, the

rate of ischemic stroke was 2.1% per year with aspirin therapy. Among 210 patients in the population-based Cardiovascular Health Study (mean age 74 y) followed without anticoagulation, the stroke rate was 2.6% per year.⁴⁶² When stratified according to the CHADS2 stroke risk scheme,⁴²⁶ patients in the ATRIA cohort with a single stroke risk factor (32% of the cohort) who were not anticoagulated had a rate of stroke and systemic embolism of 1.5% per year (95% CI 1.2% to 1.9%).⁴⁵⁸ Of 670 patients treated with aspirin in 6 clinical trials, the stroke rate was 2.2% per year for those with a CHADS2 score of 1 (95% CI 1.6% to 3.1% per year).⁴⁶³

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 trials.⁴²⁰ 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 (Figure 12), 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 patients at low risk. Individual risk varies over time, so the need for anticoagulation must be reevaluated periodically in all patients with AF.

8.1.4.2.3. Other antiplatelet agents for antithrombotic therapy in patients with atrial fibrillation. Anticoagulation with oral vitamin K antagonists has been compared with platelet cyclooxygenase inhibitors other than aspirin in 2 trials involving 1395 participants. In the Italian Studio Italiano Fibrillazione Atriale (SIFA) study,⁴⁴¹ indobufen, 100 to 200 mg twice daily, was compared with warfarin (INR 2.0 to 3.5) in 916 patients with recent cerebral ischemic events. Incidences of the combined endpoint of nonfatal stroke, intracerebral bleeding, pulmonary or systemic embolism, MI, and vascular death were not significantly different between treatment groups, but more ischemic strokes occurred in the indobufen group¹⁸ than in the warfarin group.¹⁰ In the primary prevention cohort of the Spanish National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial,⁴⁴⁵ the rate of the composite of thromboembolism plus cardiovascular death was lower with acenocoumarol than with triflusal. There was no significant difference in rates of ischemic stroke and systemic embolism. Neither indobufen nor triflusal is widely available; these agents have not been compared with aspirin for efficacy and safety, nor do they offer advantages over anticoagulation with a vitamin K antagonist in patients with AF at high risk of thromboembolism.

In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W), which was stopped on the recommendation of the Data Safety and Monitoring Board before planned follow-up was completed, the combination of the thienopyridine antiplatelet agent clopidogrel (75 mg daily) plus aspirin (75 to 100 mg daily) proved inferior to warfarin (target INR 2.0 to 3.0) in patients with an average of 2 stroke risk factors in addition to AF.⁴⁶⁴ Additional studies are ongoing to assess the impact of this therapy for patients unable or unwilling to take warfarin.

8.1.4.2.4. Combining anticoagulant and platelet-inhibitor therapy. Combinations of oral anticoagulants plus antiplatelet agents to reduce the risk of hemorrhage by allowing lower intensities of anticoagulation or to augment efficacy for selected patients at particularly high risk of thromboembolism, such as those with prior stroke, have been evaluated in several trials. Such a strategy has been successful in reducing the risk of thromboembolism in patients with mechanical heart valves.⁴⁶⁵ Still another objective of combination therapy is to enhance protection against ischemic cardiac events in patients with AF who have established coronary atherosclerosis or diabetes. In 2 trials, SPAF III and Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK) 2, the combination of low-dose oral anticoagulation (INR less than 1.5) with aspirin added little protection against stroke compared with aspirin alone in patients with AF.^{402,439}

In 2 other trials, substantially higher intensities of anticoagulation combined with platelet inhibitor agents were evaluated in patients with AF. The French Fluidione-Aspirin Combination in High Risk Patients With AF (FFAACs) study compared the oral anticoagulant fluidione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluidione alone in patients at high risk of stroke. The trial was stopped with only 157 patients enrolled (mean follow-up 0.84 y) because of excessive hemorrhage in the group receiving the combination therapy.⁴³³

In the larger Spanish National Study for Primary Prevention of Embolism in Nonrheumatic Atrial Fibrillation (NASPEAF) study, patients were stratified into a high-risk group (n = 495) with AF and rheumatic mitral stenosis or AF and a history of stroke, TIA, or systemic embolism, and a lower-risk group (n = 714) with AF and age greater than 60 y, hypertension, or HF.⁴⁴⁵ The higher-risk patients were randomized to anticoagulation with acenocoumarol (target INR 2.0 to 3.0) or to acenocoumarol (INR 1.4 to 2.4) combined with the platelet cyclooxygenase inhibitor triflusal (600 mg daily). The lower-risk patients were randomized to triflusal alone, acenocoumarol alone (INR 2.0 to 3.0), or the combination of triflusal plus acenocoumarol (INR 1.25 to 2.0). The achieved anticoagulation intensities in the anticoagulation and combination therapy arms were closer to one another than intended, however (mean INR 2.5 with acenocoumarol alone in both risk strata versus 1.96 and 2.18 for the combination arms in the lower- and higher-risk groups during median follow-up of 2.6 and 2.9 y, respectively). The primary outcome was a composite of thromboembolism plus cardiovascular death (sudden death or death due to thromboembolism, stroke, bleeding, or HF but not MI). Patients in both risk categories had a lower risk of primary events with the combination therapy than with acenocoumarol alone. These observations suggest that a combination of platelet inhibitor and anticoagulant therapy might be effective and relatively protective if targeted INR levels are closer to the standard range, but the superiority of combination therapy over monotherapy with a vitamin K antagonist for prevention of ischemic stroke and MI has not been convincingly established.

Combining aspirin with an oral anticoagulant at higher intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients.⁴⁶⁶ In a retrospective analysis of 10 093 patients with AF after hospital discharge (mean age 77 y), platelet inhibitor medication was associated

with a higher rate of intracerebral hemorrhage (relative risk 3.0, 95% CI 1.6% to 5.5%),⁴⁶⁷ but 2 case-control studies yielded conflicting results.^{454,468}

The superior efficacy of anticoagulation over aspirin for prevention of recurrent stroke in patients with AF was demonstrated in the European Atrial Fibrillation Trial.⁴⁰³ Therefore, unless a clear contraindication exists, AF patients with a recent stroke or TIA should be treated with long-term anticoagulation rather than antiplatelet therapy. There is no evidence that combining anticoagulation with an antiplatelet agent reduces the risk of stroke compared with anticoagulant therapy alone. Hence, pending further data for AF patients who sustain cardioembolic events while receiving low-intensity anticoagulation, anticoagulation intensity should be increased to a maximum target INR of 3.0 to 3.5 rather than routinely adding antiplatelet agents.

Several studies have evaluated anticoagulation in combination with aspirin for prevention of ischemic cardiac events in patients with CAD. From these it may be possible to draw inferences regarding management of antithrombotic therapy in patients who have both CAD and AF. A meta-analysis of 31 randomized trials of oral anticoagulant therapy published between 1960 and 1999 involving patients with CAD treated for at least 3 mo and stratified by the intensities of anticoagulation and aspirin therapy came to the following conclusions.⁴⁶⁹ High-intensity (INR 2.8 to 4.8) and moderate-intensity (INR 2.0 to 3.0) oral anticoagulation regimens reduced rates of MI and stroke but increased the risk of bleeding 6.0- to 7.7-fold. Combining aspirin with low-intensity anticoagulation (INR less than 2.0) was not superior to aspirin alone. While the combination of moderate- to high-intensity oral anticoagulation plus aspirin appeared promising compared with aspirin alone, the combination was associated with increased bleeding.

From the results of more contemporary trials involving long-term treatment of patients with acute myocardial ischemia⁴⁷⁰⁻⁴⁷³ and the Combined Hemotherapy and Mortality Prevention Study (CHAMP),⁴⁷⁴ it appears that high-intensity oral anticoagulation (INR 3.0 to 4.0) is more effective than aspirin but increases the risk of bleeding. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is more effective than aspirin alone but is associated with a greater risk of bleeding. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is as effective as high-intensity warfarin and associated with a similar risk of bleeding. The contemporary trials, however, have not addressed the effectiveness of moderate-intensity warfarin (INR 2.0 to 3.0) alone. In the absence of direct evidence, it cannot be assumed that moderate-intensity warfarin is superior to aspirin in preventing death or reinfarction. The choice for long-term management of patients with CAD and AF therefore involves aspirin alone, aspirin plus moderate-intensity warfarin (INR 2.0 to 3.0), or warfarin alone (INR 2.0 to 3.0). For those with risk factors for stroke, the latter 2 regimens are more effective than aspirin alone but are associated with more bleeding and inconvenience. Further, without close INR control, the combination regimen may be associated with a greater risk of bleeding. For most patients with AF who have stable CAD, warfarin anticoagulation alone (target INR 2.0 to 3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events.

The importance of platelet-inhibitor drugs for prevention of recurrent myocardial ischemia is enhanced in patients undergoing percutaneous coronary intervention, but no adequate studies have been published that specifically address this issue in patients who also require chronic anticoagulation because of AF. It is the consensus of the authors of these guidelines that the most important agent for the maintenance of coronary and stent patency is the thienopyridine derivative clopidogrel and that the addition of aspirin to the chronic anticoagulant regimen contributes more risk than benefit. Although it is usually necessary to interrupt or reduce anticoagulation to prevent bleeding at the site of peripheral arterial puncture, the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0) for 9 to 12 mo, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.

8.1.4.2.5. Emerging and investigational antithrombotic agents. While clearly efficacious against stroke in patients with AF, warfarin carries a substantial risk of hemorrhage, a narrow therapeutic margin necessitating frequent monitoring of the INR level, and interactions with numerous drugs and foods that may cause a need for dose adjustments. These limitations result in undertreatment of a considerable proportion of the AF population at risk, particularly the elderly, for whom numerous concomitant medications are typically prescribed,^{455,475} engendering a quest for safer, more convenient alternatives.

Because of its central role in thrombogenesis, thrombin (factor IIa) represents an attractive target for specific inhibition. Direct thrombin inhibitors bind to the active site of thrombin and prevent it from cleaving fibrinogen to form fibrin. These compounds also suppress thrombin-mediated activation of platelets and coagulation factors V, VIII, XI, and XIII. Ximelagatran is administered orally and converted after absorption to the active direct thrombin inhibitor melagatran. The compound appears to have stable pharmacokinetics independent of the hepatic P⁴⁵⁰ enzyme system and a low potential for food or drug interactions.⁴⁷⁶ Two long-term phase III studies compared ximelagatran with warfarin in patients with AF, SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation)-III and -V, with a combined population of more than 7000.⁴⁴⁴ In these trials, ximelagatran was administered without dose titration or coagulation monitoring and was compared with warfarin (INR 2.0 to 3.0) for the primary endpoint of all stroke (ischemic and hemorrhagic) and systemic embolism.

SPORTIF-III involved an open-label design⁴⁴⁴ and careful regulation of dosing among patients assigned to warfarin, with INR values within the therapeutic range for 66% of the duration of exposure. The relative risk reduction of 29% and absolute risk reduction of 0.7% per year according to intention-to-treat confirmed the noninferiority of ximelagatran to warfarin. By on-treatment analysis, the relative risk reduction with ximelagatran was 41% ($p = 0.018$). There was no significant difference between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major

bleeding, but when minor hemorrhages are considered as well, ximelagatran caused significantly less bleeding (25.5% vs. 29.5% per year, $p = 0.007$).

The results of the SPORTIF-V trial, in which treatment was administered in a double-blind manner, were similar to those of SPORTIF-III.⁴³⁸ The primary event rates were 1.6% per year with ximelagatran and 1.2% per year with warfarin (absolute difference 0.45% per year, 95% CI 0.13% to 1.03% per year, p less than 0.001 for the noninferiority hypothesis), and there was no difference between treatment groups in rates of major bleeding, but as in the SPORTIF-III study, total bleeding (major plus minor) was lower with ximelagatran.

In both the SPORTIF-III and V trials, serum alanine aminotransferase levels rose to greater than 3 times the upper limit of normal in about 6% of patients treated with ximelagatran. Hence, despite evidence of efficacy comparable to carefully adjusted warfarin and some advantage in terms of bleeding risk, ximelagatran will not be marketed for clinical use as an anticoagulant, mainly because of concerns about hepatic toxicity.⁴⁷⁸ Trials of a variety of investigational oral anticoagulant compounds that directly inhibit thrombin, antagonize factor Xa, or inactivate prothrombin are ongoing or planned, but there are no currently available alternatives to vitamin K antagonists.

8.1.4.2.6. Interruption of anticoagulation for diagnostic or therapeutic procedures. 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 thrombosis.^{479,480} In patients with AF who do not have mechanical valves, however, based on extrapolation from the annual rate of thromboembolism in patients with nonvalvular AF, it is the consensus of the Writing Committee that anticoagulation may be interrupted for a period of up to 1 wk for surgical or diagnostic procedures that carry a risk of bleeding without substituting heparin. In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism) or when a series of procedures requires interruption of oral anticoagulant therapy for longer periods, unfractionated or low-molecular-weight heparin may be administered intravenously or subcutaneously.

The use of low-molecular-weight heparin instead of unfractionated heparin in patients with AF is based largely on extrapolation from venous thromboembolic disease states and from limited observational studies.⁴⁸¹ 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 a 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.⁴⁸² Treatment with low-molecular-weight heparin is associated with a lower risk of heparin-induced thrombocytopenia than unfractionated heparin.⁴⁸³ 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 undergoing elective cardioversion is a promising approach that may result in cost savings.⁴⁸⁴

8.1.4.3. Nonpharmacological approaches to prevention of thromboembolism. An emerging option for patients with AF who cannot safely undergo anticoagulation, which is not yet sufficiently investigated to allow general clinical application, is obliteration of the LAA to remove a principal nidus of thrombus formation.^{485,486} In addition to direct surgical amputation or truncation of appendage, several methods are under development to achieve this with intravascular catheters or transpericardial approaches.⁴⁸⁷ The efficacy of these techniques is presumably related to the completeness and permanence of elimination of blood flow into and out of the LAA. This has been demonstrated by TEE at the time of intervention, but the durability of the effect has not been confirmed by subsequent examinations over several years. Whether mechanical measures intended to prevent embolism from thrombotic material in the LAA will prove to be comparably effective and safer than anticoagulation for some patients remains to be established.⁴⁸⁸ These must presently be considered investigational, and indications for this type of intervention have not been convincingly established.

8.1.5. Cardioversion of atrial fibrillation

Recommendations

Recommendations for Pharmacological Cardioversion of Atrial Fibrillation

Class I

Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. (Level of Evidence: A)

Class IIa

- (1) Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF. (Level of Evidence: A)
- (2) A single oral bolus dose of propafenone or flecainide ('pill-in-the-pocket') can be administered to terminate persistent AF outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. (Level of Evidence: C)
- (3) Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary. (Level of Evidence: C)

Class IIb

Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. (Level of Evidence: C)

Class III

- (1) Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. (Level of Evidence: A)

- (2) Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm. (Level of Evidence: B)

8.1.5.1. Basis for cardioversion of atrial fibrillation. Cardioversion may be performed electively to restore sinus rhythm in patients with persistent AF. The need for cardioversion may be immediate 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 is greatest when the arrhythmia has been present for longer than 48 h.

8.1.5.2. Methods of cardioversion. Cardioversion may be achieved by means of drugs or electrical shocks. Drugs were commonly used before direct-current cardioversion became a standard procedure. The development of new drugs has increased the popularity of pharmacological cardioversion, but the disadvantages include the risk of drug-induced torsades de pointes or other serious arrhythmias. Moreover, pharmacological cardioversion is less effective than direct-current cardioversion when biphasic shocks are used. The disadvantage of electrical cardioversion is that it requires conscious sedation or anesthesia, which pharmacological cardioversion 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 are therefore the same for both methods, as outlined in Section 8.1.4 (Preventing Thromboembolism). Cardioversion in patients with AF following recent heart surgery or MI is addressed later (see Section 8.4, Special Considerations).

8.1.5.3. Pharmacological cardioversion. The quality of evidence available to gauge the effectiveness of pharmacological cardioversion is limited by small samples, lack of standard inclusion criteria (many studies include both patients with AF and those with atrial flutter), variable intervals from drug administration to assessment of outcome, and arbitrary dose selection. Although pharmacological and direct-current cardioversion have not been compared directly, pharmacological approaches appear simpler but are less efficacious. The major risk is related to the toxicity of antiarrhythmic drugs. In developing these guidelines, placebo-controlled trials of pharmacological cardioversion in which drugs were administered over short periods of time specifically to restore sinus rhythm have been emphasized. Trials in which the control group was given another antiarrhythmic drug have, however, been considered as well.

Pharmacological cardioversion seems most effective when initiated within 7 d after the onset of an episode of AF.^{489–492} A majority of these patients have a first-documented episode of AF or an unknown pattern of AF at the time of treatment. (See Section 3, Classification.) A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 h.^{493–495} Spontaneous conversion is less frequent in patients with AF of longer than 7-d duration, and the efficacy of pharmacological cardioversion is markedly reduced in these patients as well. Pharmacological cardioversion may accelerate restoration of sinus rhythm in patients with recent-onset AF, but the advantage over placebo is modest after 24 to 48 h,

and drug therapy is much less effective in patients with persistent AF. Some drugs have a delayed onset of action, and conversion may not occur for several days after initiation of treatment.⁴⁹⁶ Drug treatment abbreviated the interval to cardioversion compared with placebo in some studies without affecting the proportion of patients who remained in sinus rhythm after 24 h.⁴⁹⁴ A potential interaction of antiarrhythmic drugs with vitamin K antagonist oral anticoagulants, increasing or decreasing the anticoagulant effect, is an issue whenever 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 and recommended doses is presented in *Tables 16–18*. Algorithms for pharmacological management of AF are given in *Figures 13–16*. Throughout this document, reference is made to the Vaughan Williams classification of antiarrhythmic drugs,⁴⁹⁷ modified to include drugs that became available after the original classification was developed (*Table 19*). Considerations specific to individual agents are summarized below. Within each category, drugs are listed alphabetically. The antiarrhythmic drugs listed have been approved by federal regulatory agencies in the United States and/or 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 all countries. The recommendations given in this document are based on published data and do not necessarily adhere to the regulations and labeling requirements of government agencies.

8.1.5.4. Agents with proven efficacy for cardioversion of atrial fibrillation

8.1.5.4.1. Amiodarone. Data on amiodarone are confusing because the drug may be given intravenously or orally and the effects vary with the route of administration. Five meta-analyses of trials compared amiodarone to placebo or other drugs for conversion of recent-onset AF.^{546–549} One concluded that intravenous amiodarone was no more effective than placebo,⁵⁵⁰ while another found amiodarone effective but associated with adverse reactions.⁵⁴⁶ Another meta-analysis found amiodarone more effective than placebo after 6 to 8 h and at 24 h but not at 1 to 2 h.⁵⁴⁷ Amiodarone was inferior to type IC drugs for up to 8 h, but there was no difference at 24 h, indicating delayed conversion with amiodarone. In another meta-analysis of 21 trials involving heterogeneous populations, the relative likelihood of achieving sinus rhythm over a 4-wk period with oral/intravenous amiodarone was 4.33 in patients with AF of longer than 48-h duration and 1.40 in those with AF of less than 48-h duration.⁵⁴⁸ In a meta-analysis of 18 trials, the efficacy of amiodarone ranged from 34% to 69% with bolus (3 to 7 mg/kg body weight) regimens and 55% to 95% when the bolus was followed by a continuous infusion (900 to 3000 mg daily).⁵⁵⁰ Predictors of successful conversion were shorter duration of AF, smaller LA size, and higher amiodarone dose. Amiodarone was not superior to other antiarrhythmic drugs for conversion of recent-onset AF but

Table 16 Recommendations for pharmacological cardioversion of atrial fibrillation of up to 7-d duration

Drug ^a	Route of administration	Class of recommendation	Level of evidence	References
Agents with proven efficacy				
Dofetilide	Oral	I	A	498–503
Flecainide	Oral or intravenous	I	A	489–491, 493, 504–509
Ibutilide	Intravenous	I	A	510–515
Propafenone	Oral or intravenous	I	A	491, 494, 495, 505, 509, 516–526, 557
Amiodarone	Oral or intravenous	IIa	A	496, 504, 516, 527–534
Less effective or incompletely studied agents				
Disopyramide	Intravenous	IIb	B	544
Procainamide	Intravenous	IIb	B	510, 512, 536
Quinidine	Oral	IIb	B	489, 494, 524, 529, 537–539, 698
Should not be administered				
Digoxin	Oral or intravenous	III	A	375, 494, 505, 526, 530, 542
Sotalol	Oral or intravenous	III	A	513, 538–540, 543

^aThe 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.

