ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary

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

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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 to 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 his or her tenure, he or she is 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 on 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 healthcare 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, issue of the *Journal of the American College of Cardiology*, August 15, 2006, issue of *Circulation*, and August 16, 2006, issue of the *European Heart Journal*. The full-text guidelines are e-published in the same issues of the journals noted above, 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 and the executive summary are available from all 3 organizations.

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I. Introduction

A. Organization of Committee and Evidence Review

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is

TABLE 1. Applying Classification of Recommendations and Level of Evidence†

Estimate of Certainty (Precision) of Treatment Effect	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 ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/treatment MAY BE CONSIDERED	Class III *Risk ≥ 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** *General consistency of direction and magnitude of effect*	• Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses	• 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**	• Recommendation that procedure or treatment is useful/effective • Limited evidence from single randomized trial or nonrandomized studies	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from single randomized trial or nonrandomized studies	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from single randomized trial or nonrandomized studies	• 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**	• Recommendation that procedure or treatment is useful/effective • Only expert opinion, case studies, or standard-of-care	• Recommendation in favor of treatment or procedure being useful/effective • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation's usefulness/efficacy less well established • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation that procedure or treatment is not useful/effective and may be harmful • Only expert opinion, case studies, or standard-of-care

*Data 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.

†In 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.

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 representatives of the ACC, AHA, ESC, the European Heart Rhythm Association (EHRA), and the Heart Rhythm Society (HRS). The document was reviewed by reviewers nominated by these organizations and will be reviewed annually by the Task Force and considered current unless the Task Force revises or withdraws it from distribution.

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 using the PubMed/MEDLINE and Cochrane Library databases. Searches focused on English-language sources and studies in human subjects. Articles related to animal experimentation were cited when important to understanding concepts pertinent to patient management.

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.

B. Changes Since the Initial Publication of These Guidelines in 2001

The Writing Committee considered evidence published since 2001 and drafted revised recommendations 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 are incorporated in 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 confined to human studies with compounds approved for clinical use in North America and/or Europe. As data on the management of patients prone to AF in special circumstances are more robust, recommendations are based on a higher level of evidence than in the first edition of these guidelines. Every effort was made to maintain consistency with other ACC/AHA and ESC practice guidelines.

C. Recommendations for Management of Patients With Atrial Fibrillation

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. The reader is referred to the full-text guidelines for a complete description of the rationale and evidence supporting these recommendations.

Recommendations

1. Pharmacological Rate Control During Atrial Fibrillation

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 heart failure (HF).** ***(Level of Evidence: B)***
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, left ventricular (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)***

2. Preventing Thromboembolism

(For recommendations regarding antithrombotic therapy in patients with AF undergoing cardioversion, see Section I.C.3.d.)

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 international normalized ratio (INR) of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, transient ischemic attack [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 anticoag-**

ulation, 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 the 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)*

3. Cardioversion of Atrial Fibrillation

a. Pharmacological Cardioversion

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)***

b. Direct-Current Cardioversion

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)***

c. Pharmacological Enhancement of Direct-Current Cardioversion

Class IIa

1. **Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent AF.** ***(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 IIb

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)***

d. Prevention of Thromboembolism in Patients With Atrial Fibrillation Undergoing Cardioversion

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, myocardial infarction [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 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 transesophageal echocardiography (TEE) in**

search of thrombus in the left atrium (LA) or left atrial appendage (LAA). *(Level of Evidence: B)*

2a. For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (e.g., initiated 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 an oral vitamin K antagonist (e.g., warfarin) as evidenced by an INR equal to or greater than 2.0). *(Level of Evidence: B)* Thereafter, continuation of 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)*

4. Maintenance of Sinus Rhythm

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 atrioventricular (AV) node dysfunction unless they have a functioning electronic cardiac pacemaker. *(Level of Evidence: C)*

5. Special Considerations

a. Postoperative Atrial Fibrillation

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)*

b. Acute Myocardial Infarction

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 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)***

c. Management of Atrial Fibrillation Associated With the Wolff-Parkinson-White (WPW) Preexcitation Syndrome

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 electrocardiogram (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)***

d. Hyperthyroidism

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)***

e. Management of Atrial Fibrillation During Pregnancy

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)***

f. Management of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy (HCM)