Table 17 Recommendations for pharmacological cardioversion of atrial fibrillation present for more than 7 d

Drug ^a	Route of administration	Recommendation class	Level of evidence	References
Agents with proven efficacy				
Dofetilide	Oral	I	A	498–503
Amiodarone	Oral or intravenous	IIa	A	496, 504, 516, 527–534
Ibutilide	Intravenous	IIa	A	510–515
Less effective or incompletely studied agents				
Disopyramide	Intravenous	IIb	B	544
Flecainide	Oral	IIb	B	489–491, 493, 504–509
Procainamide	Intravenous	IIb	C	510, 512, 536, 557
Propafenone	Oral or intravenous	IIb	B	494, 495, 505, 509, 516–526
Quinidine	Oral	IIb	B	489, 494, 524, 529, 537–539, 698
Should not be administered				
Digoxin	Oral or intravenous	III	B	375, 494, 505, 526, 530, 542
Sotalol	Oral or intravenous	III	B	513, 538–540, 543

^aThe 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 by class and level of evidence.

was relatively safe in patients with structural heart disease, including those with LV dysfunction for whom administration of class IC drugs is contraindicated. In addition, limited information suggests that amiodarone is equally effective for conversion of AF or atrial flutter. Because safety data are limited, randomized trials are needed to determine the benefit of amiodarone for conversion of recent-onset AF in specific patient populations.

In the SAFE-T trial involving 665 patients with persistent AF, conversion occurred in 27% of patients after 28 d of treatment with amiodarone, compared with 24% with sotalol and 0.8% with placebo.²⁹² Although the speed of response may differ during sustained oral therapy, amiodarone, propafenone, and sotalol seemed equally effective in converting persistent AF to sinus rhythm. Apart from intravenous drug therapy for conversion early after onset of AF (within 24 h), antiarrhythmic drug agents may also be given over a longer period of time in an effort to achieve cardioversion after a longer period of AF. Under these

circumstances, administration of oral amiodarone is associated with a conversion rate between 15% and 40% over 28 d.^{292,529,533,551} In a comparative study, amiodarone and propafenone were associated with similar rates (40%) of converting persistent AF averaging 5 mo in duration.⁵⁵¹ Remarkably, all cases in which conversion followed administration of amiodarone occurred after 7 d, with responses continuing to 28 d, whereas conversion occurred more rapidly with propafenone (between 1 and 14 d).

Adverse effects of amiodarone include bradycardia, hypotension, visual disturbances, thyroid abnormalities, nausea, and constipation after oral administration and phlebitis after peripheral intravenous administration. Serious toxicity has been reported, including death due to bradycardia ending in cardiac arrest.^{496,504,516,527–534,537,551}

8.1.5.4.2. Dofetilide. Oral dofetilide is more effective than placebo for cardioversion of AF that has persisted longer than 1 wk, but available studies have not further stratified

Table 18 Recommended doses of drugs proven effective for pharmacological cardioversion of atrial fibrillation

Drug ^a	Route of administration	Dosage ^b	Potential adverse effects	References	
Amiodarone	Oral	Inpatient: 1.2 to 1.8 g per day in divided dose until 10 g total, then 200 to 400 mg per day maintenance or 30 mg/kg as single dose	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)	496, 504, 516, 527–534, 537, 545	
	Intravenous/oral	Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance 5 to 7 mg/kg over 30 to 60 min, then 1.2 to 1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200 to 400 mg per day maintenance			
Dofetilide	Oral	Creatinine Clearance (mL/min)	Dose (mcg BID)	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age	498–503
		More than 60	500		
		40 to 60	250		
		20 to 40	125		
		Less than 20	Contraindicated		
Flecainide	Oral	200 to 300 mg ^c	Hypotension, atrial flutter with high ventricular rate	489–491, 493, 504, 505, 507–509	
	Intravenous	1.5 to 3.0 mg/kg over 10 to 20 min ^c			
Ibutilide	Intravenous	1 mg over 10 min; repeat 1 mg when necessary	QT prolongation, torsades de pointes	510–515	
Propafenone	Oral	600 mg	Hypotension, atrial flutter with high ventricular rate	491, 494, 495, 505, 506, 509, 516–526, 557	
	Intravenous	1.5 to 2.0 mg/kg over 10 to 20 min ^c			
Quinidine ^d	Oral	0.75 to 1.5 g in divided doses over 6 to 12 h, usually with a rate-slowing drug	QT prolongation, torsades de pointes, GI upset, hypotension	489, 494, 524, 529, 537–539	

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

^aDrugs are listed alphabetically.

^bDosages given in the table may differ from those recommended by the manufacturers.

^cInsufficient 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.

^dThe 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.

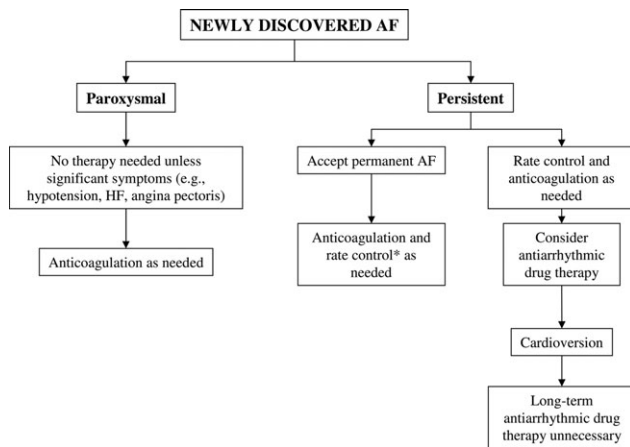


Figure 13 Pharmacological management of patients with newly discovered atrial fibrillation (AF). *See Figure 15. HF indicates heart failure.

patients on the basis of the duration of the arrhythmia. Dofetilide appears more effective for cardioversion of atrial flutter than of AF. A response may take days or weeks when the drug is given orally. The intravenous form is investigational.^{498–502}

8.1.5.4.3. Flecainide. Flecainide administered orally or intravenously was effective for cardioversion of recent-onset AF in placebo-controlled trials. In 7 studies, the success of a single oral loading dose (300 mg) for cardioversion of recent-onset AF ranged from 57% to 68% at 2 to 4 h and 75% to 91% at 8 h after drug administration.⁵⁵² Single oral loading and intravenous loading regimens of flecainide were equally efficacious, but a response usually occurs within 3 h after oral administration and 1 h 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 are slightly more frequent with flecainide than with propafenone, and these drugs should be avoided in patients with underlying organic heart disease involving abnormal ventricular function.^{489–491,493,504,505,507–509}

8.1.5.4.4. Ibutilide. In placebo-controlled trials, intravenous ibutilide has proved effective for 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 may be used in patients who fail to convert following treatment with propafenone⁵⁵³ or in those in whom the arrhythmia recurs during treatment with propafenone or flecainide.⁵⁵⁴ The risk of torsades de pointes was about 1% in these studies, lower than the approximate 4% incidence observed during ibutilide monotherapy.⁵⁵⁵ Presumably, this is related to the protective effect of sodium channel blockade with type IC drugs.⁵⁵⁴ Ibutilide is more effective for conversion of atrial flutter than of AF. An effect may be expected within 1 h after administration. In clinical practice, there is a 4% risk of torsades de pointes ventricular tachycardia and appropriate resuscitation equipment must therefore be immediately available. Women are more susceptible than men to this complication

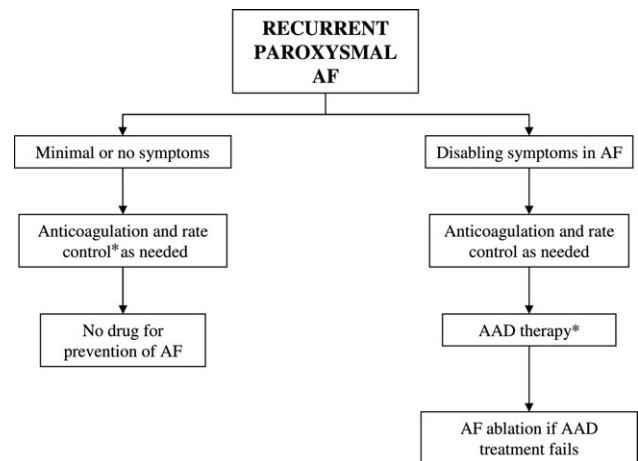


Figure 14 Pharmacological management of patients with recurrent paroxysmal atrial fibrillation (AF). *See Figure 15. AAD indicates antiarrhythmic drug.

(5.6% vs. 3% in a meta-analysis).⁵⁵⁵ Ibutilide should be avoided in patients with very low ejection fractions or HF because of the higher risk of ventricular proarrhythmia.⁵⁵⁶ 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.^{510–515}

8.1.5.4.5. Propafenone. Placebo-controlled trials have verified that propafenone, given orally or intravenously, is effective for pharmacological cardioversion of recent-onset AF. The effect occurs between 2 and 6 h after oral administration and earlier after intravenous injection, so that when compared with the intravenous regimen, oral propafenone resulted in fewer conversions in the first 2 h. In 12 placebo-controlled trials, the success rate of oral propafenone (600 mg) for cardioversion of recent-onset AF ranged from 56% to 83%.⁵⁵⁷ Oral propafenone was as efficacious as flecainide but superior to oral amiodarone and quinidine plus digoxin.^{494,558} Limited data suggest reduced efficacy in patients with persistent AF, in conversion of atrial flutter, and in patients with structural heart disease. 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 HF or severe obstructive lung disease.^{491,495,505,506,509,516–526,557}

8.1.5.5. Less effective or incompletely studied agents for cardioversion of atrial fibrillation

8.1.5.5.1. Quinidine. Quinidine is used less frequently than other pharmacological agents, due to the perception that it is less efficacious and has more frequent side effects, although direct comparative studies are lacking. Quinidine is usually administered after digoxin or verapamil has been given to control the ventricular response rate. Potential adverse effects include QT-interval prolongation that may precede torsades de pointes, nausea, diarrhea, fever, hepatic

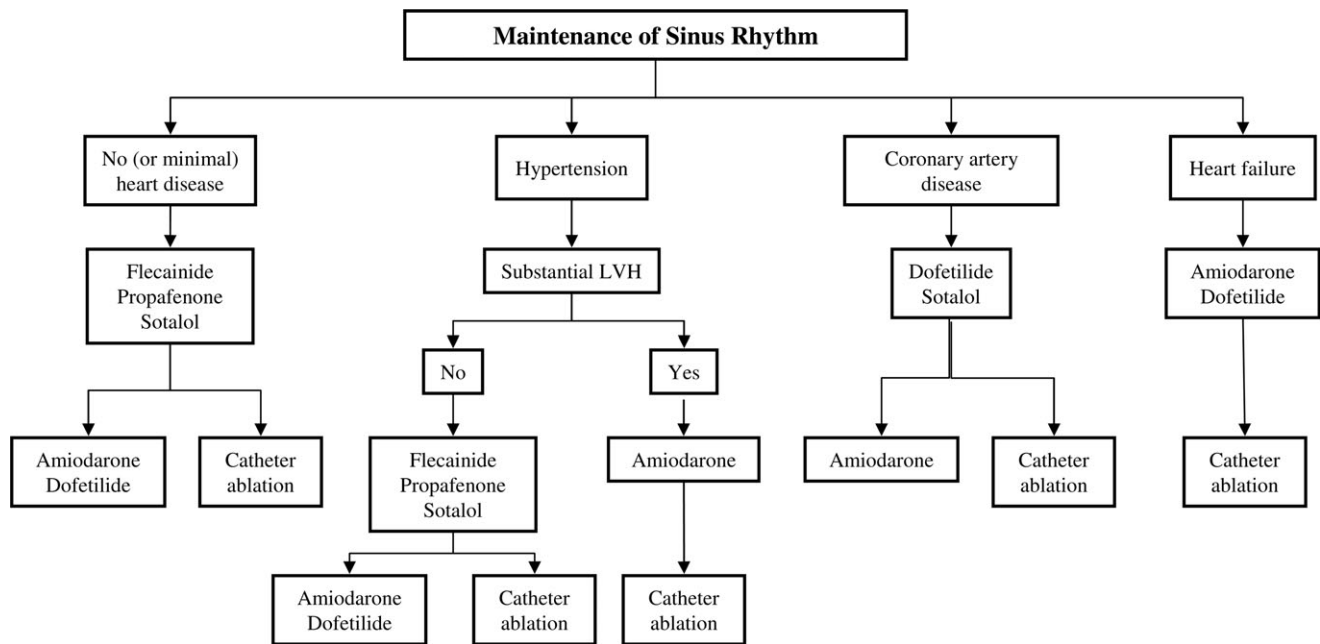


Figure 15 Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. See Section 8.3.3.3 for details. LVH indicates left ventricular hypertrophy.

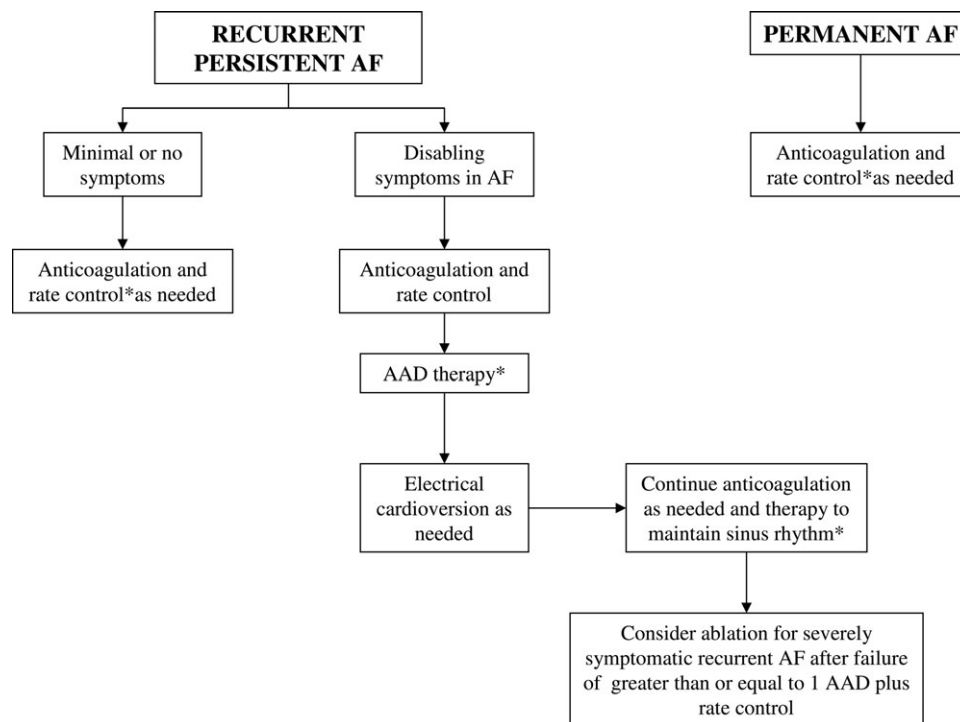


Figure 16 Pharmacological management of patients with recurrent persistent or permanent atrial fibrillation (AF). Initiate drug therapy before cardioversion to reduce the likelihood of early recurrence of AF. *See Figure 15. AAD indicates antiarrhythmic drug.

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.^{489,491,494,524,529,537-539,545}

8.1.5.5.2. Procainamide. Intravenous procainamide has been used extensively for conversion within 24 h of onset of AF, and several studies suggest that it may be superior to placebo.^{510,512,536} Procainamide appears less useful than some other drugs and has not been tested adequately in

Table 19 Vaughan Williams classification of antiarrhythmic drugs

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

Table includes compounds introduced after publication of the original classification.

Modified with permission from Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 1984;24:129–47.⁴⁹⁷ © 1984 by Sage Publications Inc.

patients with persistent AF. Hypotension is the major adverse effect after intravenous administration.

8.1.5.5.3. 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. Conversion is probably mediated through slowing of the ventricular rate. 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 after initiation of intravenous infusion. Hypotension and bronchospasm are the major adverse effects of esmolol and other beta blockers.^{492,559}

8.1.5.5.4. Nondihydropyridine calcium channel antagonists (verapamil and diltiazem). The nondihydropyridine calcium channel antagonists verapamil and diltiazem have not been found effective for pharmacological cardioversion of recent-onset or persistent AF, but they act rapidly to control the rate of ventricular response.^{373,491,492,532} The negative inotropic effects of nondihydropyridine calcium channel blockers might result in hypotension; caution should be used in patients with HF.

8.1.5.5.5. Digoxin. Digitalis glycosides are generally not 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,³⁷⁵ 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 increased ventricular ectopy, but all manifestations of digitalis toxicity are dose related.^{375,378,494,505,526,530,540,542}

8.1.5.5.6. Disopyramide. Disopyramide has not been tested adequately for conversion of AF but may be effective when administered intravenously. Adverse effects include dryness of mucous membranes, especially in the mouth, constipation, urinary retention, and depression of LV contractility. The last reaction makes it a relatively unattractive option for pharmacological conversion of AF.

8.1.5.5.7. Sotalol. In contrast to its relative efficacy for maintenance of sinus rhythm, sotalol has no proved efficacy for pharmacological cardioversion of recent-onset or persistent AF when given either orally or intravenously. It does, however, control the heart rate.^{513,538–540,543} In patients who tolerate AF relatively well, a wait-and-see approach using oral sotalol is an appropriate option. Side effects consist mainly of QT prolongation associated with torsades de pointes.

8.1.6. Pharmacological agents to maintain sinus rhythm

8.1.6.1. Agents with proven efficacy to maintain sinus rhythm. Thirty-six controlled trials evaluating 7 antiarrhythmic drugs for the maintenance of sinus rhythm in patients with paroxysmal or persistent AF, 14 controlled trials of drug prophylaxis involving patients with paroxysmal AF, and 22 trials of drug prophylaxis for maintenance of sinus rhythm in patients with persistent AF were identified. Comparative data are not sufficient to permit subclassification by drug or etiology. Individual drugs, listed alphabetically, are described below, and doses for maintenance of sinus rhythm are given in *Table 20*. It should be noted that any membrane-active agent may cause proarrhythmia.

8.1.6.1.1. Amiodarone. Available evidence suggests that amiodarone is more effective than either class I drugs, sotalol, or placebo in the long-term maintenance of sinus rhythm in patients with paroxysmal or persistent AF refractory to other drugs.^{560–574} However, amiodarone is associated with a relatively high incidence of potentially severe extracardiac toxic effects, making it a second-line or last-resort agent in many cases. The use of low-dose amiodarone (200 mg daily or less) may be effective and associated with fewer side effects^{537,561,565,566} than higher-dose regimens. In patients with LVH, HF, CAD, and/or previous MI, amiodarone is associated with a low risk of proarrhythmia, making it an appropriate initial choice to prevent recurrent AF in these situations. Use of amiodarone for AF is associated with the added benefit of effective rate control, frequently eliminating the need for other drugs to control the ventricular rate.

A majority of the 403 patients in the CTAF study⁵⁶¹ had first-time paroxysmal (46%) or persistent (54%) AF of less than 6-mo duration. AF was considered persistent when more than half the previous episodes had required cardioversion, implying that many of the cases designated as persistent AF actually had spontaneously terminating paroxysmal AF. Amiodarone maintained sinus rhythm more successfully than propafenone or sotalol (69% vs. 39%) over a 16-mo follow-up period. The reduced recurrence of AF was associated with improved quality of life, fewer AF-related procedures, and lower cost.³⁴⁷ Nevertheless, 18% of patients stopped amiodarone because of side effects after a mean of 468 d, compared with 11% of patients assigned to sotalol or propafenone.

Table 20 Typical doses of drugs used to maintain sinus rhythm in patients with atrial fibrillation^a

Drug ^b	Daily Dosage	Potential Adverse Effects
Amiodarone ^c	100 to 400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications
Disopyramide	400 to 750 mg	Torsades de pointes, HF, glaucoma, urinary retention, dry mouth
Dofetilide ^d	500 to 1000 mcg	Torsades de pointes
Flecainide	200 to 300 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Propafenone	450 to 900 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Sotalol ^d	160 to 320 mg	Torsades de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

AF indicates atrial fibrillation; AV, atrioventricular; GI, gastrointestinal; HF, heart failure.

^aDrugs and doses given here have been determined by consensus on the basis of published studies.

^bDrugs are listed alphabetically.

^cA loading dose of 600 mg per day is usually given for one month or 1000 mg per day for 1 week.

^dDose should be adjusted for renal function and QT-interval response during in-hospital initiation phase.

Of 222 patients randomized to either amiodarone or class I agents in the AFFIRM study, 62% treated with amiodarone remained in sinus rhythm at 1 y compared with 23% on class I agents. In 256 patients randomized between amiodarone and sotalol, 60% versus 38% sustained sinus rhythm.⁵⁷⁰ In patients with paroxysmal AF, amiodarone was more effective than propafenone⁵⁷⁵ and sotalol,⁵⁶² but this advantage was offset by a higher incidence of side effects.⁵⁶² In patients who develop recurrent AF during long-term therapy with oral amiodarone, intravenous amiodarone exerted an additional therapeutic effect to terminate recurrences.⁵⁷⁶

Amiodarone increases the success rate of electric cardioversion and prevents relapses by suppressing atrial ectopy in patients with persistent AF.⁵⁷⁷⁻⁵⁷⁹

Experimentally, amiodarone, but not dofetilide or flecainide, reverses pacing-induced atrial remodeling and inhibits the inducibility and stability of AF.⁵⁸⁰ 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 of patients postcardioversion⁵³⁷ stratified according to age, duration of AF, mitral valve disease, and cardiac surgery. After 6 mo, amiodarone was more effective (83% of patients remaining in sinus rhythm) than quinidine (43%). Amiodarone was associated with fewer side effects than quinidine over 6 mo, but side effects often occur after more prolonged treatment with amiodarone. In a crossover study of 32 patients who had persistent AF for more than 3 wk randomized to amiodarone or quinidine⁵³⁷ when pharmacological conversion did not occur with quinidine (direct-current cardioversion was not used), amiodarone was better tolerated and far more effective in achieving restoration and long-term maintenance of sinus rhythm. After 9 mo, 18 of 27 (67%) amiodarone-treated patients were in sinus rhythm versus 2 of 17 (12%) taking quinidine.

The double-blind, placebo-controlled SAFE-T trial²⁹² involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received sotalol, and 137 received placebo. After a run-in period of 28 d allowing for a full antiarrhythmic effect, spontaneous conversion occurred in 27% of those given amiodarone, 24% on sotalol, and 0.8% on placebo. Among patients who did not

experience conversion pharmacologically, direct-current shocks subsequently failed in 28%, 26.5%, and 32% of patients in the 3 treatment groups, respectively. This indicates that sotalol and amiodarone, when given on a chronic basis, are equally effective in converting persistent AF to sinus rhythm (see Section 8.1.5.4, Agents With Proven Efficacy for Cardioversion of Atrial Fibrillation). The median times to recurrence of AF were significantly longer with amiodarone (487 d) than with sotalol (74 d) or placebo (6 d). In patients with ischemic heart disease, the median time to AF recurrence did not differ between amiodarone (569 d) and sotalol (428 d). There were no significant differences in major adverse events, but the duration of amiodarone therapy may have been insufficient to expose toxicity. Although amiodarone is more effective than sotalol, sotalol was equally effective in patients with CAD, for whom it is preferred because of lower toxicity.

One uncontrolled study involved 89 patients with persistent AF in whom previous treatments had failed; actuarially, 53% were in sinus rhythm after 3 y of amiodarone therapy.⁵⁶⁶ In another study⁵⁶³ of 110 patients with refractory AF (57 with paroxysmal AF) or atrial flutter in whom a median of 2 class I agents had failed, 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 over 5 y. Several other uncontrolled studies also support the use of amiodarone as an agent of last resort.^{564,568,581,582} In one, a dose of 200 mg daily appeared effective in patients for whom cardioversion had failed; 52% underwent repeated cardioversion with success for 12 mo.⁵³¹

8.1.6.1.2. Beta blockers. Beta blockers are generally not considered primary therapy for maintenance of sinus rhythm in patients with AF and structural heart disease. Various beta blockers have shown moderate but consistent efficacy to prevent AF recurrence or reduce the frequency of paroxysmal AF, comparable to conventional antiarrhythmic drugs.⁵⁸³⁻⁵⁸⁶ One placebo-controlled study⁵⁸³ of 394 patients with persistent AF found a lower risk of early recurrence after cardioversion and slower ventricular response with sustained-release metoprolol than

placebo.⁵⁸³ Two studies found atenolol⁵⁸⁷ and bisoprolol⁵⁸⁴ as effective as sotalol and better than placebo in reducing the frequency and duration of paroxysmal AF and in reducing the probability of relapse after cardioversion, but proarrhythmic events occurred more often during treatment with sotalol. In patients with persistent AF, carvedilol and bisoprolol initiated after cardioversion produced similar reductions in relapse over the course of 1 y.⁵⁸⁵ These results confirm a previous observational study in which beta blockers reduced the risk of developing AF during an average follow-up of 3.2 y.²⁵ Beta blockers have the advantage of controlling the ventricular rate when AF recurs and reduce or abolish associated symptoms, but unawareness of recurrent AF may have disadvantages. These agents may be effective in postoperative patients but potentially aggravate vagally mediated AF.

8.1.6.1.3. Dofetilide. Two large-scale, double-blind, randomized studies support the efficacy of dofetilide for prevention of AF or atrial flutter.⁵⁰³ Results from the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study found dofetilide associated with conversion to sinus rhythm,⁵⁰³ most (87%) within 30 h after treatment was initiated. In SAFIRE-D,⁵⁰³ dofetilide (500 mcg daily) exhibited 58% efficacy in maintaining sinus rhythm 1 y after cardioversion compared with only 25% in the placebo group. In the Distensibility Improvement And Remodeling in Diastolic Heart Failure (DIAMOND)⁵⁸⁸ study of patients with compromised LV function, sinus rhythm was maintained in 79% of the dofetilide group compared with 42% of the placebo group. The incidence of torsades de pointes was 0.8%. Four of 5 such events occurred in the first 3 d. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital at a dose titrated to renal function and the QT interval.

8.1.6.1.4. Disopyramide. Several small, randomized studies support the efficacy of disopyramide to prevent recurrent AF after direct-current cardioversion. One study comparing propafenone and disopyramide showed equal efficacy, but propafenone was better tolerated.⁵⁸⁹ Treatment with disopyramide for more than 3 mo after cardioversion was associated with an excellent long-term outcome in an uncontrolled study: 98 of 106 patients were free of recurrent AF, and 67% remained in sinus rhythm after a mean of 6.7 y. Although the duration of AF was more than 12 mo in most 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.⁵⁴⁴ Disopyramide has negative inotropic and negative dromotropic effects that may cause HF or AV block.^{544,589-592} Disopyramide may be considered first-line therapy in vagally induced AF, and its negative inotropic effects may be desirable in patients with HCM associated with dynamic outflow tract obstruction.⁵⁹³

8.1.6.1.5. Flecainide. Two placebo-controlled studies^{594,595} found flecainide effective in postponing the first recurrence of AF and the overall time spent in AF; and in other randomized studies^{596,597} efficacy was comparable to quinidine with fewer side effects. Several uncontrolled studies⁵⁹⁸⁻⁶⁰⁰ found that flecainide delayed recurrence. Severe ventricular proarrhythmia or sudden death was not observed at a mean dose of 199 mg daily among patients with little or no

structural heart disease. Side effects in 5 patients (9%) were predominantly related to negative dromotropism, with or without syncope. Flecainide (200 mg daily) was superior to long-acting quinidine (1100 mg daily) in preventing recurrent AF after cardioversion and associated with fewer side effects, but one patient died a month after entry, presumably due to proarrhythmia.⁶⁰⁰

8.1.6.1.6. Propafenone. The United Kingdom Paroxysmal Supraventricular Tachycardia (UK PSVT) study was a large, randomized, placebo-controlled trial of propafenone in which transtelephonic monitoring was used to detect relapses to AF.⁶⁰¹ The primary endpoint was time to first recurrence or adverse event. A dose of 300 mg twice daily was effective and 300 mg 3 times daily even more effective, but the higher dose was associated with more frequent side effects. In a small, placebo-controlled study,⁶⁰² propafenone, compared with placebo, reduced days in AF from 51% to 27%. Propafenone was more effective than quinidine in another randomized comparison.⁶⁰³ In an open-label randomized study involving 100 patients with AF (with balanced proportions of paroxysmal and persistent AF), propafenone and sotalol were equally effective in maintaining sinus rhythm (30% vs. 37% of patients in sinus rhythm at 12 mo, respectively).⁶⁰⁴ The pattern of AF (paroxysmal or persistent), LA size, and previous response to drug therapy did not predict efficacy, but statistical power for this secondary analysis was limited. Other uncontrolled studies, usually involving selected patients refractory to other antiarrhythmic drugs, also support the efficacy of propafenone.⁶⁰⁵⁻⁶⁰⁹

In a randomized study, propafenone and disopyramide appeared equally effective in preventing postcardioversion AF, but propafenone was better tolerated.⁵⁸⁹ A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone effective in terms of maintenance of sinus rhythm and reduction of arrhythmia-related complaints.⁶⁰⁸

In 2 placebo-controlled studies on patients with symptomatic AF,^{610,611} a sustained-release formulation of propafenone (225, 325, and 425 mg twice daily) delayed the first symptomatic recurrence and reduced the ventricular rate at the time of relapse.

Like other highly effective class IC drugs, propafenone should not be used in patients with ischemic heart disease or LV dysfunction due to the high risk for proarrhythmic effects. Close follow-up is necessary to avoid adverse effects due to the development of ischemia or HF.

8.1.6.1.7. Sotalol. Sotalol is not effective for conversion of AF to sinus rhythm, but it may be used to prevent AF. Two placebo-controlled studies^{612,613} involving patients in sinus rhythm and at least one documented prior episode of AF found sotalol safe and effective at doses ranging from 80 to 160 mg twice daily. Patients considered at risk of proarrhythmia, HF, or AV conduction disturbances were excluded; whether any of the participants had undergone previous direct-current cardioversion was not reported.^{561,612} The effects of the reverse use dependence of sotalol and proarrhythmic risk may be greater after conversion to slower rates in sinus rhythm than during AF with a rapid ventricular response.

In another study,⁶⁰⁴ sotalol and propafenone seemed equally effective for maintenance of sinus rhythm in patients with AF. In the CTAF study, sotalol and propafenone (given separately) were less effective than amiodarone as assessed

by 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 beginning with propafenone and, after failure, then sotalol, paroxysmal AF occurred in nearly 50% of patients, but only 27% of those with persistent AF converted to sinus rhythm at 6 mo.⁶⁰⁹

Sotalol was as effective as and better tolerated than slow-release quinidine sulfate for preventing recurrent AF in a multicenter study.⁶¹⁴ Moreover, sotalol was more effective in suppressing symptoms in patients who relapsed into AF, probably because it induced a slower ventricular rate. In patients with recurrent AF, propafenone was as effective as sotalol in maintaining sinus rhythm 1 y after cardioversion. Recurrences occurred later and were less symptomatic with either drug than with placebo.⁶¹⁵ Several studies found sotalol and the combination of quinidine and verapamil equally effective after cardioversion of AF, although ventricular arrhythmias (including torsades de pointes) were more frequent with quinidine.^{538,615} Sotalol should be avoided in patients with asthma, HF, renal insufficiency, or QT interval prolongation.

8.1.6.2. Drugs with unproven efficacy or no longer recommended

8.1.6.2.1. Digoxin. Available evidence 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 it does not usually reduce symptoms associated with recurrent paroxysmal AF.³⁰

8.1.6.2.2. Procainamide. No adequate studies of procainamide are available. Long-term treatment is frequently associated with development of antinuclear antibodies and is occasionally associated with arthralgia or agranulocytosis.

8.1.6.2.3. Quinidine. Quinidine has not been evaluated extensively in patients with paroxysmal AF but appears approximately as effective as class IC drugs.^{596,597,616} In one study,⁶⁰³ quinidine was less effective than propafenone (22% of patients free from AF 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 of 6 trials found quinidine superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients, respectively, over 1 y). However, 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%).⁶⁰⁹ In a registry analysis,⁶¹⁶ 6 of 570 patients less than 65 y old died shortly after restoration of sinus rhythm while taking quinidine. Up to 30% of patients taking quinidine experience intolerable side effects, most commonly diarrhea. Other investigators⁶¹⁴ found sotalol and quinidine equally effective for maintaining sinus rhythm after direct-current cardioversion of AF. Sotalol, but not quinidine, reduced heart rate in patients with recurrent AF, and there were fewer symptoms with sotalol.^{535,592,614,617-624}

In 2 European multicenter studies, the combination of quinidine plus verapamil was as effective as or superior to sotalol in preventing recurrences of paroxysmal and persistent AF. In the Suppression Of Paroxysmal Atrial Tachyarrhythmias (SOPAT) trial,⁶²⁵ 1033 patients (mean age 60 y, 62%

male) with frequent episodes of symptomatic paroxysmal AF either received high-dose quinidine (480 mg per day) plus verapamil (240 mg per day; 263 patients), low-dose quinidine (320 mg per day) plus verapamil (160 mg per day; 255 patients), sotalol (320 mg per day; 264 patients), or placebo (251 patients). Each of the active treatments was statistically superior to placebo and not different from one another with respect to time to first recurrence or drug discontinuation. The symptomatic AF burden also improved (3.4%, 4.5%, 2.9%, and 6.1% of days for each treatment group, respectively). Four deaths, 13 episodes of syncope, and 1 episode of ventricular tachycardia were documented, with 1 death and occurrence of VT related to quinidine plus verapamil. Sotalol and the quinidine-verapamil combination were associated with more severe side effects.

The Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial²⁸⁷ compared the efficacy and safety of the combination of quinidine plus verapamil (377 patients), sotalol (383 patients), and placebo (88 patients) in patients with persistent AF or following direct-current cardioversion, with daily transtelephonic monitoring for detection of recurrent AF. AF recurrence or death occurred in 572 patients (67%), and AF recurrence became persistent in 348 (41%). Over 1 y, recurrence rates were 83% with placebo, 67% with sotalol, and 65% with the combination of quinidine plus verapamil, the last mentioned statistically superior to placebo but not different from sotalol. Persistent AF occurred in 77%, 49%, and 38%, respectively, with the quinidine-verapamil combination superior to placebo and to sotalol. About 70% of AF recurrences were asymptomatic. Adverse events were comparable on sotalol and quinidine/verapamil, except that torsades de pointes was confined to the sotalol group. Therefore, the combination of quinidine plus verapamil appeared useful to prevent recurrent AF after cardioversion of persistent AF.

8.1.6.2.4. 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 recurrent AF. In one study, diltiazem reduced the number of AF episodes occurring in a 3-mo period by approximately 50%.⁶²⁶

8.1.7. Out-of-hospital initiation of antiarrhythmic drugs in patients with atrial fibrillation

A frequent issue related to pharmacological cardioversion of AF is whether to initiate antiarrhythmic drug therapy in hospital or on an outpatient basis. The major concern is the potential for serious adverse effects, including torsades de pointes (Table 21). With the exception of those involving low-dose oral amiodarone,⁵³³ virtually all studies of pharmacological cardioversion have involved hospitalized patients. However, one study⁶²⁷ provided a clinically useful approach with out-of-hospital patient-controlled conversion using class IC drugs (see Tables 6–8).

The 'pill-in-the-pocket' strategy consists of the self-administration of a single oral dose of drug shortly after the onset of symptomatic AF to improve quality of life, decrease hospital admission, and reduce cost.⁶²⁸ Recommendations for out-of-hospital initiation or intermittent use of antiarrhythmic drugs differ for patients with paroxysmal and persistent AF. In patients with paroxysmal AF, the

Table 21 Types of proarrhythmia during treatment with various antiarrhythmic drugs for AF or atrial flutter according to the Vaughan Williams classification

Ventricular proarrhythmia
Torsades de pointes (VW types IA and III drugs ^a)
Sustained monomorphic ventricular tachycardia (usually VW type IC drugs)
Sustained polymorphic ventricular tachycardia/VF without long QT (VW types IA, IC, and III drugs)
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)
Abnormalities of conduction or impulse formation
Acceleration of ventricular rate during AF (VW types IA and IC drugs)
Accelerated conduction over accessory pathway (digoxin, intravenous verapamil, or diltiazem ^b)
Sinus node dysfunction, atrioventricular block (almost all drugs)

Vaughan Williams (VW) classification of antiarrhythmic drugs from Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 1984;24:129–47.

AF indicates atrial fibrillation; VF, ventricular fibrillation.

^aThis complication is rare with amiodarone.

^bAlthough the potential for beta blockers to potentiate conduction across the accessory pathway is controversial, caution should also be exercised for the use of these agents in patients with AF associated with preexcitation.

aims are to terminate an episode or to prevent recurrence. In patients with persistent AF, the aims are to achieve pharmacological cardioversion of AF, obviating the need for direct-current cardioversion, or to enhance the success of direct-current cardioversion by lowering the defibrillation threshold and prevent early recurrence of AF.

In patients with lone AF without structural heart disease, class IC drugs may be initiated on an outpatient basis. For other selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease, 'pill-in-the-pocket' administration of propafenone and flecainide outside the hospital becomes an option once treatment has proved safe in hospital given the relative safety (lack of organ toxicity and low estimated incidence of proarrhythmia).^{181,557,629–631} Before these agents are initiated, however, a beta blocker or nondihydropyridine calcium channel antagonist is generally recommended to prevent rapid AV conduction in the event of atrial flutter.^{632–636} Unless AV node conduction is impaired, a short-acting beta blocker or nondihydropyridine calcium channel antagonist should be given at least 30 min before administration of a type IC antiarrhythmic agent to terminate an acute episode of AF, or the AV nodal blocking agents should be prescribed as continuous background therapy. Sudden death related to idiopathic ventricular fibrillation may occur in patients with the Brugada syndrome following administration of class I antiarrhythmic drugs even in patients with structurally normal hearts.^{637,638} Because termination of paroxysmal AF may be associated with bradycardia due to sinus node or AV node dysfunction, an initial conversion

trial should be undertaken in hospital before a patient is declared fit for outpatient 'pill-in-the-pocket' use of flecainide or propafenone for conversion of subsequent recurrences of AF. Table 22 lists other factors associated with proarrhythmic toxicity, including proarrhythmic effects, which vary according to the electrophysiological properties of the various drugs. For class IC agents, risk factors for proarrhythmia include female gender.

Few prospective data are available on the relative safety of initiating antiarrhythmic drug therapy in the outpatient versus inpatient setting, and the decision to initiate therapy out of hospital should be carefully individualized. The efficacy and safety of self-administered oral loading of flecainide and propafenone in terminating recent-onset AF outside of hospital were analyzed in 268 patients with minimal heart disease with hemodynamically well-tolerated recent-onset AF.⁶²⁷ Fifty-eight patients (22%) were excluded because of treatment failure or side effects. Using resolution of palpitations within 6 h after drug ingestion as the criterion of efficacy, treatment was successful in 534 episodes (94%), during 15-mo follow-up, with conversion occurring over a mean of 2 h. Compared with conventional care, the numbers of emergency department visits and hospitalizations were significantly reduced. Among patients with recurrences, treatment was effective in 84%, and adverse effects were reported by 7% of patients. Despite efficacy, 5% of patients dropped out of the study because of multiple recurrences, side effects (mostly nausea), or anxiety. Thus, the 'pill-in-the-pocket' approach appears feasible and safe for selected patients with AF, but the safety of this approach without previous inpatient evaluation remains uncertain.

As long as the baseline uncorrected QT interval is less than 450 ms, serum electrolytes are normal, and risk factors associated with class III drug-related proarrhythmia are considered (Table 23), sotalol may be initiated in outpatients with little or no heart disease. It is safest to start sotalol when the patient is in sinus rhythm. Amiodarone can also usually be given safely on an outpatient basis, even in patients with persistent AF, because it causes minimal depression of myocardial function and has low proarrhythmic potential,⁵⁶⁶ but in-hospital loading may be necessary for earlier restoration of sinus rhythm in patients with HF or other forms of hemodynamic compromise related to AF. Loading regimens typically call for administration of 600 mg daily for 4 wk⁵⁶⁶ or 1 g daily for 1 wk,⁵³¹ followed by lower maintenance doses. Amiodarone, class IA or IC agents, or sotalol can be associated with bradycardia requiring permanent pacemaker implantation⁶³⁹; this is more frequent with amiodarone, and amiodarone-associated bradycardia is more common in women than in men. Quinidine, procainamide, and disopyramide should not be started out of hospital. Currently, out-of-hospital initiation of dofetilide is not permitted. Transtelephonic monitoring or other methods of ECG surveillance may be used to monitor cardiac rhythm and conduction as pharmacological antiarrhythmic therapy is initiated in patients with AF. Specifically, the PR interval (when flecainide, propafenone, sotalol, or amiodarone are used), QRS duration (with flecainide or propafenone), and QT interval (with dofetilide, sotalol, or amiodarone) should be measured. As a general rule, antiarrhythmic drugs should be started at a relatively low dose and titrated based on response, and the ECG

Table 22 Factors predisposing to drug-induced ventricular proarrhythmia

VW types IA and III agents	VW type IC agents
Long QT interval (QTc greater than or equal to 460 ms)	Wide QRS duration (more than 120 ms)
Long QT interval syndrome	Concomitant VT
Structural heart disease, substantial LVH	Structural heart disease
Depressed LV function ^a	Depressed LV function ^a
Hypokalemia/hypomagnesemia ^a	
Female gender	
Renal dysfunction ^a	
Bradycardia ^a	Rapid ventricular response rate ^a
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 R-R sequences	
Rapid dose increase	Rapid dose increase
High dose (sotalol, dofetilide), drug accumulation ^a	High dose, drug accumulation ^a
Addition of drugs ^a	Addition of drugs ^a
1. Diuretics	1. Negative inotropic drugs
2. Other QT-prolonging antiarrhythmic drugs	
3. Nonantiarrhythmic drugs listed in http://www.torsades.org/	
Previous proarrhythmia	
After initiation of drug	
Excessive QT lengthening	Excessive (more than 150%) QRS widening

AF indicates atrial fibrillation; AV, atrioventricular; LV, left ventricular; LVH, left ventricular hypertrophy; QTc, corrected QT interval; VT, ventricular tachycardia.

Vaughan Williams (VW) classification of antiarrhythmic drugs from Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* 1984;24:129-47.⁴⁹⁷

^aSome of these factors may develop later after initiation of drug treatment. See Section 8.3.3.3 in the full-text guidelines for details.