Class I

Oral anticoagulation (INR 2.0 to 3.0) is recommended in patients with HCM 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 HCM. 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)***

g. Management of Atrial Fibrillation in Patients With Pulmonary Disease

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)***

II. Definition

A. Atrial Fibrillation

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function. On the ECG, rapid oscillations, or fibrillatory waves that vary in amplitude, shape, and timing, replace consistent P waves, and there is an irregular ventricular response that is rapid when conduction is intact (1). The ventricular response depends on electrophysiological properties of the AV node and other conducting tissues, vagal and sympathetic tone, the presence or absence of accessory pathways, and the action of drugs (2). When AV block or ventricular or AV junctional tachycardia is present, the cardiac cycles (R-R intervals) may be regular. In patients with pacemakers, diagnosis of AF may require pacemaker inhibition to expose fibrillatory activity. An irregular, sustained, wide-QRS-complex tachycardia suggests AF with conduction over an accessory pathway or AF with bundle-branch block. Atrial flutter is usually readily distinguished from AF. Extremely rapid rates (greater than 200 beats per minute) suggest an accessory pathway or ventricular tachycardia.

B. Related Arrhythmias

AF may occur in association with atrial flutter or atrial tachycardia. The typical form of atrial flutter 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 V_1. If untreated, the atrial rate typically ranges from 240 to 320 beats per minute, with *f* waves inverted in ECG leads II, III, and aVF and upright in lead V_1. The direction of activation in the right atrium (RA) may be reversed, resulting in upright *f* waves in leads II, III, and aVF

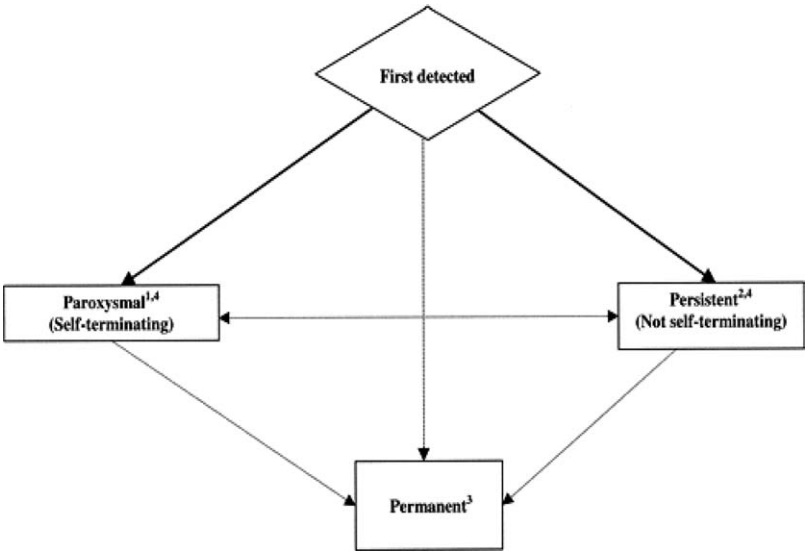

Figure 1. Patterns of atrial fibrillation (AF). 1, Episodes that generally last 7 d or less (most less than 24 h); 2, episodes that usually last more than 7 d; 3, cardioversion failed or not attempted; and 4, both paroxysmal and persistent AF may be recurrent.

and inversion in lead V_1. Atrial flutter may degenerate into AF, and AF may convert to atrial flutter. Atrial flutter is usually readily distinguished from AF, but misdiagnosis may occur when fibrillatory atrial activity is prominent in more than 1 ECG lead (3).

Focal atrial tachycardias, AV reentrant tachycardias, and AV nodal reentrant tachycardias may also trigger AF. In these tachycardias, distinct P waves are typically separated by an isoelectric baseline, and their morphology may localize the origin of the arrhythmia.

III. Classification

Various classification systems have been proposed for AF based on the ECG pattern (1), epicardial (4) or endocavitary recordings, mapping of atrial electrical activity, or clinical features. Although the pattern of AF can change over time, it may be helpful to characterize the arrhythmia at a given moment. The classification scheme recommended here represents a consensus driven by a desire for simplicity and clinical relevance.