Table 23 Pharmacological treatment before cardioversion in patients with persistent AF: Effects of various antiarrhythmic drugs on immediate recurrence, outcome of transthoracic direct-current shock, or both

Efficacy	Enhance conversion by DC shock and prevent IRAF ^a	Recommendation class	Level of evidence	Suppress SRAF and maintenance therapy class
Known	Amiodarone Flecainide Ibutilide Propafenone Sotalol	Ia	B	All drugs in recommendation class I (except ibutilide) plus beta blockers
Uncertain/unknown	Beta blockers Diltiazem Disopyramide Dofetilide Procainamide Verapamil	Ib	C	Diltiazem Dofetilide Verapamil

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

should be reassessed after each dose change. The heart rate should be monitored at approximately weekly intervals by checking the pulse rate, using an event recorder, or reading ECG tracings obtained at the office. The dose of other medication for rate control should be reduced when the rate slows after initiation of amiodarone and stopped if the rate slows excessively. Concomitant drug therapies (see *Table 19*) should be monitored closely, and both the patient and the physician should be alert to possible deleterious interactions. The doses of digoxin and warfarin, in particular, should usually be reduced upon initiation of amiodarone in anticipation of the rises in serum digoxin levels and INR that typically occur.

8.1.8. Drugs under development

To overcome the limited efficacy and considerable toxicity of available drugs for maintaining sinus rhythm, selective blockers of atrial ion channels and nonselective ion channel blockers are under development. Use of nonantiarrhythmic drugs, such as inhibitors of the renin-angiotensin system, n-3 polyunsaturated fatty acids, and statins, which might modify the underlying atrial remodeling, have not been extensively investigated for this purpose.⁶⁴⁰⁻⁶⁴⁵

8.1.8.1. Atrioselective agents. The finding that the ultra-rapid delayed rectifier (IKur) exists in atrial but not ventricular tissue opened the possibility that atrioselective

drugs without ventricular proarrhythmic toxicity could be developed for treatment of patients with AF.^{643,646} IKur blockers (NIP-142, RSD1235, AVE0118) prolong atrial refractoriness (left more than right) with no effect on ventricular repolarization and show strong atrial antiarrhythmic efficacy.^{642,644,645,647} AVE0118 is an IKur and Ito blocker that, unlike dofetilide, increases refractoriness in electrically remodeled atria, prolongs atrial wavelength, and converts persistent AF to sinus rhythm without disturbing intra-atrial conduction velocity or prolonging the QT interval.⁶⁴⁸

8.1.8.2. Nonselective ion channel-blocking drugs. Azimilide and dronedarone block multiple potassium, sodium, and calcium currents and prolong the cardiac action potential without reverse use-dependence.^{641-643,645}

Azimilide has a long elimination half-life (114 h), allowing for once-daily administration. In patients with paroxysmal SVT enrolled in 4 clinical trials, azimilide at doses of 100 and 125 mg daily prolonged time to recurrence of AF and atrial flutter^{647,649} and reduced symptoms associated with recurrence.⁶⁵⁰ Patients with ischemic heart disease and HF displayed greater efficacy than those without structural heart disease. In a placebo-controlled trial involving 3717 survivors of MI with LV systolic dysfunction,⁶⁵¹ azimilide, 100 mg daily, was associated with a 1-y mortality rate similar to placebo. Fewer patients in the azimilide group developed AF or new or worsening HF than those given placebo,⁶⁵¹ and more patients in the azimilide group converted from AF to sinus rhythm.⁶⁵² The major adverse effects of azimilide were severe neutropenia (less than 500 cells per microliter) in 0.9% and torsades de pointes in 0.5% of treated patients.⁶⁵¹

Dronedarone is a noniodinated amiodarone derivative.^{653,654} In a randomized, placebo-controlled study involving 204 patients undergoing cardioversion of persistent AF,⁶⁵⁵ dronedarone (800 mg daily) delayed first recurrence from 5.3 to 60 d. Higher doses (1200 and 1600 mg daily) were no more effective and associated with gastrointestinal side effects (diarrhea, nausea, and vomiting). To date, neither organ toxicity nor proarrhythmia has been reported. In 2 placebo-controlled trials, European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for Maintenance of Sinus Rhythm (EURIDIS)⁶⁵⁶ and American-Australian Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for Maintenance of Sinus Rhythm (ADONIS),⁶⁵⁷ dronedarone prolonged the time to first documented AF/atrial flutter recurrence and helped control the ventricular rate.

Tedisamil, an antianginal agent, blocks several potassium channels and causes a reverse rate-dependent QT-interval prolongation. Tedisamil (0.4 and 0.6 mg/kg) was superior to placebo for rapid conversion (within 35 min) of recent-onset AF or atrial flutter.⁶⁵⁸ The main side effects were pain at the injection site and ventricular tachycardia.

8.2. Direct-current cardioversion of atrial fibrillation and flutter

Recommendations

Class I

- (1) When a rapid ventricular response does not respond promptly to pharmacological measures for patients

with AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or HF, immediate R-wave synchronized direct-current cardioversion is recommended. (Level of Evidence: C)

- (2) Immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs. (Level of Evidence: B)
- (3) Cardioversion is recommended in patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after cardioversion, repeated direct-current cardioversion attempts may be made following administration of antiarrhythmic medication. (Level of Evidence: C)

Class IIa

- (1) Direct-current cardioversion can be useful to restore sinus rhythm as part of a long-term management strategy for patients with AF. (Level of Evidence: B)
- (2) Patient preference is a reasonable consideration in the selection of infrequently repeated cardioversions for the management of symptomatic or recurrent AF. (Level of Evidence: C)

Class III

- (1) Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple cardioversion procedures despite prophylactic antiarrhythmic drug therapy. (Level of Evidence: C)
- (2) Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia. (Level of Evidence: C)

8.2.1. Terminology

Direct-current cardioversion involves delivery of an electrical shock synchronized with the intrinsic activity of the heart by sensing the R wave of the ECG to ensure that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle.⁶⁵⁹ Direct-current 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 because R-wave synchronization is not feasible, but not for AF.

8.2.2. Technical aspects

Successful cardioversion of AF depends on the underlying heart disease and the current density delivered to the atrial myocardium. Current may be delivered through external chest wall electrodes or through an internal cardiac electrode. Although the latter technique has been considered superior to external countershocks in obese patients and in patients with obstructive lung disease, it has not been widely applied. The frequency of recurrent AF does not differ between the 2 methods.^{355,660-664}

The current density delivered to the heart by transthoracic electrodes depends on the defibrillator capacitor voltage, output waveform, size and position of the electrode paddles, and thoracic impedance. For a given paddle surface area, current density decreases with increasing impedance, related to the thickness and composition of the paddles, contact medium between electrodes and

skin, distance between paddles, body size, respiratory phase, number of shocks, and interval between shocks.⁶⁶⁵

Use of electrolyte-impregnated pads can minimize the electrical resistance between electrode and skin. Pulmonary tissue between paddles and the heart inhibits conduction, so shocks delivered during expiration or chest compression deliver higher energy to the heart. Large paddles lower impedance but may make current density in cardiac tissue insufficient; conversely, undersized paddles may cause injury due to excess current density. Animal experiments have shown that the optimum diameter approximates the cross-sectional area of the heart. There are no firm data regarding the best paddle size for cardioversion of AF, but a diameter of 8 to 12 cm⁶⁶⁵ is generally recommended.

Because the combination of high impedance and low energy reduces the success of cardioversion, measurement of impedance has been proposed to shorten the procedure and improve outcomes.^{666,667} Kerber *et al.*⁶⁶⁸ reported better efficacy by automatically increasing energy delivery when the impedance exceeded 70 ohms.

The output waveform also influences energy delivery during direct-current cardioversion. In a randomized trial, 77 patients treated with sinusoidal monophasic shocks had a cumulative success rate of 79% compared with 94% in 88 subjects cardioverted with rectilinear biphasic shocks, and the latter required less energy. In addition to rectilinear biphasic shocks, independent correlates of successful conversion were thoracic impedance and the duration of AF.⁶⁶⁹ For cardioversion of AF, a biphasic shock waveform has greater efficacy, requires fewer shocks and lower delivered energy, and results in less dermal injury than a monophasic shock waveform, and represents the present standard for cardioversion of AF.⁶⁷⁰

In their original description of cardioversion, Lown *et al.*^{659,671} recommended an anterior-posterior electrode configuration over anterior-anterior positioning, but others disagree.^{665,672,673} Anterior-posterior positioning allows current to reach a sufficient mass of atrial myocardium to achieve cardioversion of AF when the pathology involves both atria (as in patients with atrial septal defects or cardiomyopathy). A drawback of this configuration is the amount of pulmonary tissue separating the anterior paddle and the heart, particularly in patients with emphysema. Placing the anterior electrode to the left of the sternum reduces electrode separation. The paddles should be placed directly against the chest wall, under rather than over the breast tissue. Other paddle positions result in less current flow through crucial parts of the heart.⁶⁶⁵ In a randomized study involving 301 subjects undergoing elective external cardioversion, the energy required was lower and 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%).⁶⁷⁴ Animal experiments show a wide margin of safety between the energy required for cardioversion of AF and that associated with myocardial depression.^{675,676} Even without apparent myocardial damage, transient ST-segment elevation may appear on the ECG after cardioversion^{677,678} and blood levels of creatine kinase may rise. Serum troponin-T and troponin-I levels did not rise significantly in a study of 72 cardioversion attempts with average energy over 400 J (range 50 to 1280 J).⁶⁷⁹ In 10% of the patients, creatine kinase-MB levels rose

beyond levels attributable to skeletal muscle trauma, and this was related to energy delivered. Microscopic myocardial damage related to direct-current cardioversion has not been confirmed and is probably clinically insignificant.

8.2.3. Procedural aspects

Cardioversion should be performed with the patient under adequate general anesthesia in a fasting state. Short-acting anesthetic drugs or agents that produce conscious sedation are preferred to enable rapid recovery after the procedure; overnight hospitalization is seldom required.⁶⁸⁰ The electric shock should be synchronized with the QRS complex, triggered by monitoring the R wave with an appropriately selected ECG lead that also clearly displays atrial activation to facilitate assessment of outcome. The initial energy may be low for cardioversion of atrial flutter, but higher energy is required for AF. The energy output has traditionally been increased successively in increments of 100 J to a maximum of 400 J, but some physicians begin with higher energies to reduce the number of shocks and thus the total energy delivered. To avoid myocardial damage, some have suggested that the interval between consecutive shocks should be at least 1 min.⁶⁸¹ In 64 patients randomly assigned to initial monophasic waveform energies of 100, 200, or 360 J, high initial energy was significantly more effective than low levels (immediate success rates 14% with 100 J, 39% with 200 J, and 95% with 360 J, respectively), resulting in fewer shocks and less cumulative energy when 360 J was delivered initially.⁶⁸² These data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence, an initial energy of 200 J or greater is recommended. A similar recommendation to start with 200 J applies to biphasic waveforms, particularly when cardioverting patients with AF of long duration.⁶⁸³ External cardioversion of AF with a rectilinear biphasic waveform (99.1% of 1877 procedures in 1361 patients) was more effective than a monophasic sinusoidal waveform (92.4% of 2818 procedures in 2025 patients; *p* less than 0.001), but comparable for patients with atrial flutter (99.2% and 99.8%, respectively). The median successful energy level was 100 J with the biphasic waveform compared with 200 J with the monophasic waveform.⁶⁸⁴

8.2.4. Direct-current cardioversion in patients with implanted pacemakers and defibrillators

When appropriate precautions are taken, cardioversion of AF is safe in patients with implanted pacemaker or defibrillator devices. Pacemaker generators and defibrillators are designed with circuits protected against sudden external electrical discharges, but programmed data may be altered by current surges. Electricity conducted along an implanted electrode may cause endocardial injury and lead to a temporary or permanent increase in stimulation threshold, resulting in loss of ventricular capture. To ensure appropriate function, the implanted device should be interrogated and, if necessary, reprogrammed before and after cardioversion. Devices are typically implanted anteriorly, so the paddles used for external cardioversion should be positioned as distantly as possible, 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, and lower with the anterior-posterior electrode configuration and

with bipolar electrode systems.^{685,686} Low-energy internal cardioversion does not interfere with pacemaker function in patients with electrodes positioned in the RA, coronary sinus, or left pulmonary artery.⁶⁸⁷

8.2.5. Risks and complications of direct-current cardioversion of atrial fibrillation

The risks of direct-current cardioversion are mainly related to thromboembolism and arrhythmias. Thromboembolic events have been reported in 1% to 7% of patients not given prophylactic anticoagulation before cardioversion of AF.^{688,689} Prophylactic antithrombotic therapy is discussed below. (See Section 8.2.7, Prevention of Thromboembolism in Patients With Atrial Fibrillation Undergoing Cardioversion.)

Various benign arrhythmias, especially ventricular and supraventricular premature beats, bradycardia, and short periods of sinus arrest, may arise after cardioversion and commonly subside spontaneously.⁶⁹⁰ More dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may arise in the face of hypokalemia, digitalis intoxication, or improper synchronization.^{691,692} Serum potassium levels should be in the normal range for safe, effective cardioversion. Magnesium supplementation does not enhance cardioversion.⁶⁹³ Cardioversion is contraindicated in cases of digitalis toxicity because resulting ventricular tachyarrhythmia 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,⁶⁹⁴ so it is not routinely necessary to interrupt digoxin before elective cardioversion of AF. It is important, however, to exclude clinical and ECG signs of digitalis excess and delay cardioversion until a toxic state has been corrected, which usually requires withdrawal of digoxin for longer 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 this in mind so a transvenous or transcutaneous pacemaker can be used prophylactically.⁶⁹⁵

8.2.6. Pharmacological enhancement of direct-current cardioversion

Recommendations
Class Ila

- (1) Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent atrial fibrillation. (Level of Evidence: B)
- (2) In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure following prophylactic administration of antiarrhythmic medication. (Level of Evidence: C)

Class I Ib

- (1) For patients with persistent AF, administration of beta blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain. (Level of Evidence: C)

- (2) Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF. (Level of Evidence: C)
- (3) Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient. (Level of Evidence: C)

Although most recurrences of AF occur within the first month after direct-current cardioversion, research with internal atrial cardioversion⁶⁹⁶ and postconversion studies using transthoracic shocks⁶⁹⁷ have established several patterns of AF recurrence (Figure 17). In some cases, direct-current countershock fails to elicit even a single isolated sinus or ectopic atrial beat, tantamount to a high atrial defibrillation threshold. In others, AF recurs within a few minutes after a period of sinus rhythm,^{698,699} and recurrence after cardioversion is sometimes delayed for days or weeks.⁶⁹⁷ Complete shock failure and immediate recurrence occur in approximately 25% of patients undergoing direct-current cardioversion of AF, and subacute recurrences occur within 2 wk in almost an equal proportion.⁶⁹⁸

Restoration and maintenance of sinus rhythm are less likely when AF has been present for longer than 1 y than in patients with AF of shorter duration. The variation in immediate success rates for direct-current cardioversion from 70% to 99% in the literature^{617,682,684,700,701} is partly explained by differences in patient characteristics and the waveform used but also depends upon the definition of success, because the interval at which the result is evaluated ranges from moments to several days. Over time, the proportion of AF caused by rheumatic heart disease has declined, the average age of the AF population has increased,⁷⁰⁰⁻⁷⁰² and the incidences of lone AF have

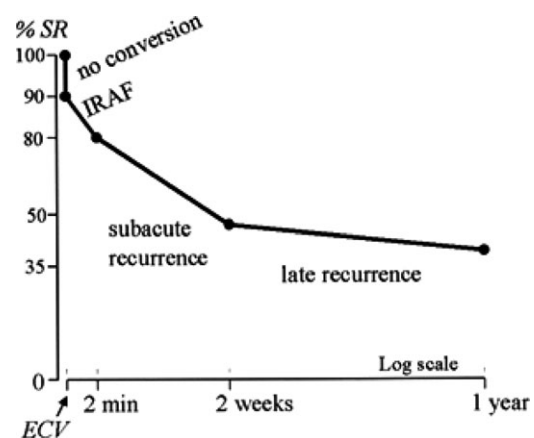


Figure 17 Hypothetical illustration of cardioversion failure. Three types of recurrences after electrical cardioversion of persistent atrial fibrillation (AF) are shown. The efficacy of drugs varies in enhancement of shock conversion and suppression of recurrences. Modified with permission from van Gelder IC, Tuinenburg AE, Schoonderwoerd BS, *et al*. Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation. *Am J Cardiol* 1999;84:147R-51R, with permission from Excerpta Medica Inc.⁷⁰⁴ ECV indicates external cardioversion; IRAF, immediate recurrence of AF defined as the first recurrence of AF after cardioversion; SR, sinus rhythm.

remained constant, making it difficult to compare the outcome of cardioversion across various studies.

In a large consecutive series of patients undergoing cardioversion of AF published in 1991, 24% were classified as having ischemic heart disease, 24% with rheumatic valvular disease, 15% with lone AF, 11% with hypertension, 10% with cardiomyopathy, 8% with nonrheumatic valvular disease, 6% with congenital heart disease, and 2% with hyperthyroidism.⁷⁰⁰ Seventy percent were in sinus rhythm 24 h after cardioversion. Multivariate analysis found a short duration of AF, atrial flutter, and younger age to be independent predictors of success, whereas LA enlargement, underlying organic heart disease, and cardiomegaly were associated with HF. A decade later, a study of 166 consecutive patients followed after first direct-current cardioversion found that short duration of AF, smaller LA size, and treatment with beta blockers, verapamil, or diltiazem were clinical predictors of both initial success and maintenance of sinus rhythm.⁷⁰³ In another series of 100 patients, the primary success rate assessed 3 d after cardioversion was 86%,⁷⁰¹ increasing to 94% when the procedure was repeated during treatment with quinidine or disopyramide. Only 23% of patients remained in sinus rhythm after 1 y, however, and 16% remained after 2 y. In those who relapsed to AF, repeated cardioversion after administration of antiarrhythmic medication resulted in sinus rhythm in 40% and 33% after 1 and 2 y, respectively. For patients who relapsed again, a third cardioversion resulted in sinus rhythm in 54% after 1 y and 41% after 2 y. Thus, sinus rhythm can be restored in a substantial proportion of patients by direct-current cardioversion, but the rate of relapse is high without concomitant antiarrhythmic drug therapy⁷⁰⁴ (Figure 17).

When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic medication therapy are to increase the likelihood of success (e.g., by lowering the cardioversion threshold) and to prevent recurrent AF. Enhanced efficacy may involve multiple mechanisms, such as decreasing the energy required to achieve cardioversion, prolonging atrial refractory periods, and suppressing atrial ectopy that may cause early recurrence of AF.^{580,705} Antiarrhythmic medications may be initiated out of hospital or in hospital immediately prior to direct-current cardioversion. (See Section 8.1.7, Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients With Atrial Fibrillation.) The risks of pharmacological treatment include the possibility of paradoxically increasing the defibrillation threshold, as described with flecainide,⁶⁰⁰ accelerating the ventricular rate when class IA or IC drugs are given without an AV nodal blocking agent,^{632-636,706} and inducing ventricular arrhythmias (see Table 21).

Prophylactic drug therapy to prevent early recurrence of AF should be considered individually for each patient. Patients with lone AF of relatively short duration are less prone to early recurrence of AF than are those with heart disease and longer AF duration, who therefore stand to gain more from prophylactic administration of antiarrhythmic medication. Pretreatment with pharmacological agents is most appropriate in patients who fail to respond to direct-current cardioversion and in those who develop immediate or subacute recurrence of AF. In patients with late recurrence and those undergoing initial cardioversion of persistent AF, pretreatment is optional. Antiarrhythmic drug therapy is recommended in conjunction with a

second cardioversion attempt, particularly when early relapse has occurred. Additional cardioversion, beyond a second attempt, is of limited value and should be reserved for carefully selected patients. Infrequently repeated cardioversions may be acceptable in patients who are highly symptomatic upon relapse to AF.