The clinician should distinguish a *first-detected episode of AF*, whether or not symptomatic or self-limited, recognizing the uncertainty about the actual duration of the episode and about previous undetected episodes (Fig. 1). After 2 or more episodes, AF is considered *recurrent*. If the arrhythmia terminates spontaneously, recurrent AF is designated *paroxysmal*; when sustained beyond 7 d, it is termed *persistent*. Termination with pharmacological therapy or direct-current cardioversion does not alter the designation. First-detected AF may be either paroxysmal or persistent. The category of persistent AF also includes cases of long-standing AF (e.g., longer than 1 y), usually leading to *permanent AF*, in which cardioversion has failed or has been foregone.

These categories are not mutually exclusive, and a particular patient may have several episodes of paroxysmal AF and occasional persistent AF, or the reverse, but it is practical to categorize a given patient by his or her most frequent presentation. The definition of permanent AF is often arbitrary, and the duration refers both to individual episodes and to how long the diagnosis has been present in a given patient. Thus, in a patient with paroxysmal AF, episodes lasting seconds to hours may occur repeatedly for years.

This terminology applies to episodes lasting longer than 30 s without a reversible cause. Secondary AF in the setting of acute MI, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, or acute pulmonary disease is considered separately. In these situations, AF is not the primary problem, and concurrent treatment of the underlying disorder usually terminates the arrhythmia. Conversely, when AF occurs in the course of a concurrent disorder like well-controlled hypothyroidism, the general principles for management of the arrhythmia apply.

The term *lone AF* applies to individuals younger than 60 y without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension (5). These patients have a favorable prognosis with respect to thromboembolism and mortality. Over time, patients move out of the lone AF category due to aging or development of cardiac abnormalities such as enlargement of the LA, and the risks of thromboembolism and mortality rise. The term *nonvalvular AF* refers to cases without rheumatic mitral valve disease, prosthetic heart valve, or valve repair.

IV. Epidemiology and Prognosis

AF is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. An estimated 2.3 million people in North America and 4.5 million people in the European Union have paroxysmal or persistent AF (9). During the past 20 y, hospital admissions for AF have increased by 66% (7) due to the aging of the population, a rising prevalence of chronic heart disease, more frequent diagnosis through use of ambulatory monitoring devices, and other factors. AF is an extremely expensive public health problem (approximately €3000 [approximately U.S. $3600] annually per patient) (8); the total cost burden approaches €13.5 billion (approximately U.S. $15.7 billion) in the European Union.

A. Prevalence

The estimated prevalence of AF is 0.4% to 1% in the general population (9), increasing with age to 8% in those older than 80 y (10). Among men, the age-adjusted prevalence has more than doubled over a generation (10), while the prevalence in women has remained constant (11). The median age of patients with AF is about 75 y. The number of men and women with AF is about equal, but approximately 60% of those over 75 y old are female. Based on limited data, the age-adjusted risk of developing AF in blacks seems less than half that in whites.

In population-based studies, patients with no history of cardiopulmonary disease account for fewer than 12% of all cases of AF (10). In case series, however, the observed proportion of lone AF was sometimes greater than 30% (12).

B. Incidence

In prospective studies, the incidence of AF increases from less than 0.1% per year in people younger than 40 y to over 1.5% per year among women and 2% among men older than 80 y (13). In patients treated for HF, the 3-y incidence of AF was almost 10% (14). Angiotensin inhibition may be associated with a reduced incidence of AF in patients with HF (15) and hypertension (16).

C. Prognosis

AF is associated with an increased long-term risk of stroke (17), HF, and all-cause mortality, especially among women (18). The mortality rate of patients with AF is about double that of patients in normal sinus rhythm and is linked to the severity of underlying heart disease (19). In the Etude en Activité Libérale sur la Fibrillation Auriculaire Study (ALFA), about two thirds of the 5% annualized mortality was attributed to cardiovascular causes (12). In large HF trials (COMET [Carvedilol Or Metoprolol European Trial], Val-HeFT [Valsartan Heart Failure Trial]), AF was a strong independent risk factor for mortality and morbidity (20,21). HF promotes AF, AF aggravates HF, and individuals with either condition who develop the alternate condition share a poor prognosis (22). Thus, managing patients with the associated conditions is a major challenge, and randomized trials are needed to investigate the impact of AF on prognosis in HF.

The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of people without AF (23). One of every 6 strokes occurs in a patient with AF, and when TIAs and clinically "silent" strokes detected by brain imaging are considered, the rate of brain ischemia accompanying nonvalvular AF exceeds 7% per year (24). In patients with rheumatic heart disease and AF in the Framingham Heart Study, stroke risk was increased 17-fold compared with age-matched controls (25), and attributable risk was 5 times greater than in those with nonrheumatic AF (23). The risk of stroke increased with age; the annual risk of stroke attributable to AF was 1.5% in participants aged 50 to 59 y and 23.5% in those aged 80 to 89 y (23).

V. Pathophysiological Mechanisms

A. Atrial Factors

1. Atrial Pathology as a Cause of Atrial Fibrillation

The most frequent histopathological changes in AF are atrial fibrosis and loss of atrial muscle mass, but it is difficult to distinguish changes due to AF from those due to associated heart disease. Atrial fibrosis may precede the onset of AF (26), and juxtaposition of patchy fibrosis with normal atrial fibers may account for nonhomogeneity of conduction (27). Interstitial fibrosis may result from apoptosis leading to replacement of atrial myocytes (28), loss of myofibrils, accumulation of glycogen granules, disruption of cell coupling at gap junctions (29), and organelle aggregates (30) and may be triggered by atrial dilation in any type of heart disease associated with AF.

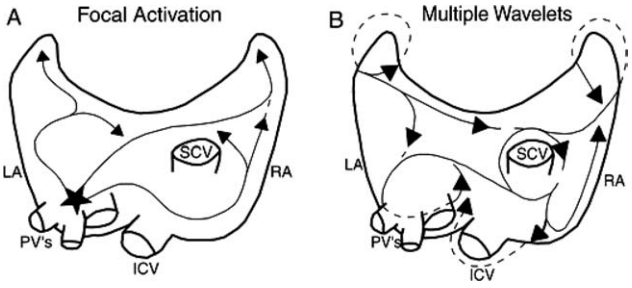

Figure 2. Posterior view of principal electrophysiological mechanisms of atrial fibrillation. A, Focal activation. The initiating focus (indicated by the star) often lies within the region of the pulmonary veins. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. B, Multiple-wavelet reentry. Wavelets (indicated by arrows) randomly re-enter 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;89:1665–1680 (45). LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium.

Patients with valvular heart disease who have mild fibrosis respond more successfully to cardioversion than those with severe fibrosis, and fibrosis is thought to contribute to persistent AF (31). 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, and these changes may contribute to atrial dilation in patients with longstanding AF. Dilation of the atria activates several molecular pathways, including the renin-angiotensin-aldosterone system (RAAS). Angiotensin II is upregulated in response to stretch (32), and atrial tissue from patients with persistent AF demonstrates increased expression of angiotensin-converting enzyme (ACE) (33). Angiotensin inhibition may prevent AF by reducing fibrosis (34). Atrial dilation and interstitial fibrosis in HF facilitate sustained AF (35). The regional electrical silence (suggesting scar), voltage reduction, and conduction slowing described in patients with HF are similar to changes in the atria that occur as a consequence of aging (36).

2. Mechanisms of Atrial Fibrillation

Available data support a "focal" triggering mechanism involving automaticity or multiple reentrant wavelets, but these mechanisms are not mutually exclusive and may coexist (Fig. 2).

The important observation that a focal source for AF could be identified and ablation of this source could extinguish AF (37) supported a focal origin. While pulmonary veins (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 (37–40). In histological studies, cardiac muscle with preserved electrical properties extends into the PVs (41), and the primacy of PVs as triggers of AF has prompted substantial research into the anatomical and electrophysiological properties of these structures. Atrial tissue in the PVs of patients with AF has shorter refractory periods than in control patients or other parts of the atria in patients with AF (42,43). This heterogeneity of conduction may promote reentry and form a substrate for sustained AF (44).