Specific Pharmacological Agents for Prevention of Recurrent AF in Patients Undergoing Electrical Cardioversion

8.2.6.1. Amiodarone. In patients with persistent AF, treatment with amiodarone for 6 wk before and after cardioversion increased the conversion rate and the likelihood of maintaining sinus rhythm and reduced supraventricular ectopic activity that may trigger recurrent AF.⁵⁷⁹ Prophylactic treatment with amiodarone was also effective when an initial attempt at direct-current cardioversion had failed.^{531,569} In patients with persistent AF randomly assigned to treatment with carvedilol, amiodarone, or placebo for 4 wk before direct-current cardioversion, the 2 drugs yielded similar cardioversion rates, but amiodarone proved superior at maintaining sinus rhythm after conversion.⁷⁰⁷

8.2.6.2. Beta-adrenergic antagonists. Although beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, they may reduce subacute recurrences.⁵⁸³

8.2.6.3. Nondihydropyridine calcium channel antagonists. Therapy with calcium-channel antagonists prior to electrical cardioversion of AF has yielded contradictory results. Several studies found that verapamil^{708,709} reduced immediate or early recurrences of AF. On the other hand, verapamil and diltiazem may increase AF duration, shorten refractoriness, and increase the spatial dispersion of refractoriness leading to more sustained AF.^{710,711} In patients with persistent AF, the addition of verapamil to class I or class II drugs can prevent immediate recurrence after cardioversion,⁷¹² and prophylaxis against subacute recurrence was enhanced when this combination was given for 3 d before and after cardioversion.^{713,714} Verapamil also reduced AF recurrence when a second cardioversion was performed after early recurrence of AF.⁷¹⁴ In a comparative study,⁷¹⁵ amiodarone and diltiazem were more effective than digoxin for prevention of early recurrence, whereas at 1 mo the recurrence rate was lower with amiodarone (28%) than with diltiazem (56%) or digoxin (78%). In patients with persistent AF, treatment with verapamil 1 mo before and after direct-current cardioversion did not improve the outcome of cardioversion.⁷¹⁶

8.2.6.4. Quinidine. A loading dose of quinidine (1200 mg orally 24 h before direct-current cardioversion) significantly reduced the number of shocks and the energy required in patients with persistent AF. Quinidine prevented immediate recurrence in 25 cases, whereas recurrence developed in 7 of 25 controls.⁶⁹⁸ When quinidine (600 to 800 mg 3 times daily for 2 d) failed to convert the rhythm, there was no difference in defibrillation threshold between patients randomized to continue or withdraw the drug.⁶¹⁷

8.2.6.5. Type IC antiarrhythmic agents. In-hospital treatment with oral propafenone started 2 d before direct-current cardioversion decreases early recurrence of AF after shock, thus allowing more patients to be discharged from the hospital with sinus rhythm. Compared with placebo, propafenone did not influence either the mean

defibrillation threshold or the rate of conversion (shock efficacy 84% vs. 82%, respectively) but suppressed immediate recurrences (within 10 min), and 74% versus 53% of patients were in sinus rhythm after 2 d.⁵²² In patients with persistent AF, pretreatment with intravenous flecainide had no significant effect on the success of direct-current cardioversion.⁷¹⁷

8.2.6.6. Type III Antiarrhythmic agents. Controlled studies are needed to determine the most effective treatment of immediate and subacute recurrences of AF. Type III antiarrhythmic drugs may suppress subacute recurrences less effectively than late recurrences of AF (Table 23). Available data suggest that starting pharmacological therapy and establishing therapeutic plasma drug concentrations before direct-current cardioversion enhance immediate success and suppress early recurrences. After cardioversion to sinus rhythm, patients receiving drugs that prolong the QT interval should be monitored in the hospital for 24 to 48 h to evaluate the effects of heart rate slowing and allow for prompt intervention in the event torsades de pointes develops.

In randomized studies of direct-current cardioversion, patients pretreated with ibutilide were more often converted to sinus rhythm than untreated controls, and those in whom cardioversion initially failed could more often be converted when the procedure was repeated after treatment with ibutilide.^{556,718} Ibutilide was more effective than verapamil in preventing immediate recurrence of AF.⁷⁰⁵

8.2.7. Prevention of thromboembolism in patients with atrial fibrillation undergoing cardioversion

Recommendations

Class I

- (1) For patients with AF of 48-h duration or longer, or when the duration of AF is unknown, anticoagulation (INR 2.0 to 3.0) is recommended for at least 3 wk prior to and 4 wk after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. (Level of Evidence: B)
- (2) For patients with AF of more than 48-h duration requiring immediate cardioversion because of hemodynamic instability, heparin should be administered concurrently (unless contraindicated) by an initial intravenous bolus injection followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the reference control value. Thereafter, oral anticoagulation (INR 2.0 to 3.0) should be provided for at least 4 wk, as for patients undergoing elective cardioversion. Limited data support subcutaneous administration of low-molecular-weight heparin in this indication. (Level of Evidence: C)
- (3) For patients with AF of less than 48-h duration associated with hemodynamic instability (angina pectoris, MI, shock, or pulmonary edema), cardioversion should be performed immediately without delay for prior initiation of anticoagulation. (Level of Evidence: C)

Class IIa

- (1) During the first 48 h after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism. (Level of Evidence: C)

- (2) As an alternative to anticoagulation prior to cardioversion of AF, it is reasonable to perform TEE in search of thrombus in the LA or LAA. (Level of Evidence: B) 2a. For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (e.g., initiate by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value until oral anticoagulation has been established with a vitamin K antagonist (e.g., warfarin), as evidenced by an INR equal to or greater than 2.0.). (Level of Evidence: B) Thereafter, oral anticoagulation (INR 2.0 to 3.0) is reasonable for a total anticoagulation period of at least 4 wk, as for patients undergoing elective cardioversion. (Level of Evidence: B)

Limited data are available to support the subcutaneous administration of a low-molecular-weight heparin in this indication. (Level of Evidence: C) 2b. For patients in whom thrombus is identified by TEE, oral anticoagulation (INR 2.0 to 3.0) is reasonable for at least 3 wk prior to and 4 wk after restoration of sinus rhythm, and a longer period of anticoagulation may be appropriate even after apparently successful cardioversion, because the risk of thromboembolism often remains elevated in such cases. (Level of Evidence: C)

- (3) For patients with atrial flutter undergoing cardioversion, anticoagulation can be beneficial according to the recommendations as for patients with AF. (Level of Evidence: C)

Randomized studies of antithrombotic therapy are lacking for patients undergoing cardioversion of AF or atrial flutter, but in case-control series, the risk of thromboembolism was between 1% and 5%.^{689,719} The risk was near the low end of this spectrum when anticoagulation (INR 2.0 to 3.0) was given for 3 to 4 wk before and after conversion.^{54,181,695} It is now common practice to administer anticoagulant drugs when preparing patients with AF of more than 2-d duration for cardioversion. Manning *et al.*³⁰⁴ suggested that TEE might be used to identify patients without LAA thrombus who do not require anticoagulation, but a subsequent investigation³²⁴ and meta-analysis found this approach to be unreliable.⁷²⁰

If most AF-associated strokes result from embolism of stasis-induced thrombus from the LAA, then restoration and maintenance of atrial contraction should logically reduce thromboembolic risk. LV function can also improve after cardioversion,⁷²¹ potentially lowering embolic risk and improving cerebral hemodynamics.⁷²² There is no evidence, however, that cardioversion followed by prolonged maintenance of sinus rhythm effectively reduces thromboembolism in AF patients. Conversion of AF to sinus rhythm results in transient mechanical dysfunction of the LA and LAA⁴¹⁷ known as 'stunning,' which can occur after spontaneous, pharmacological,^{723,724} or electrical⁷²⁴⁻⁷²⁶ conversion of AF or after radiofrequency catheter ablation of atrial flutter²²⁶ and which may be associated with SEC.⁴¹⁷ Recovery of mechanical function may be delayed for several weeks, depending in part on the duration of AF before conversion.^{191,727,728} This could explain why some patients without demonstrable LA thrombus on TEE before cardioversion subsequently experience thromboembolic

events.³²⁴ Presumably, thrombus forms during the period of stunning and is expelled after the return of mechanical function, explaining the clustering of thromboembolic events during the first 10 d after cardioversion.²¹²

Patients with AF or atrial flutter in whom LAA thrombus is identified by TEE are at high risk of thromboembolism and should be anticoagulated for at least 3 wk prior to and 4 wk after pharmacological or direct-current cardioversion. In a multicenter study, 1222 patients with either AF persisting longer than 2 d or atrial flutter and previous AF⁷²⁹ were randomized to a TEE-guided or conventional strategy. In the group undergoing TEE, cardioversion was postponed when thrombus was identified, and warfarin was administered for 3 wk before TEE was repeated to confirm resolution of thrombus. Anticoagulation with heparin was used briefly before cardioversion and with warfarin for 4 wk after cardioversion. The other group received anticoagulation for 3 wk before and 4 wk after cardioversion without intercurrent TEE. Both approaches were associated with comparably low risks of stroke (0.81% with the TEE approach and 0.50% with the conventional approach) after 8 wk, there were no differences in the proportion of patients achieving successful cardioversion, and the risk of major bleeding did not differ significantly. The clinical benefit of the TEE-guided approach was limited to saving time before cardioversion.

Anticoagulation is recommended for 3 wk prior to and 4 wk 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 deliver therapeutic anticoagulation, but intravenous unfractionated heparin or subcutaneous injection of a low-molecular-weight heparin should be initiated before cardioversion by 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 with or without symptoms and on the 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. Pooled data from 32 studies of cardioversion of AF or atrial flutter suggest that 98% of clinical thromboembolic events occur within 10 d.²¹² These data, not yet verified by prospective studies, support administration of an anticoagulant for at least 4 wk after cardioversion, and continuation of anticoagulation for a considerably longer period may be warranted even after apparently successful cardioversion.

Stroke or systemic embolism has been reported in patients with atrial flutter undergoing cardioversion,⁷³⁰⁻⁷³² 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.^{600,733}

8.3. Maintenance of sinus rhythm

Recommendations

Class I

Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)

Class IIa

- (1) Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (Level of Evidence: C)
- (2) Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (Level of Evidence: C)
- (3) Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. (Level of Evidence: C)
- (4) In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. (Level of Evidence: B)
- (5) Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with class III drug-related proarrhythmia are not present. (Level of Evidence: C)
- (6) Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement. (Level of Evidence: C)

Class III

- (1) Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. (Level of Evidence: A)
- (2) Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (Level of Evidence: C)

8.3.1. Pharmacological therapy

8.3.1.1. Goals of treatment. Whether paroxysmal or persistent, AF is a chronic disorder, and recurrence at some point is likely in most patients^{704,734,735} (see Figure 13). Many patients eventually need prophylactic antiarrhythmic drug therapy to maintain sinus rhythm, suppress symptoms, improve exercise capacity and hemodynamic function, and prevent tachycardia-induced cardiomyopathy due to AF. Because factors that predispose to recurrent AF (advanced age, HF, hypertension, LA enlargement, and LV dysfunction) are risk factors for thromboembolism, the risk of stroke may not be reduced by correction of the rhythm disturbance. It is not known whether maintenance of sinus rhythm prevents thromboembolism, HF, or death in patients with a history of AF.^{736,737} Trials in which rate- versus rhythm-control strategies were compared in patients with persistent and paroxysmal AF^{293,294,296,343,344} found no reduction in death, disabling stroke, hospitalizations, new

arrhythmias, or thromboembolic complications in the rhythm-control group.²⁹⁶ Pharmacological maintenance of sinus rhythm may reduce morbidity in patients with HF,^{501,738} but one observational study demonstrated that serial cardioversion in those with persistent AF did not avoid complications.⁷³⁹ Pharmacological therapy to maintain sinus rhythm is indicated in patients who have troublesome symptoms related to paroxysmal AF or recurrent AF after cardioversion who can tolerate antiarrhythmic drugs and have a good chance of remaining in sinus rhythm over an extended period (e.g., young patients without organic heart disease or hypertension, a short duration of AF, and normal LA size).^{293,740} When antiarrhythmic medication does not result in symptomatic improvement or causes adverse effects, however, it should be abandoned.

8.3.1.2. Endpoints in antiarrhythmic drug studies. 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; endpoints vary, and few studies meet current standards of good clinical practice. The arrhythmia burden and quality of life have not been assessed consistently. In studies of patients with paroxysmal AF, the time to first recurrence, number of recurrences over a specified interval, proportion of patients without recurrence during follow-up, and combinations of these data have been reported. The proportion of patients in sinus rhythm during follow-up is a less useful endpoint in studies of paroxysmal rather than persistent AF. Most studies of persistent AF involved antiarrhythmic drug therapy administered before or after direct-current cardioversion. Because of clustering of recurrences in the first few weeks after cardioversion,^{697,713} the median time to first recurrence detected by transtelephonic monitoring may not differ between 2 treatment strategies. Furthermore, because recurrent AF tends to persist, neither the interval between recurrences nor the number of episodes in a given period represents a suitable endpoint unless a serial cardioversion strategy is employed. Given these factors, the appropriate endpoints for evaluation of treatment efficacy in patients with paroxysmal and persistent AF have little in common. This hampers comparative evaluation of treatments aimed at maintenance of sinus rhythm in cohorts containing patients with both patterns of AF, and studies of mixed cohorts therefore do not contribute heavily to these guidelines. The duration of follow-up varied considerably among studies and was generally insufficient to permit meaningful extrapolation to years of treatment in what is often a lifelong cardiac rhythm disorder.

Recurrence of AF is not equivalent to treatment failure. In several studies,^{594,598} patients with recurrent AF often chose to continue antiarrhythmic treatment, perhaps because episodes of AF became less frequent, briefer, or less symptomatic. A reduction in arrhythmia burden may therefore constitute therapeutic success for some patients, while to others any recurrence of AF may seem intolerable. Assessment based upon time to recurrence in patients with paroxysmal AF or upon the number of patients with persistent AF who sustain sinus rhythm after cardioversion may overlook potentially valuable treatment strategies. Available studies are heterogeneous in other respects as well. The efficacy of treatment for atrial flutter and AF is usually not reported separately. Underlying heart disease or extracardiac disease is present in 80% of patients with

persistent AF, but this is not always described in detail. It is often not clear when patients first experienced AF or whether AF was persistent, and the frequencies of previous AF episodes and cardioversions are not uniformly described. Most controlled trials of antiarrhythmic drugs included few patients at risk of drug-induced HF, proarrhythmia, or conduction disturbances, and this should be kept in mind in applying the recommendations below.

The AFFIRM substudy investigators found that with AF recurrence, if one is willing to cardiovert the rhythm and keep the patient on the same antiarrhythmic drug, or cardiovert the rhythm and treat the patient with a different antiarrhythmic drug, about 80% of all patients will be in sinus rhythm by the end of 1 y.⁵⁷⁰

8.3.1.3. Predictors of recurrent AF. Most patients with AF, except those with postoperative or self-limited AF secondary to transient or acute illness, eventually experience recurrence. Risk factors for frequent recurrence of paroxysmal AF (more than 1 episode per month) include female gender and underlying heart disease.⁷⁴¹ In one study of patients with persistent AF, the 4-y arrhythmia-free survival rate was less than 10% after single-shock direct-current cardioversion without prophylactic drug therapy.⁷³⁵ Predictors of recurrences within that interval included hypertension, age over 55 y, and AF duration longer than 3 mo. Serial cardioversions and prophylactic drug therapy resulted in freedom from recurrent AF in approximately 30% of patients,⁷³⁵ and with this approach predictors of recurrence included age over 70 y, AF duration beyond 3 mo, and HF.⁷³⁵ Other risk factors for recurrent AF include LA enlargement and rheumatic heart disease.

8.3.2. General approach to antiarrhythmic drug therapy

Before administering any antiarrhythmic agent, reversible precipitants of AF should be identified and corrected. Most are related to coronary or valvular heart disease, hypertension, or HF. Patients who develop HF in association with alcohol intake should abstain from alcohol consumption. Indefinite antiarrhythmic treatment is seldom prescribed after a first episode, although a period of several weeks may help stabilize sinus rhythm after cardioversion. Similarly, patients experiencing breakthrough arrhythmias may not require a change in antiarrhythmic drug therapy when recurrences are infrequent and mild. Beta-adrenergic antagonist medication may be effective in patients who develop AF only during exercise, but a single, specific inciting cause rarely accounts for all episodes of AF, and the majority of patients do not sustain sinus rhythm without antiarrhythmic therapy. Selection of an appropriate agent is based first on safety, tailored to whatever underlying heart disease may be present, considering the number and pattern of prior episodes of AF.⁷⁴²

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 therapies. 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 theoretical choice. In that situation, flecainide and amiodarone represent secondary and tertiary treatment options, respectively, 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 represents a less appealing selection. Vagally induced AF can occur by itself, but more typically it is part of the overall patient profile. In patients with nocturnal AF, the possibility of sleep apnea should be considered (see *Figure 15*).

When treatment with a single antiarrhythmic drug fails, combinations may be tried. Useful combinations include a beta blocker, sotalol, or amiodarone with a class IC agent. The combination of a calcium channel blocker, such as diltiazem, with a class IC agent, such as flecainide or propafenone, is advantageous in some patients. A drug that is initially safe may become proarrhythmic if coronary disease or HF develops or if the patient begins other medication that exerts a proarrhythmic interaction. Thus, the patient should be alerted to the potential significance of such symptoms as syncope, angina, or dyspnea and warned about the use of noncardiac drugs that might prolong the QT interval. A useful source of information on this topic is the Internet site <http://www.torsades.org>.

The optimum method for monitoring antiarrhythmic drug treatment varies with the agent involved as well as with patient factors. Prospectively acquired data on upper limits of drug-induced prolongation of QRS duration or QT interval are not available. Given recommendations represent the consensus of the writing committee. With class IC drugs, prolongation of the QRS interval should not exceed 50%. Exercise testing may help detect QRS widening that occurs only at rapid heart rates (use-dependent conduction slowing). For class IA or class III drugs, with the possible exception of amiodarone, the corrected QT interval in sinus rhythm should be kept 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 assessment of LV function is indicated, especially when clinical HF develops during treatment of AF.

8.3.3. Selection of antiarrhythmic agents in patients with cardiac diseases

Pharmacological management algorithms to maintain sinus rhythm in patients with AF (see *Figures 13–16*) and applications in specific cardiac disease states are based on available evidence and extrapolated from experience with these agents in other situations.

8.3.3.1. Heart failure. Patients with HF are particularly prone to the ventricular proarrhythmic effects of antiarrhythmic drugs because of myocardial vulnerability and electrolyte imbalance. Randomized trials have demonstrated the safety of amiodarone and dofetilide (given separately) in patients with HF,^{501,743} and these are the recommended drugs for maintenance of sinus rhythm in patients with AF in the presence of HF.

In a subgroup analysis of data from the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) study,⁷³⁸ amiodarone reduced the incidence of AF over 4 y in patients with HF to 4% compared with 8% with placebo.

Conversion to sinus rhythm occurred in 31% of patients on amiodarone versus 8% with placebo and was associated with significantly better survival.

The Danish Investigations of Arrhythmias and Mortality on Dofetilide in Heart Failure (DIAMOND-CHF) trial randomized 1518 patients with symptomatic HF. In a substudy of 506 patients with HF and AF or atrial flutter,^{501,588} dofetilide (0.5 mg twice daily initiated in hospital) increased the probability of sinus rhythm after 1 y to 79% compared with 42% with placebo. In the dofetilide group, 44% of patients with AF converted to sinus rhythm compared with 39% in the placebo group. Dofetilide had no effect on mortality, but the combined endpoint of all-cause mortality and HF hospitalization was lower in the treated group than with placebo.^{501,588} Torsades de pointes developed in 25 patients treated with dofetilide (3.3%), and three-quarters of these events occurred within the first 3 d of treatment.

Patients with LV dysfunction and persistent AF should be treated with beta blockers and ACE inhibitors and/or angiotensin II receptor antagonists, because these agents help control the heart rate, improve ventricular function, and prolong survival.^{744–747} In patients with HF or LV dysfunction post-MI, ACE inhibitor therapy reduced the incidence of AF.^{36,748,749} In a retrospective analysis of patients with LV dysfunction in the SOLVD trials,³⁸ enalapril reduced the incidence of AF by 78% relative to placebo. In the CHARM and Val-HeFT studies, angiotensin II receptor antagonists given in combination with ACE inhibitors were superior to ACE inhibitors alone for prevention of AF. A post hoc analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS II), however, found no impact of bisoprolol on survival or hospitalization for HF in patients with AF.⁷⁵⁰ In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN)⁷⁵¹ and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials,⁷⁵² AF and atrial flutter were more common in the placebo groups than in patients treated with carvedilol. Retrospective analysis of patients in the U.S. Carvedilol Heart Failure Trial program with AF complicating HF⁷⁵³ suggested that carvedilol improved LV ejection fraction. In a study by Khand *et al.*,⁷⁵⁴ the combination of carvedilol and digoxin reduced symptoms, improved ventricular function, and improved ventricular rate control compared with either agent alone.

8.3.3.2. Coronary artery disease. In stable patients with CAD, beta blockers may be considered first, although their use is supported by only 2 studies^{583,587} and data on efficacy for maintenance of sinus rhythm in patients with persistent AF after cardioversion are not convincing.⁵⁸³ When antiarrhythmic therapy beyond beta blockers is needed for control of AF in survivors of acute MI, several randomized trials have demonstrated that sotalol,⁷⁵⁵ amiodarone,^{756,757} dofetilide,⁷⁵⁸ and azimilide⁶⁵¹ have neutral effects on survival. Sotalol has substantial beta-blocking activity and may be the preferred initial antiarrhythmic agent in patients with AF who have ischemic heart disease, because it is associated with less long-term toxicity than amiodarone. Amiodarone increases the risk of bradyarrhythmia requiring permanent pacemaker implantation in elderly patients with AF who have previously sustained MI⁷⁵⁹ but may be preferred over sotalol in patients with HF.^{755–757} Neither flecainide nor propafenone is recommended in these situations, but quinidine, procainamide, and disopyramide may be considered as

third-line choices in patients with coronary disease. The Danish Investigations of Arrhythmias and Mortality on Dofetilide in Myocardial Infarction (DIAMOND-MI) trial⁷⁵⁸ involved selected post-MI patients in whom the antiarrhythmic benefit of dofetilide balanced the risk of proarrhythmic toxicity, making this a second-line antiarrhythmic agent. In patients with coronary disease who have not developed MI or HF, however, it is uncertain whether the benefit of dofetilide outweighs risk, and more experience is needed before this drug can be recommended even as a second-line agent in such patients.

8.3.3.3. Hypertensive heart disease. Hypertension is the most prevalent and potentially modifiable independent risk factor for the development of AF and its complications, including thromboembolism.^{760,761} Blood pressure control may become an opportune strategy for prevention of AF. Patients with LVH may face an increased risk of torsades de pointes related to early ventricular afterdepolarizations.^{742,762,763} Thus, class IC agents and amiodarone are preferred over type IA and type III antiarrhythmic agents as first-line therapy. In the absence of ischemia or LVH, propafenone or flecainide is a reasonable choice. Proarrhythmia with one agent does not predict this response to another, and patients with LVH who develop torsades de pointes during treatment with a class III agent may tolerate a class IC agent. Amiodarone prolongs the QT interval but carries a very low risk of ventricular proarrhythmia. Its extracardiac toxicity relegates it to second-line therapy in these individuals, but it becomes a first-line agent in the face of substantial LVH. When amiodarone and sotalol either fail or are inappropriate, disopyramide, quinidine, or procainamide represents a reasonable alternative.

Beta blockers may be the first line of treatment to maintain sinus rhythm in patients with MI, HF, and hypertension. Compared with patients with lone AF, those with hypertension are more likely to maintain sinus rhythm after cardioversion of persistent AF when treated with a beta blocker.⁷⁶⁴ Drugs modulating the renin-angiotensin system reduce structural cardiac changes,⁷⁶⁵ and ACE inhibition was associated with a lower incidence of AF compared with calcium channel blockade in patients with hypertension during 4.5 y of follow-up in a retrospective, longitudinal cohort study from a database of 8 million patients in a managed care setting.⁴² In patients at increased risk of cardiovascular events, therapy with either the ACE inhibitor ramipril⁷⁶⁶⁻⁷⁶⁸ or angiotensin receptor antagonist losartan^{769,770} lowered the risk of stroke. A similar benefit has been reported with perindopril in a subset of patients with AF treated for prevention of recurrent stroke.⁷⁷¹ New-onset AF and stroke were significantly reduced by losartan compared with atenolol in hypertensive patients with ECG-documented LVH, despite a similar reduction of blood pressure.⁴¹ The benefit of losartan was greater in patients with AF than those with sinus rhythm for the primary composite endpoint (cardiovascular mortality, stroke, and MI) and for cardiovascular mortality alone.⁷⁷² Presumably, the beneficial effects of beta blockers and drugs modulating the renin-angiotensin system are at least partly related to lower blood pressure.

8.3.4. Nonpharmacological therapy for atrial fibrillation

The inconsistent efficacy and potential toxicity of antiarrhythmic drug therapies have stimulated exploration of a

wide spectrum of alternative nonpharmacological therapies for the prevention and control of AF.

8.3.4.1. Surgical ablation. Over the past 25 y, surgery has contributed to understanding of both the anatomy and electrophysiology of commonly encountered arrhythmias, including the WPW syndrome, AV nodal reentry, ventricular tachycardia, and atrial tachycardia. A decade of research in the 1980s demonstrated the critical elements necessary to cure AF surgically, including techniques that entirely eliminate macroreentrant circuits in the atria while preserving sinus node and atrial transport functions. The surgical approach was based on the hypothesis that reentry is the predominant mechanism responsible for the development and maintenance of AF,⁷⁷³ leading to the concept that atrial incisions at critical locations would create barriers to conduction and prevent sustained AF. The procedure developed to accomplish these goals was based on the concept of a geographical maze, accounting for the term 'maze' procedure used to describe this type of cardiac operation.⁷⁷⁴

Since its introduction, the procedure has gone through 3 iterations (maze I, II, and III) using cut-and-sew techniques that ensure transmural lesions to isolate the PV, connect these dividing lines to the mitral valve annulus, and create electrical barriers in the RA that prevent macroreentrant rhythms—atrial flutter or AF—from becoming sustained.⁷⁷⁵ Success rates of around 95% over 15 y of follow-up have been reported in patients undergoing mitral valve surgery.⁷⁷⁶ Other studies suggest success rates around 70%.⁷⁷⁷ Atrial transport function is maintained and, when combined with amputation or obliteration of the LAA, postoperative thromboembolic events are substantially reduced. Risks include death (less than 1% when performed as an isolated procedure), the need for permanent pacing (with right-sided lesions), recurrent bleeding requiring reoperation, impaired atrial transport function, delayed atrial arrhythmias (especially atrial flutter), and atrioesophageal fistula.

Variations of the maze procedure have been investigated at several centers to determine the lesion sets necessary for success. Studies in patients with persistent AF have demonstrated the importance of complete lesions that extend to the mitral valve annulus; electrical isolation of the PV alone is associated with a lower success rate. Bipolar radiofrequency,⁷⁷⁸ cryoablation, and microwave energy have been used as alternatives to the 'cut-and-sew' technique. In one study, maintenance of sinus rhythm following the maze procedure in patients with AF was associated with improvement in some aspects of quality of life.³⁴⁸

Despite its high success rate, the maze operation has not been widely adopted other than for patients undergoing cardiac surgery because of the need for cardiopulmonary bypass. A wide variety of less invasive modifications are under investigation, including thoracoscopic and catheter-based epicardial techniques.⁷⁷⁷ If the efficacy of these adaptations approaches that of the endocardial maze procedure and they can be performed safely, they may become acceptable alternatives for a larger proportion of patients with AF.

8.3.4.2. Catheter ablation. Early radiofrequency catheter ablation techniques emulated the surgical maze procedure by introducing linear scars in the atrial endocardium.⁷⁷⁹ While the success rate was approximately 40% to 50%, a relatively high complication rate diminished enthusiasm for this approach.¹⁰⁵ The observation that potentials arising

in or near the ostia of the PV often provoked AF, and demonstration that elimination of these foci abolished AF escalated enthusiasm for catheter-based ablation.¹⁰⁵ Initially, areas of automaticity within the PV were targeted, and in a series of 45 patients with paroxysmal AF, 62% became free of symptomatic AF over a mean follow-up of 8 mo, but 70% required multiple procedures.¹⁰⁵ In another study, the success rate was 86% over a 6-mo follow-up.⁷⁸⁰ Subsequent research has demonstrated that potentials may arise in multiple regions of the RA and LA, including the LA posterior wall, superior vena cava, vein of Marshall, crista terminalis, interatrial septum, and coronary sinus,¹⁰⁹ and modification of the procedures has incorporated linear LA ablation, mitral isthmus ablation, or both for selected patients.⁷⁸¹

The technique of ablation has continued to evolve from early attempts to target individual ectopic foci within the PV to circumferential electrical isolation of the entire PV musculature. In a series of 70 patients, 73% were free from AF following PV isolation without antiarrhythmic medications during a mean follow-up of 4 mo, but 29 patients required a second procedure to reach this goal. However, postablation AF may occur transiently in the first 2 mo.⁷⁸² Advances involving isolation of the PV at the antrum using a circular mapping catheter, guided by intracardiac echocardiography, have reportedly yielded approximately 80% freedom of recurrent AF or atrial flutter after the first 2 mo in patients with paroxysmal AF,⁷⁸³ but success rates were lower in patients with cardiac dysfunction.⁷⁸⁴ Still another approach^{785,786} uses a nonfluoroscopic guidance system and radiofrequency energy delivered circumferentially outside the ostia of the PV. In a series of 26 patients, 85% were free of recurrent AF during a mean follow-up of 9 mo, including 62% taking no antiarrhythmic medications. The accumulated experience involves nearly 4000 patients,⁷⁸⁶ with approximately 90% success in cases of paroxysmal AF and 80% in cases of persistent AF.^{784,787,788} Another anatomic approach to radiofrequency catheter ablation targets complex fractionated electrograms,⁷⁸⁹ with 91% efficacy reported at 1 y. Restoration of sinus rhythm after catheter ablation for AF significantly improved LV function, exercise capacity, symptoms, and quality of life (usually within the first 3 to 6 mo), even in the presence of concurrent heart disease and when ventricular rate control was adequate before ablation.⁷⁹⁰ While that study lacked a control group of patients with HF, in another study catheter ablation of AF was associated with reduced mortality and morbidity due to HF and thromboembolism.⁷⁹¹

In selected patients, radiofrequency catheter ablation of the AV node and pacemaker insertion decreased symptoms of AF and improved quality-of-life scores compared with medication therapy.^{363,387,388,792-794} Baseline quality-of-life scores are generally lower for patients with AF or atrial flutter than for those undergoing ablation for other arrhythmias.⁷⁹⁵ A meta-analysis of 10 studies of patients with AF³⁸⁹ found improvement in both symptoms and quality-of-life scores after ablation and pacing. Although these studies involved selected patients who remained in AF, the consistent improvement suggests that quality of life was impaired before intervention. Two studies have described improvement in symptoms and quality of life after radiofrequency catheter ablation of atrial flutter.^{796,797} New studies comparing strict versus lenient rate control are under way to investigate this issue further.

Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrate 1 y or more free from recurrent AF in most (albeit carefully selected) patients.⁷⁹⁸⁻⁸⁰⁰ It is important to bear in mind, however, that AF can recur without symptoms and be unrecognized by the patient or the physician. Therefore, it remains uncertain whether apparent cures represent elimination of AF or transformation into an asymptomatic form of paroxysmal AF. The distinction has important implications for the duration of anticoagulation therapy in patients with risk factors for stroke associated with AF. In addition, little information is yet available about the late success of ablation in patients with HF and other advanced structural heart disease, who may be less likely to enjoy freedom from AF recurrence.

8.3.4.2.1. Complications of catheter-based ablation. Complications of catheter ablation include the adverse events associated with any cardiac catheterization procedure in addition to those specific to ablation of AF. Major complications have been reported in about 6% of procedures and include PV stenosis, thromboembolism, atriopharyngeal fistula, and LA flutter.⁷⁸⁸ The initial ablation approach targeting PV ectopy was associated with an unacceptably high rate of PV stenosis,^{780,801} but the incidence has dramatically decreased as a result of changes in technique. Current approaches avoid delivering radiofrequency energy within the PV and instead target areas outside the veins to isolate the ostia from the remainder of the LA conducting tissue. Use of intracardiac echocardiographically detected microbubble formation to titrate radiofrequency energy has also been reported to reduce the incidence of PV stenosis.⁷⁸³

Embolic stroke is among the most serious complications of catheter-based ablation procedures in patients with AF. The incidence varies from 0% to 5%. A higher intensity of anticoagulation reduces the risk of thrombus formation during ablation.⁸⁰² A comparison of 2 heparin dosing regimens found LA thrombus in 11.2% of patients when the activated clotting time (ACT) was 250 to 300 s compared with 2.8% when the ACT was kept greater than 300 s. Based on these observations, it seems likely that more aggressive anticoagulation may reduce the incidence of thromboembolism associated with catheter-based ablation of AF.

Atriopharyngeal fistula has been reported with both the circumferential Pappone approach^{803,804} and the Haissaguerre PV ablation techniques⁸⁰⁴ but is relatively rare. This complication may be more likely to occur when extensive ablative lesions are applied to the posterior LA wall, increasing the risk of atrial perforation. The typical manifestations include sudden neurological symptoms or endocarditis, and the outcome in most cases is, unfortunately, fatal.

Depending on the ablation approach, LA flutter may develop during treatment of AF,⁸⁰⁵ and this is typically related to scars created during catheter ablation. An incomplete line of ablation is an important predictor of postprocedural LA flutter, and extending the ablation line to the mitral annulus may reduce the frequency of this complication. In most cases, LA flutter is amenable to further ablation.⁸⁰⁶

8.3.4.2.2. Future directions in catheter-based ablation therapy for atrial fibrillation. Catheter-directed ablation of AF represents a substantial achievement that promises better therapy for a large number of patients presently

resistant to pharmacological or electrical conversion to sinus rhythm. The limited available studies suggest that catheter-based ablation offers benefit to selected patients with AF, but these studies do not provide convincing evidence of optimum catheter positioning or absolute rates of treatment success. Identification of patients who might benefit from ablation must take into account both potential benefits and short- and long-term risks. Rates of success and complications vary, sometimes considerably, from one study to another because of patient factors, patterns of AF, criteria for definition of success, duration of follow-up, and technical aspects. Registries of consecutive case series should incorporate clear and prospectively defined outcome variables. Double-blind studies are almost impossible to perform, yet there is a need for randomized trials in which evaluation of outcomes is blinded as to treatment modality. A comprehensive evaluation of the favorable and adverse effects of various ablation techniques should include measures of quality of life and recurrence rates compared with pharmacological strategies for rhythm control and, when this is not successful, with such techniques of rate control as AV node ablation and pacing. Generation of these comparative data over relatively long periods of observation would address the array of invasive and conservative management approaches available for management of patients with AF and provide a valuable foundation for future practice guidelines.

8.3.4.3. *Suppression of atrial fibrillation through pacing.*

Several studies have examined the role of atrial pacing, either in the RA alone or in more than one atrial location, to prevent recurrent paroxysmal AF. In patients with symptomatic bradycardia, the risk of AF is lower with atrial than with ventricular pacing.⁸⁰⁷ In patients with sinus node dysfunction and normal AV conduction, data from several randomized trials support atrial or dual-chamber rather than ventricular pacing for prevention of AF.⁸⁰⁸⁻⁸¹¹ The mechanisms by which atrial pacing prevents AF in patients with sinus node dysfunction include prevention of bradycardia-induced dispersion of repolarization and suppression of atrial premature beats. Atrial or dual-chamber pacing also maintains AV synchrony, preventing retrograde ventriculoatrial conduction that can cause valvular regurgitation and stretch-induced changes in atrial electrophysiology. When ventricular pacing with dual-chamber devices is unavoidable because of concomitant disease of the AV conduction system, the evidence is less clear that atrial-based pacing is superior.

While atrial pacing is effective in preventing development of AF in patients with symptomatic bradycardia, its utility as a treatment for paroxysmal AF in patients without conventional indications for pacing has not been proved.⁸¹² In the Atrial Pacing Peri-Ablation for the Prevention of AF (PA3) study, patients under consideration for AV junction ablation received dual-chamber pacemakers and were randomized to atrial pacing versus no pacing. There was no difference in time to first occurrence of AF or total AF burden.⁸¹² In a continuation of this study comparing atrial pacing with AV synchronous pacing, patients were randomized to DDDR versus VDD node pacing after ablation of the AV junction. Once again, there was no difference in time to first recurrence of AF or AF burden, and 42% of the patients lapsed into permanent AF by the end of 1 y.⁸¹³

It has been suggested that the incidence of AF may be lower with atrial septal pacing or multisite atrial pacing than with pacing in the RA appendage.⁸¹⁴ Pacing at right interatrial septal sites results in preferential conduction to the LA via Bachmann's bundle. Pacing from this site shortens P-wave duration and interatrial conduction time. Clinical trials of pacing in the interatrial septum to prevent episodes of paroxysmal AF have yielded mixed results.⁸¹⁵⁻⁸¹⁷ While 2 small randomized trials found that atrial septal pacing reduced the number of episodes of paroxysmal AF and the incidence of persistent AF at 1 y compared with RA appendage pacing,^{815,816} a larger trial showed no effect on AF burden despite reduction in symptomatic AF.⁸¹⁷

Both bi-atrial (RA appendage and either the proximal or distal coronary sinus) and dual-site (usually RA appendage and coronary sinus ostium) pacing have been studied as means of preventing AF. A small trial of biatrial pacing to prevent recurrent AF found no benefit compared with conventional RA pacing,⁸¹⁸ and a larger trial revealed no benefit from dual-site compared with single-site pacing, except in certain subgroups.⁸¹⁹ The greater complexity and more extensive apparatus required have limited the appeal of dual-site pacing.

Several algorithms have been developed to increase the percentage of atrial pacing time to suppress atrial premature beats, prevent atrial pauses, and decrease atrial cycle length variation in the hope of preventing AF. Prospective studies of devices that incorporate these algorithms have yielded mixed results. In one large trial, these pacemaker algorithms decreased symptomatic AF burden, but the absolute difference was small, and there was no gain in terms of quality of life, mean number of AF episodes, hospitalizations, or mean duration of AF detected by the pacemaker's automatic mode-switching algorithm.⁸²⁰ Other trials have failed to show any benefit of atrial pacing in preventing AF.^{817,821}

In addition to pacing algorithms to prevent AF, some devices are also capable of pacing for termination of AF. While efficacy has been shown for termination of more organized atrial tachyarrhythmias, there has been little demonstrated effect on total AF burden.^{821,822}

In summary, atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, but the value of pacing as a primary therapy for prevention of recurrent AF has not been proven.

8.3.4.4. *Internal atrial defibrillators.*

In a sheep model of internal cardioversion of AF,³⁵⁴ delivery of synchronous shocks between the high RA and coronary sinus effectively terminated episodes of AF. A clinical trial of a low-energy transvenous atrial cardioverter that delivered a 3/3-ms biphasic waveform shock synchronized to the R wave established the safety of internal atrial cardioversion, but the energy required in patients with persistent AF was relatively high (mean 3.5 J).³⁵⁵ Intense basic and clinical research to find more tolerable shock waveforms led to evaluation of an implantable device capable of both atrial sensing and cardioversion and ventricular sensing and pacing in 290 patients with mean LV ejection fraction greater than 50% who had not responded satisfactorily to therapy with 4 antiarrhythmic drugs.³⁵⁵ In total, 614 episodes of AF were treated with 1497 shocks (mean 2.4 shocks per episode), and the rate of conversion to sinus

rhythm was 93%. As spontaneous episodes were treated quickly, the interval between episodes of AF lengthened.

Several available devices combining both atrial cardioversion and ventricular defibrillation capabilities with dual-chamber sensing and pacing have been designed to treat both atrial and ventricular arrhythmias by pacing before delivering low- or high-energy shocks. A number of other techniques to terminate AF by pacing are also under investigation, but indications may be limited to atrial tachycardia and atrial flutter. Because these units accurately record the occurrence of AF, however, they provide valuable representation of AF control.

An important limitation of atrial defibrillators, unrelated to efficacy, is that most patients find discharge energies over 1 J uncomfortable without sedation requiring a medical setting, and the mean cardioversion threshold is approximately 3 J, making such devices in their current form unacceptable for wide clinical use. Optimal devices would use atrial pacing to maintain sinus rhythm after cardioversion, and some patients require additional therapy to avoid frequent paroxysms of AF. Candidates for atrial cardioverters with infrequent episodes of poorly tolerated AF are typically also candidates for catheter ablation. As a result, implanted devices have limited utility, except for patients with LV dysfunction who are candidates for implantable ventricular defibrillators.

8.4. Special considerations

8.4.1. Postoperative AF

Recommendations

Class I

- (1) Unless contraindicated, treatment with an oral beta blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery. (Level of Evidence: A)
- (2) Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF. (Level of Evidence: B)

Class IIa

- (1) Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF. (Level of Evidence: A)
- (2) It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide or direct-current cardioversion in patients who develop postoperative AF as advised for nonsurgical patients. (Level of Evidence: B)
- (3) It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF. (Level of Evidence: B)
- (4) It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients. (Level of Evidence: B)

Class IIb

Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. (Level of Evidence: B)

Although AF may occur after noncardiac surgery, the incidence of atrial arrhythmias including AF after open-heart

surgery is between 20% and 50%,⁸²³⁻⁸²⁵ depending on definitions and methods of detection. The incidence of postoperative AF is increasing, perhaps more because of the age of surgical patients than because of technical factors, and this is associated with increased morbidity and costs.

8.4.1.1. Clinical and pathophysiological correlates. Postoperative AF usually occurs within 5 d of open-heart surgery, with a peak incidence on the second day. A number of studies have examined the predictors of AF, cost impact, length of hospital stay, and the effects of various prophylactic interventions aimed at reducing the incidence of AF,^{824,826-830} but many of these reflect earlier models of patient management. In an observational study of 4657 patients undergoing coronary artery bypass graft (CABG) surgery at 70 centers between 1996 and 2000, predictors of AF included age, a history of AF, COPD, valvular heart disease, atrial enlargement, perioperative HF, and withdrawal of either beta blocker or ACE inhibitor medications before or after surgery⁸³¹ (Table 24). Many patients have none of these factors, however, and it is likely that the greater collagen content of the atria in older patients or other factors related to the biology of aging are responsible⁸²⁵ for the greater propensity of elderly patients to develop AF after cardiac surgery⁸³² (Table 24). Other contributing factors are pericarditis⁸²⁶ and increased sympathetic tone. In a review of 8051 consecutive patients without previously documented AF (mean 64 y, 67% males) undergoing cardiac surgery (84% involving CABG only) between 1994 and 2004, there was a strong, independent association between obesity (body mass index over 30.1 kg/m²) and the development of postoperative AF. During the index hospitalization, AF developed in 22.5% of all cases, and 52% of those over age 85 y, compared with 6.2% of patients younger than 40 y. Among the extremely obese, the relative risk of postoperative AF was 2.39. 'Off-pump' CABG was associated with 39% lower likelihood of developing AF than conventional on-pump surgery, and the risk of AF correlated with the duration of cardiopulmonary bypass.⁸³³ The arrhythmia is usually self-correcting, and sinus rhythm

Table 24 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 (Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg* 1993;56:539-49).⁸²⁴

resumes in more than 90% of patients by 6 to 8 wk after surgery,⁸³² a rate of spontaneous resolution higher than for other forms of AF. Patients with postoperative AF have a higher inpatient mortality than patients without this arrhythmia (4.7% vs. 2.1%) and longer hospital stay (median difference 2 d).⁸³¹ In another study, postoperative AF was an independent predictor of long-term mortality (adjusted odds ratio [OR] 1.5, p less than 0.001 in retrospective cohort, and OR 3.4, $p = 0.0018$ in a case-control analysis) over 4 to 5 y.⁸³⁴

8.4.1.2. Prevention of postoperative AF. A meta-analysis of 13 randomized trials of prophylactic antiarrhythmic therapy involving 1783 patients undergoing cardiac surgery in which effects on hospital length of stay were addressed found that while these consistently showed decreases in the incidence of AF, the effects on hospital stay were less concordant and amounted to a 1.0 plus or minus 0.2 d overall decrease in length of hospital stay (p less than 0.001).⁸³⁵ A systematic Cochrane database review found 58 studies with a total of 8565 participants in which interventions included amiodarone, beta blockers, sotalol, and pacing. By meta-analysis, the effect size for prevention of stroke by prophylactic treatment for AF was not statistically significant, nor was the effect on length or cost of hospital stay. Beta blockers had the greatest magnitude of effect across 28 trials (4074 patients).⁸³⁶ In a meta-analysis of 24 trials⁸²⁵ limited to patients with ejection fraction greater than 30% undergoing CABG, prophylactic administration of beta-blocker medication protected against supraventricular tachycardia (OR 0.28, 95% CI 0.21 to 0.36). In a meta-analysis of 27 trials including 3840 patients, sotalol (80 or 120 mg twice daily) was more effective in reducing postoperative AF than either other beta-blocker medication or placebo,⁸²⁹ but the results were not confirmed in another study,⁴⁹¹ in which the difference between sotalol and beta-blocker treatment was small.

When the prophylactic value of amiodarone, 600 mg per day, initiated at least 7 d preoperatively, was evaluated in 124 patients undergoing cardiac surgery, the incidence of AF was 25% in the treated group compared with 53% in patients randomized to placebo ($p = 0.003$).⁸³⁷ This approach is impractical unless patients are identified and treatment started at least 1 wk before surgery. The Amiodarone Reduction in Coronary Heart (ARCH) trial involving 300 patients found that postoperative intravenous administration of amiodarone (1 g daily for 2 d) reduced the incidence of postoperative AF from 47% to 35% compared with placebo ($p = 0.01$). The higher overall incidence of postoperative AF and less pronounced prophylactic effect than in other studies may have been partly related to less-frequent use of beta blockers.⁸³⁸ More convincing evidence of the efficacy of amiodarone for prevention of AF in patients undergoing cardiac surgery comes from the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early after Revascularization, Valve Replacement, or Repair (PAPABEAR) trial, in which a 13-d perioperative course of oral amiodarone (10 mg/kg daily beginning 6 d before and continuing for 6 d after surgery) halved the incidence of postoperative atrial tachyarrhythmias, including AF patients undergoing CABG, valve replacement, or valve repair surgery with or without CABG surgery.⁸³⁹ Although efficacy was evident whether or not beta-blocking medication was given concurrently, rates

of beta-blocker therapy withdrawal were not reported; hence, differential withdrawal of beta blockers from more patients in the placebo group may have exaggerated the apparent effect of amiodarone.⁸⁴⁰

Pretreatment with either digoxin or verapamil does not reliably prevent postoperative AF.^{825,841,842} Results with procainamide have been inconsistent, and this drug is not widely used for prevention of postoperative AF.⁸⁴³ One report suggested that n-3 polyunsaturated fatty acids may be effective for prevention of AF in patients undergoing CABG surgery.⁸⁴⁴

There is limited evidence that single-chamber and biatrial overdrive pacing prevents postoperative AF. In a randomized trial involving 132 patients undergoing CABG, postoperative biatrial pacing significantly reduced the incidence of AF in the biatrial pacing group by 12.5% compared with the other 3 groups (36% LA pacing, 33% RA pacing, and 42% without pacing; $p < 0.05$). The length of hospital stay was also significantly reduced in the biatrial pacing group.⁸⁴⁵ A meta-analysis of 10 randomized trials comparing various types of atrial pacing to routine care after CABG surgery found that AF was reduced by RA pacing (OR 0.68, 95% CI 0.39 to 1.19), LA pacing (OR 0.57, 95% CI 0.28 to 1.16), and biatrial pacing (OR 0.46, 95% CI 0.30 to 0.71), but the number of enrolled patients was small and the pacing sites and protocols varied.⁸⁴⁶ Available data suggest that biatrial pacing may be superior to either LA or RA pacing for prevention of postoperative AF, but evidence is insufficient to permit firm conclusions or recommendations about this prophylactic modality.

8.4.1.3. Treatment of postoperative AF. Comorbidity including adrenergic stress often makes it difficult to control the ventricular rate in patients with postoperative AF. Short-acting beta-blocker agents are particularly useful when hemodynamic instability is a concern. Other AV nodal blocking agents, such as the nondihydropyridine calcium channel antagonist agents, can be used as alternatives, but digoxin is less effective when adrenergic tone is high. Intravenous amiodarone has been associated with improved hemodynamics in this setting.³⁷⁹

Given the self-limited course of postoperative AF, direct-current cardioversion is usually unnecessary except when the arrhythmia develops in the early hypothermic period. In the highly symptomatic patient or when rate control is difficult to achieve, cardioversion may be performed using the same precautions regarding anticoagulation as in nonsurgical cases. A variety of pharmacological agents, including amiodarone,^{837,838,847} procainamide,⁸⁴¹ ibutilide, and sotalol, may be effective to convert AF to sinus rhythm. Although a class III agent (e.g., ibutilide) was more effective than placebo for treatment of postoperative AF in one study,⁸⁴⁸ 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 seems less effective than others for cardioversion of AF.

A number of studies have shown an increased risk of stroke in post-CABG patients. Accordingly, anticoagulation with heparin or oral anticoagulation is appropriate when AF persists longer than 48 h.^{849,850} 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,⁸⁵¹ but pharmacological therapy is similar. Prevention of postoperative atrial flutter is as difficult as prevention of AF, but atrial overdrive pacing is generally useful for termination of atrial flutter when epicardial electrodes are in place.

8.4.2. Acute myocardial infarction

Recommendations

Class I

- (1) Direct-current cardioversion is recommended for patients with severe hemodynamic compromise or intractable ischemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with acute MI and AF. (Level of Evidence: C)
- (2) Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF and improve LV function in patients with acute MI. (Level of Evidence: C)
- (3) Intravenous beta blockers and nondihydropyridine calcium antagonists are recommended to slow a rapid ventricular response to AF in patients with acute MI who do not display clinical LV dysfunction, bronchospasm, or AV block. (Level of Evidence: C)
- (4) For patients with AF and acute MI, administration of unfractionated heparin by either continuous intravenous infusion or intermittent subcutaneous injection is recommended in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 to 2.0 times the control value, unless contraindications to anticoagulation exist. (Level of Evidence: C)

Class IIa

Intravenous administration of digitalis is reasonable to slow a rapid ventricular response and improve LV function in patients with acute MI and AF associated with severe LV dysfunction and HF. (Level of Evidence: C)

Class III

The administration of class IC antiarrhythmic drugs is not recommended in patients with AF in the setting of acute MI. (Level of Evidence: C)

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 beneficiaries 65 y or older hospitalized for acute MI had AF.²⁷⁰ In the Trandolapril Cardiac Evaluation (TRACE) study of patients with LV dysfunction associated with acute MI, 21% had AF.⁸⁵² Lower rates of AF were observed in patients selected for other prospective trials, such as the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study, in which the incidence was 10.4%,⁸⁵³ but this may reflect the younger age of patients presenting with acute MI associated with ST-segment elevation on the ECG. AF is more commonly associated with acute MI in older patients and those with higher Killip class or LV dysfunction.

AF is associated with increased in-hospital mortality in the setting of acute MI (25.3% with AF vs. 16.0% without AF), 30-d mortality (29.3% vs. 19.1%), and 1-y mortality (48.3% vs. 32.7%).²⁷⁰ Patients who developed AF during hospitalization had a worse prognosis than those with AF on admission.²⁷⁰ Stroke rates are also increased in patients with MI and AF compared with those without AF.⁸⁵³ Outcomes for patients

with AF and acute MI have improved in the thrombolytic era compared with prior experience, but a stroke rate of 3.1%⁸⁵³ emphasizes the importance of this association in contemporary clinical practice.

Specific recommendations for management of patients with AF in the setting of acute MI are based primarily on consensus, because no adequate trials have tested alternative strategies. The recommendations in this document are intended to comply with the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction.⁸⁵⁴ Physicians should apply the guidelines for management outlined elsewhere in this document with emphasis on recognition of AF and risk stratification and recognize the significance of the arrhythmia as an independent predictor of poor long-term outcome in patients with acute MI.^{855,856}

Urgent direct-current cardioversion is appropriate in acute MI patients presenting with AF and intractable ischemia or hemodynamic instability. Intravenous administration of a beta blocker is indicated for rate control in patients with acute MI to reduce myocardial oxygen demands. Digoxin is an appropriate alternative for patients with acute MI associated with severe LV dysfunction and HF. Anticoagulants are indicated in those with large anterior infarcts and in survivors of acute MI who develop persistent AF. Treatment with ACE inhibitors appears to reduce the incidence of AF in patients with LV dysfunction after acute MI.⁸⁵⁷ In patients with reduced LV systolic function after MI, the placebo-controlled CAPRICORN trial demonstrated a significant reduction in the incidence of AF and/or atrial flutter in patients treated with carvedilol (5.4% vs. 2.3%).⁸⁵⁸

8.4.3. Wolff-Parkinson-White (WPW) preexcitation Syndromes

Recommendations

Class I

- (1) Catheter ablation of the accessory pathway is recommended 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 direct-current cardioversion is recommended to prevent ventricular fibrillation in patients with a short anterograde bypass tract refractory period in whom AF occurs with a rapid ventricular response associated with hemodynamic instability. (Level of Evidence: B)
- (3) Intravenous procainamide or ibutilide is recommended 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) or with a rapid preexcited ventricular response. (Level of Evidence: C)

Class IIa

Intravenous flecainide or direct-current cardioversion is reasonable when very rapid ventricular rates occur in patients with AF involving conduction over an accessory pathway. (Level of Evidence: B)

Class IIb

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

Class III

Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists is not recommended in patients with WPW syndrome who have preexcited ventricular activation during AF. (Level of Evidence: B)

Although the most feared complication of AF in patients with WPW syndrome is ventricular fibrillation and sudden death resulting from antegrade conduction of atrial impulses across a bypass tract, this actually occurs infrequently. The incidence of sudden death ranges from 0% to 0.6% per year in patients with WPW syndrome.^{460,634,823,859} In contrast, a large population-based study in Olmsted County, Minnesota, found 4 newly diagnosed cases of WPW syndrome per 100 000 people per year. There were only 2 sudden deaths over 1338 patient-y of follow-up, however. Among 113 patients with WPW syndrome, 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).^{178,860} In patients prone to ventricular fibrillation, there is also a higher incidence of multiple pathways.¹⁷⁸

When a patient with a preexcited tachycardia is clinically stable, intravenous procainamide may be given to convert AF 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 via the intravenous route may have adverse hemodynamic effects.

Flecainide can slow the ventricular rate in patients who have AF associated with a very rapid tachycardia due to an accessory pathway and may terminate AF⁸⁶¹⁻⁸⁶⁴ by prolonging the shortest preexcited cycle length during AF. Propafenone seems less effective in this respect.⁸⁶¹

For patients with preexcitation syndromes and AF who have syncope (suggesting rapid heart rate) or a short antegrade bypass tract refractory period, immediate direct-current cardioversion followed by catheter ablation of the accessory pathway is the preferred therapy.⁸⁶⁵ Ablation of the bypass tract does not necessarily prevent AF, however, especially in older patients, and additional pharmacological therapy may be required. Once the accessory pathway has been eliminated, the selection of pharmacological therapy can parallel that for patients without preexcitation.

8.4.4. Hyperthyroidism**Recommendations****Class I**

- (1) Administration of a beta blocker is recommended 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, administration of a nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis. (Level of Evidence: B)
- (3) In patients with AF associated with thyrotoxicosis, oral anticoagulation (INR 2.0 to 3.0) is recommended to

prevent thromboembolism, as recommended for AF patients with other risk factors for stroke. (Level of Evidence: C)

- (4) Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism. (Level of Evidence: C)

AF occurs in 10% to 25% of patients with hyperthyroidism, more commonly in men and elderly patients than in women or patients younger than 75 y.⁸⁶⁶ Treatment is directed primarily toward restoring a euthyroid state, which is usually associated with a spontaneous reversion to sinus rhythm. Antiarrhythmic drugs and direct-current cardioversion are generally unsuccessful while the thyrotoxic condition persists.^{867,868} Beta blockers are effective in controlling the ventricular rate in this situation, and aggressive treatment with intravenous beta blockers is particularly important in cases of thyroid storm, when high doses may be required. Nondihydropyridine calcium channel antagonists may also be useful.⁸⁶⁹ Although specific evidence is lacking in AF caused by hyperthyroidism, oral anticoagulation is recommended to prevent systemic embolism.⁸⁷⁰

Several reports suggest that patients with AF in the setting of thyrotoxicosis, which is often associated with decompensated HF, are also at high risk,^{418,419,422} although the mechanism underlying this enhanced embolic potential is not clear.^{203,416,423} The notion of increased thromboembolic risk in thyrotoxic AF has been challenged on the basis of comparison with patients in sinus rhythm, and logistic regression analysis found age the only independent predictor of cerebral ischemic events.³¹⁹ 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),^{203,268,320} there was no adjustment for duration of observation or time to event. When TIAs are discounted, the increased risk of stroke in patients with AF reached statistical significance ($p = 0.03$).³¹⁹ Although it remains controversial whether patients with AF associated with thyrotoxicosis are at increased risk of thromboembolic cerebrovascular events,⁴²¹ 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 HF has been cured.

8.4.5. Pregnancy**Recommendations****Class I**

- (1) Digoxin, a beta blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF. (Level of Evidence: C)
- (2) Direct-current cardioversion is recommended in pregnant patients who become hemodynamically unstable due to AF. (Level of Evidence: C)
- (3) Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy. (Level of Evidence: C)

Class IIb

- (1) Administration of heparin may be considered during the first trimester and last month of pregnancy for patients

with AF and risk factors for thromboembolism. 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 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)

- (2) Despite the limited data available, subcutaneous administration of low-molecular-weight heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism. (Level of Evidence: C)
- (3) Administration of an oral anticoagulant may be considered during the second trimester for pregnant patients with AF at high thromboembolic risk. (Level of Evidence: C)
- (4) Administration of quinidine or procainamide may be considered to achieve pharmacological cardioversion in hemodynamically stable patients who develop AF during pregnancy. (Level of Evidence: C)

AF is rare during pregnancy and usually has an identifiable underlying cause, such as mitral stenosis,⁸⁷⁵ congenital heart disease,⁸⁷⁶ or hyperthyroidism.⁸⁷⁷ 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 arrhythmia are the first priorities. The ventricular rate should be controlled with digoxin, a beta blocker, or a nondihydropyridine calcium channel antagonist.⁸⁷⁸⁻⁸⁸⁰ All currently available antiarrhythmic drugs have the potential to cross the placenta and enter breast milk and should therefore be avoided if possible. Quinidine,⁸⁷⁹ sotalol,⁸⁸¹ flecainide,⁸⁸¹ and amiodarone^{870,876-878} have all been used successfully during pregnancy, however, in relatively small numbers 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.^{497,879} In the event of hemodynamic embarrassment, direct-current cardioversion can be performed without fetal damage.⁸⁷⁹

The role of anticoagulation to prevent systemic arterial embolism has not been systematically studied in pregnant patients with AF, but the arrhythmia 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.⁸⁸⁰⁻⁸⁸⁶ Heparin is the preferred anticoagulant because it does not cross the placenta. The safety and efficacy of subcutaneous unfractionated heparin or low-molecular-weight heparin in preventing ischemic stroke in patients with AF during pregnancy have not been proved, and experience with these agents mainly involves patients with prosthetic heart valves or venous thromboembolism. In patients with prosthetic valves who have AF, unfractionated heparin can be administered either by continuous intravenous infusion or by twice-daily subcutaneous injections in a dose between 10 000 and 20 000 units adjusted to prolong the mid-interval activated partial thromboplastin time to 1.5 times the control value. The same strategies are proposed for

patients without prosthetic valves who have AF and risk factors for thromboembolism.^{887,888}

8.4.6. Hypertrophic cardiomyopathy

Recommendations

Class I

Oral anticoagulation (INR 2.0 to 3.0) is recommended in patients with hypertrophic cardiomyopathy who develop AF, as for other patients at high risk of thromboembolism. (Level of Evidence: B)

Class IIa

Antiarrhythmic medications can be useful to prevent recurrent AF in patients with hypertrophic cardiomyopathy. Available data are insufficient to recommend one agent over another in this situation, but (a) disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist or (b) amiodarone alone is generally preferred. (Level of Evidence: C)

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 those patients who developed AF experienced hemodynamic deterioration that was ameliorated by restoration of sinus rhythm.⁸⁸⁹ 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.⁴⁰² 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.⁸⁹⁰ The natural history of HCM is better defined by the combined experience of 3 large centers following 717 cases for a mean of 8 plus or minus 7 y, during which there were 86 deaths (12%), 51% of which were sudden (mean age 45 plus or minus 20 y). Death was attributable to HF in 36% of the patients (mean age 56 plus or minus 19 y) and to stroke in 13% (mean age 73 plus or minus 14 y). Although most sudden deaths were attributed to ventricular arrhythmias, cardiogenic embolism may have been underestimated as a contributory mechanism. Ten of 11 fatal strokes were associated with AF. In a study of 480 patients the prevalence of AF was 22% over 9 y. AF was associated with an increased risk of HCM-related death (odds ratio 3.7) due to excess HF-related mortality but not sudden cardiac death. AF patients were at increased risk for stroke (odds ratio 17.7) and severe functional limitation (odds ratio for NYHA Class III or IV 2.8).⁸⁹¹

Studies of patients with HCM and AF⁸⁹² have consistently reported a high incidence of stroke and systemic embolism.⁸⁷¹⁻⁸⁷⁴ 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 y, 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,⁸⁷⁴ hypertension,⁸⁷² mitral annular calcification, and LA enlargement.⁸⁷² By multivariate analysis, age and AF were independent predictors of thromboembolism.⁸⁷⁴ 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 medication when AF persists for longer than 48 h or when recurrence is likely.

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. Deedwania *et al.*⁷³⁸ advocate administration of amiodarone both to prevent episodes of AF and to modulate the rate of ventricular response. The use of electrical pacing to prevent AF has not been studied.

8.4.7. Pulmonary diseases

Recommendations

Class I

- (1) Correction of hypoxemia and acidosis is the recommended primary therapeutic measure for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease. (Level of Evidence: C)
- (2) A nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with obstructive pulmonary disease who develop AF. (Level of Evidence: C)
- (3) Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of AF. (Level of Evidence: C)

Class III

- (1) Theophylline and beta-adrenergic agonist agents are not recommended in patients with bronchospastic lung disease who develop AF. (Level of Evidence: C)
- (2) Beta blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease who develop AF. (Level of Evidence: C)

Supraventricular arrhythmias, including AF, are common in patients with COPD.^{893,894} AF has adverse prognostic implications in patients with acute exacerbations of COPD.⁸⁹⁵ Treatment of the underlying lung disease and correction of hypoxia and acid-base imbalance are of primary importance in this situation. Theophylline and beta-adrenergic agonists, which are commonly used to relieve bronchospasm, can precipitate AF and make control of the ventricular response rate difficult. Beta blockers, sotalol, propafenone, and adenosine are contraindicated in patients with bronchospasm. Rate control can usually be achieved safely with nondihydropyridine calcium channel antagonists⁸⁹⁶; digoxin offers no advantage over calcium channel antagonists in this situation. Pharmacological antiarrhythmic therapy and direct-current cardioversion may be ineffective against AF unless respiratory decompensation has been corrected. Intravenous flecainide may be efficacious in restoring sinus rhythm in some patients,⁵⁰⁸ however, and direct-current cardioversion may be attempted in hemodynamically unstable patients. In patients refractory to drug therapy, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate. Although anticoagulation has not been studied specifically in patients with AF due to pulmonary lung disease, the general recommendations for risk-based antithrombotic therapy apply.

8.5. Primary prevention

Although measures aimed at the primary prevention of AF have not been widely investigated, it has been suggested

that atrial or AV synchronous pacing may reduce the incidence of subsequent AF in patients with bradycardia compared with ventricular pacing.^{807,808} On the other hand, studies in patients with intermittent atrial tachyarrhythmias failed to illustrate a general benefit of atrial pacing.^{808,822,897} Another potential avenue for primary prevention has been suggested following secondary analysis of placebo-controlled trials of treatment with ACE inhibitors.^{36,749} In the LIFE⁴¹ and CHARM⁸⁹⁸ trials, the angiotensin receptor antagonists losartan and candesartan reduced the incidence of AF in hypertensive patients with LVH⁴¹ and symptomatic HF,^{40,898} respectively. These results, together with their favorable safety profile compared with antiarrhythmic agents, suggest a role for ACE inhibitors or angiotensin receptor antagonists for primary prevention of initial or recurrent episodes of AF associated with hypertension, MI, HF, or diabetes mellitus. An overview of 11 clinical trials involving more than 56 000 patients with different underlying cardiovascular diseases suggests that ACE inhibitors or angiotensin receptor blockers may reduce the occurrence and recurrence of AF.⁴³

Yet inadequately explored, the use of statins has also been suggested to protect against AF,^{335,899} and dietary lipid components may influence the propensity of patients to develop AF.⁹⁰⁰ In 449 patients with CAD followed for 5 y, statin therapy reduced the incidence of AF—an effect not observed with other lipid-lowering drugs.⁸⁹⁹ In a canine sterile pericarditis model, atorvastatin prevented atrial electrophysiological and structural changes associated with inflammation and reduced the incidence of AF.¹¹⁹ Insufficient data are available at this time to permit recommendations for primary prevention of AF in populations at risk using dietary interventions, pharmacological interventions, or pacing or other devices.

9. Proposed management strategies

9.1. Overview of algorithms for management of patients with atrial fibrillation

Management of patients with AF requires knowledge of its pattern of presentation (paroxysmal, persistent, or permanent), underlying conditions, and decisions about restoration and maintenance of sinus rhythm, control of the ventricular rate, and antithrombotic therapy. These issues are addressed in the various management algorithms for each presentation of AF (see *Figures 13–16*).

9.1.1. Newly discovered atrial fibrillation

It is not always clear whether the initial presentation of AF is actually the first episode, particularly in patients with minimal or no symptoms related to the arrhythmia. In patients who have self-limited episodes of AF, antiarrhythmic drugs are usually unnecessary to prevent recurrence unless AF is associated with severe symptoms related to hypotension, myocardial ischemia, or HF. Regarding anticoagulation, the results of the AFFIRM study²⁹⁶ indicate that patients with AF who are at high risk for stroke on the basis of identified risk factors generally benefit from anticoagulation even after sinus rhythm has been restored. Therefore, unless there is a clear reversible precipitating factor for AF, such as hyperthyroidism that has been corrected, the diagnosis of AF in a patient with risk factors for thromboembolism should prompt long-term anticoagulation.

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, the AFFIRM study showed no difference in survival or quality of life with rate-control compared with rhythm-control strategies.²⁹⁶ Other trials that addressed this issue reached similar conclusions.^{293,294,343,344} Hence, the decision to attempt restoration of sinus rhythm should be based on the severity of arrhythmia-related symptoms and the potential risk of antiarrhythmic drugs. If the decision is made to attempt to restore and maintain sinus rhythm, then 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 that has been present for more than 3 mo, early recurrence is common after cardioversion. In such cases, antiarrhythmic medication may be initiated before cardioversion (after adequate anticoagulation) to reduce the likelihood of recurrence, and the duration of drug therapy would be brief (e.g., 1 mo).

9.1.2. Recurrent paroxysmal atrial fibrillation

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 a given patient, several antiarrhythmic drugs may be effective, and the initial selection is based mainly on safety and tolerability (see *Figure 15*). For individuals with no or minimal heart disease, flecainide, propafenone, or sotalol is recommended as initial antiarrhythmic therapy because these drugs are generally well tolerated and carry relatively little risk of toxicity. For patients with recurrent episodes of symptomatic AF who tolerate these agents, an as-needed, pill-in-the-pocket approach may reduce the risk of toxicity compared with sustained therapy. When these drugs prove ineffective or are associated with side effects, the second- or third-line choices include amiodarone, dofetilide, disopyramide, procainamide, or quinidine, all of which carry greater potential for adverse reactions. As an alternative to treatment with amiodarone or dofetilide when first-line antiarrhythmic drugs fail or are not tolerated, PV isolation or LA substrate modification may be considered. When a consistent initiating scenario suggests vagally mediated AF, drugs such as disopyramide or flecainide are appropriate initial agents, and a beta blocker or sotalol is suggested for patients with adrenergically induced AF. In particularly symptomatic patients, nonpharmacological options such as LA ablation may be considered when antiarrhythmic drug treatment alone fails to control the arrhythmia.

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 category best describes the individual patient. For patients with HF, safety data support the selection of amiodarone or dofetilide to maintain sinus rhythm. Patients with CAD 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 should consider disopyramide, procainamide, or quinidine on an individual basis.

The selection of antiarrhythmic drugs for patients with a history of hypertension is confounded by the dearth of prospective, controlled trials comparing the safety and efficacy of drug therapy for AF. In patients with hypertension without LVH, drugs such as flecainide and propafenone, which do not prolong repolarization or 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 represents an appropriate secondary choice. Disopyramide, procainamide, and quinidine are considered third-line agents in this situation. Hypertrophied myocardium may be prone to proarrhythmic toxicity and torsades de pointes ventricular tachycardia. Amiodarone is suggested as first-line therapy in patients with LVH because of its relative safety compared with several other agents. Because neither ECG nor echocardiography reliably detects LVH as defined by measurement of myocardial mass, clinicians may face a conundrum.

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 by consensus and is subject to revision as additional evidence emerges.

9.1.3. Recurrent persistent atrial fibrillation

Patients with minimal or no symptoms referable to AF who have undergone at least one attempt to restore sinus rhythm may remain in AF after recurrence, 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. If patients remain symptomatic with heart rate control, and antiarrhythmic medication is either not tolerated or ineffective, then nonpharmacological therapies may be considered. These include LA ablation, the maze operation, and AV nodal ablation and pacing.

9.1.4. Permanent atrial fibrillation

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.

Staff

American College of Cardiology Foundation:
 Thomas E. Arend, Jr, Esq., Interim Chief Staff Officer
 Allison B. McDougall, Specialist, Practice Guidelines
 Mark D. Stewart, MPH, Associate Director, Evidence-Based Medicine

Susan A. Keller, RN, BSN, MPH, Senior Specialist, Evidence-Based Medicine
 Erin A. Barrett, Specialist, Clinical Policy and Documents
 Kristina Petrie, MS, Associate Director, Practice Guidelines
 Peg Christiansen, Librarian
American Heart Association
 M. Cass Wheeler, Chief Executive Officer

Rose Marie Robertson, MD, FACC, FAHA, Chief Science Officer
 Kathryn A. Taubert, PhD, FAHA, Senior Scientist.
European Society of Cardiology
 Alan J. Howard, Chief Executive, ESC Group
 Keith H. McGregor, Scientific Director
 Veronica L. Dean, Operations Manager, Practice Guidelines

Appendix I Relationships with industry—ACC/AHA committee to update the 2001 guidelines for the management of patients with atrial fibrillation

Committee member	Research grant	Speakers bureau	Stock ownership	Board of directors	Consultant/advisory member
Dr. David S. Cannom	Guidant	AstraZeneca L.P. Guidant Medtronic	None	None	Cardionet Cryden DSMB Guidant
Dr. Harry J.G.M. Crijns	AstraZeneca L.P. Guidant Medtronic Sanofi-Aventis	None	None	None	AstraZeneca L.P. Sanofi-Aventis
Dr. Anne B. Curtis	Medtronic St. Jude	Guidant Medtronic St. Jude Medical	None	None	Medtronic
Dr. Kenneth A. Ellenbogen	AstraZeneca Bristol Myers Squibb/Sanofi Partnership Guidant Medtronic Pfizer St. Jude Medical	None	None	None	Ablation Frontiers Biosense Webster Stereotaxis
Dr. Valentin Fuster	None	None	None	GlaxoSmithKline	GlaxoSmithKline Kereos Vasogen
Dr. Jonathan L. Halperin	None	None	None	None	Astellas Pharma AstraZeneca Bayer AG HealthCare Boehringer Ingelheim Daiichi Medical Research GlaxoSmithKline Sanofi-Aventis Vasogen
Dr. Jean-Yves Le Heuzey	Sanofi Aventis Medtronic	None	None	None	3M AstraZeneca L.P. GlaxoSmithKline Guidant
Dr. G. Neal Kay	None	None	None	None	None
Dr. James E. Lowe	None	None	None	None	None
Dr. S. Bertil Olsson	AstraZeneca L.P.	None	AstraZeneca L.P.	None	AstraZeneca L.P.
Dr. Eric N. Prystowsky	Sanofi-Aventis	Reliant	Upjohn CardioNet	CardioNet	Boehringer-Ingelheim Bard Guidant Sanofi-Aventis Stereotaxis Sanofi-Aventis
Dr. Lars E. Rydén	AFA Insurance AstraZeneca Pfizer Sanofi-Aventis Swedish Heart Lung Foundation	Occasional lectures at various meetings	None	Chair SBU Alert (A governmental Swedish HTA organization evaluating new medical technology)	
Dr. Juan Luis Tamargo	None	None	None	None	None
Dr. Samuel Wann	None	None	None	None	None

DSMB, Data and Safety Monitoring Board
 This table represents the actual or potential relationships with industry that were reported at the initial writing committee meeting on August 27, 2004.
 This table will be updated in conjunction with all meetings and conference calls of the writing committee.

Appendix II Relationships with industry—external peer review for the ACC/AHA/ESC committee to update the 2001 guidelines for the management of patients with atrial fibrillation

Peer reviewer	Representation	Research grant	Speakers bureau	Stock ownership	Board of directors	Consultant/advisory member
Dr. Carina Blomstrom-Lundvist	Official—ESC	None	None	None	None	None
Dr. Mark Estes	Official—AHA; also AHA ECA Committee, AF Performance Measures Committee	Guidant	Guidant Medtronic St. Jude Medical	None	None	None
Dr. Robert Hart	Official—AHA	None	None	None	None	None
Dr. Jerry Kennett	Official—ACC Board of Trustees	None	None	None	None	None
Dr. Richard Page	Official—Guideline Task Force; ACCF EP Committee, AHA ECA Committee	None	AstraZeneca Procter and Gamble Pharmaceuticals	None	None	AstraZeneca Berlex Laboratories Cardiome Hewlett Packard Procter and Gamble Pharmaceuticals Sanofi Aventis
Dr. Panagiotis Vardas	Official—ESC	None	None	None	None	None
Dr. Mary Walsh	Official—Board of Governors	None	None	None	None	None
Dr. Jonathan Kalman	Organizational—Heart Rhythm Society	Boston Scientific EP Med Systems Guidant Medtronic St. Jude Medical	EP Med Systems St. Jude Medical	None	None	None
Dr. George Wyse	Organizational—Heart Rhythm Society	Cardiome/Astellas Medtronic Organon/Sanofi Aventis	Biovail Pharma Cardiome/Astellas Chugai Pharma Medtronic Sanofi Aventis	Cardiome	“Steering Committee or DSMB” for: Bristol Myers Squibb/Sanofi Aventis Cardiome/Astellas Medtronic Organon/Sanofi Aventis Orion/Abbott	Biovail Pharma Boehringer Ingelheim Medtronic Sanofi Aventis
Dr. Etienne Aliot	Content—ESC	None	None	None	None	None
Dr. Elliott Antman	Content—STEMI Guideline Writing Committee	Aventis Bayer Biosite Boehringer Mannheim Bristol-Myers Squibb British Biotech Centocor Cor/Millennium Corvas Dade Genentech Lilly Merck	None	None	None	Aventis

Continued

Appendix II *Continued*

Peer reviewer	Representation	Research grant	Speakers bureau	Stock ownership	Board of directors	Consultant/advisory member
Dr. Dan Atar	Content—ESC	Pfizer Sunol	None	None	None	None
Dr. Martin Borggrefe	Content—ESC, VA SCD Guideline Writing Committee	None Medtronic	None	None	None	Proctor and Gamble Synacor
Dr. Josep Brugada	Content—ESC	None	None	None	None	None
Dr. Al Buxton	Content—Board of Governors	None	None	None	None	None
Dr. John Camm	Content—ESC, VA SCD Guideline Writing Committee	None	Vitatron	None	None	Astellas Cardiome/Fusiawa Cryocor Guidant Procter and Gamble Sanofi-Aventis Servier St. Jude Medical Wyeth
Dr. Francisco Cosio	Content—ESC	Medtronic	3M Pharmaceuticals Medtronic	Medtronic (past recipient of royalties)	None	AstraZeneca
Dr. Ravin Davidoff	Content—CABG Guideline Writing Committee	None	None	None	None	None
Dr. Alan Forker	Content—Board of Governors	None	None	None	None	None
Dr. Larry Goldstein	Content—Stroke Review Committee	AGA Corp Boehringer Ingelheim CDC/UNC-Chapel Hill NIH Pfizer-Parke-Davis Veterans Admin	Bayer Pfizer-Parke-Davis	None	None	AstraZeneca BMS/Sanofi CuraGen Corp DPharm GlaxoSmithKline Johnson&Johnson Merck Research Labs Pfizer-Parke-Davis Proneuron Biotechnologies
Dr. David Haines	Content—ACCF EP Committee	None	None	None	None	None
Dr. Richard Hauer	Content—ESC	None	None	None	None	None
Dr. Stefan Hohnloser	Content—ESC	St. Jude Medical	Sanofi-Aventis	None	None	Sanofi-Aventis Solvay Pharmaceuticals St. Jude Medical
Dr. Charles Kerr	Content—AF Data Standards Writing Committee	Guidant, Canada Medtronic St. Jude Medical, Canada	AstraZeneca, Canada Medtronic	None	None	AstraZeneca Biovail Medtronic

Continued

Appendix II *Continued*

Peer reviewer	Representation	Research grant	Speakers bureau	Stock ownership	Board of directors	Consultant/advisory member
Dr. Bradley Knight	Content—ACC ECA Committee, ACCF EP Committee	Guidant Medtronic St. Jude	Guidant Medtronic	None	None	Guidant Medtronic
Dr. Lars Kober	Content—ESC	None	None	None	None	None
Dr. Peter Kowey	Content—ACCF EP Committee	None	None	None	None	None
Dr. Judith Mackall	Content—AHA ECA Committee	None	None	None	None	None
Dr. Aldo Maggioni	Content—ESC	Novartis Pharma	None	None	None	None
Dr. Barry Maron	Content—HCM CECD Committee	None	None	None	None	None
Dr. Robert McNamara	Content—AF Data Standards Committee	None	None	None	None	None
Dr. Suneet Mittal	Content—AF Data Standards Committee	None	Medtronic	None	None	None
Dr. Andrew Morris	Content—Board of Governors	None	None	None	None	None
Dr. Michael Nabauer	Content—ESC	Novartis Pharma	None	None	None	None
Dr. Melvin Scheinman	Content—SVA Writing Committee	None	Guidant	None	None	None
Dr. Lynne Warner Stevenson	Content—HF Guideline Writing Committee	None	None	None	None	None
Dr. Albert Waldo	Content—AF Performance Measures Committee	None	Bristol-Myers Squibb Reliant Pharmaceuticals	None	None	Cryocor Reliant Pharmaceuticals
Dr. Stuart Winston	Content—Board of Governors	Biotronik Guidant Medtronic St. Jude Medical	None	None	None	None
Dr. Jose Zamorano	Content—ESC	None	None	None	None	None
Dr. Douglas Zipes	Content—VA SCD Guideline Writing Committee	Medtronic	None	None	None	Burril and Company Cardiofocus CV Therapeutics Medtronic Michael Marcus and Associates Science Partners, LLC Physical Logic Solvay Pharmaceuticals

Appendix III Abbreviations	
ACE	angiotensin-converting enzyme
ACT	activated clotting time
ACTIVE-W	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events
ADONIS	American-Australian Trial with Dronedronone in Atrial Fibrillation or Flutter Patients for Maintenance of Sinus Rhythm
AF	atrial fibrillation
AFASAK	Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation
AF-CHF	Atrial Fibrillation and Congestive Heart Failure
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFI	Atrial Fibrillation Investigators
ALFA	Etude en Activité Libérale sur la Fibrillation Auriculaire
ANP	atrial natriuretic peptide
APT	Ablate and Pace Trial
ARCH	Amiodarone Reduction in Coronary Heart
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AV	atrioventricular
BAATAF	Boston Area Anticoagulation Trial for Atrial Fibrillation
BNP	B-type natriuretic peptide
CABG	coronary artery bypass
CAD	coronary artery disease
CAFA	Canadian Atrial Fibrillation Anticoagulation
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction trial
CHADS ₂	Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]
CHAMP	Combined Hemotherapy and Mortality Prevention Study
CHARM	Candesartan in Heart failure, Assessment of Reduction in Mortality and morbidity
CHF-STAT	Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure
CI	confidence interval
CIBIS	Cardiac Insufficiency Bisoprolol Study
COMET	Carvedilol Or Metoprolol European Trial
CONSENSUS	Co-operative North Scandinavian Enalapril Survival Study
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
COPD	Chronic obstructive pulmonary disorder
CRP	C-reactive protein
CTGF	connective tissue growth factor
CVF-1	type 1 collagen volume fraction
DIAMOND	Danish Investigations of Arrhythmias and Mortality on Dofetilide
DIAMOND-MI	Danish Investigations of Arrhythmia and Mortality on Dofetilide-Myocardial Infarction
EAFI	European Atrial Fibrillation Trial
ECG	electrocardiogram
ELAT	Embolism in the Left Atrial Thrombi
EMERALD	European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide study
EP	electrophysiological
ERK-2-mRNA	>extracellular signal-regulated kinase messenger-RNA
ERP	effective refractory period
ESPS II	European Stroke Prevention Study II
EURIDIS	European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedronone for Maintenance of Sinus Rhythm
FFAACs	The French Fluindione-Aspirin Combination in High Risk Patients With AF
GESICA	Grupo Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (V)
GUSTO-1	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HCM	hypertrophic cardiomyopathy
HF	heart failure
HOT CAFÉ	How to Treat Chronic Atrial Fibrillation
HRV	heart rate variability
IMP-2	atrial insulin-like growth factor-II mRNA-binding protein 2
INR	international normalized ratio
IRAF	immediate recurrence of atrial fibrillation
IVC	inferior vena cava
LA	left atrium
LAA	LA appendage
LASAF	Low-dose Aspirin, Stroke, Atrial Fibrillation
LIFE	Losartan Intervention For End Point Reduction in Hypertension study
LMWH	low-molecular-weight heparin
LV	left ventricle
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MI	myocardial infarction
MMP-2	matrix metalloproteinase 2
NASPEAF	National Study for Prevention of Embolism in Atrial Fibrillation
PAFAC	Prevention of atrial fibrillation after cardioversion
PAPABEAR	Prevention of Arrhythmias that Begin Early after Revascularization, Valve Replacement, or Repair
PATAF	Prevention of Arterial Thromboembolism in Atrial Fibrillation
PAVE	Post AV Node Ablation Evaluation
PIAF	Pharmacological Intervention in Atrial Fibrillation
PV	pulmonary veins
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RACE	Rate Control vs. Electrical cardioversion for persistent atrial fibrillation
RV	right ventricular
SAFE-T	Sotalol Amiodarone Atrial Fibrillation Efficacy Trial
SAFIRE-D	Symptomatic Atrial Fibrillation Investigative Research on Dofetilide
SEC	spontaneous echo contrast
SIFA	Studio Italiano Fibrillazione Atriale
SOLVD	Studies of Left Ventricular Dysfunction
SOPAT	Suppression of paroxysmal atrial tachyarrhythmias
SPAF	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention in Nonrheumatic Atrial Fibrillation
SPORTIF	Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients with Atrial Fibrillation
SRAF	subacute recurrence of atrial fibrillation
STAF	Strategies of Treatment of Atrial Fibrillation
SVC	superior vena cava
TEE	transesophageal echocardiography
TGF-beta1	transforming growth factor-beta1
TIA	transient ischemic attack
TRACE	Trandolapril Cardiac Evaluation
UK-TIA	The United Kingdom transient ischaemic attack aspirin trial
Val-HeFT	Valsartan Heart Failure Trial
VF	ventricular fibrillation
WPW	Wolff-Parkinson-White

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Keywords

ACC/AHA/ESC Guidelines; atrial fibrillation; pacing cardioversion