The multiple-wavelet hypothesis as the mechanism of reentrant AF (46) involves fractionation of wave fronts propagating through the atria and 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 (47). Although the multiple-wavelet hypothesis was for years the dominant theory explaining the mechanism of AF, data from experimental (47a) and clinical (47b,47c) mapping studies challenge this notion. In patients with idiopathic paroxysmal AF, widespread distribution of abnormal electrograms in the RA predicts development of persistent AF (48), suggesting the importance of an abnormal substrate in the maintenance of AF. Furthermore, in patients with persistent AF undergoing conversion to sinus rhythm, intra-atrial conduction is prolonged compared with a control group, especially among those who develop recurrent AF (49). Among patients with HF, prolongation of the P wave on signal-averaged ECG analysis was more frequent in those prone to paroxysmal AF (50). Because many of these observations were made prior to onset of clinical AF, the findings cannot be ascribed to atrial remodeling that occurs as a consequence of AF, and the degree to which changes in the atrial architecture contribute to the initiation and maintenance of AF is not known.

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 (51), 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 (52). 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 (52). The increasing propensity to AF was related to progressive shortening of effective refractory periods with increasing episode duration, a phenomenon known as electrophysiological remodeling.

In addition to remodeling and changes in electrical refractoriness, prolonged AF disturbs atrial contractile function. After a period of persistent AF, recovery of atrial contraction can be delayed for days or weeks following the restoration of sinus rhythm, and this has important implications for the duration of anticoagulation after cardioversion. (See Section VIII.B.2, Preventing Thromboembolism.)

4. Other Factors Contributing to Atrial Fibrillation

Data are accumulating on the importance of the RAAS in the genesis of AF (53). Irbesartan plus amiodarone was associated with a lower incidence of recurrent AF after cardioversion than amiodarone alone (15), and treatment with angiotensin inhibitors and diuretics reduced the incidence of AF after catheter ablation of atrial flutter (54). Inhibition of the RAAS, alone or in combination with other therapies, may prevent the onset or maintenance of AF through several mechanisms (55), including 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, reducing blood pressure, prevention or amelioration of HF, and avoidance of hypokalemia. Treatment with trandolapril reduced the incidence of AF in patients with LV dysfunction following acute MI (56), but it remains to be clarified whether this effect is related to reversal of structural or electrical remodeling in the atria or to another mechanism.

Other factors potentially involved in the induction or maintenance of AF are outlined in Table 2. Among these is inflammation, and ongoing studies are exploring the use of statin-type lipid-lowering drugs with this mechanism in mind.

B. Atrioventricular Conduction

1. General Aspects

In the absence of an accessory pathway or His-Purkinje dysfunction, the AV node limits conduction during AF (57). Of the multiple atrial inputs to the AV node that have been identified, 2 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 plays a prominent role in determining the ventricular response during AF (58) by altering the refractoriness of the AV node and slowing or blocking atrial impulses and may explain the irregularity of ventricular response during AF (59). When the atrial rate is relatively slow during AF, the ventricular rate tends to rise and, conversely, 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 (58). Vagal tone also enhances the negative chronotropic effects of concealed conduction in the AV node (60). Fluctuations in autonomic tone can produce disparate ventricular responses to AF, 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.

TABLE 2. Etiologies and Factors Predisposing Patients to AF

Electrophysiological abnormalities
Enhanced automaticity (focal AF)
Conduction abnormality (reentry)
Atrial pressure elevation
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
Atrial ischemia
Coronary artery disease
Inflammatory or infiltrative atrial disease
Pericarditis
Amyloidosis
Myocarditis
Age-induced atrial fibrotic changes
Drugs
Alcohol
Caffeine
Endocrine disorders
Hyperthyroidism
Pheochromocytoma
Changes in autonomic tone
Increased parasympathetic activity
Increased sympathetic activity
Primary or metastatic disease in or adjacent to the atrial wall
Postoperative
Cardiac, pulmonary, or esophageal
Congenital heart disease
Neurogenic
Subarachnoid hemorrhage
Nonhemorrhagic, major stroke
Idiopathic (lone AF)
Familial AF

AF indicates atrial fibrillation.

2. Atrioventricular Conduction in Preexcitation Syndromes

Conduction across an accessory pathway during AF can result in dangerously rapid ventricular rates (2). Transition of AV reentry into AF in patients with the WPW syndrome can produce a rapid ventricular response that degenerates into lethal ventricular fibrillation (61). Drugs that lengthen refractoriness and slow conduction across the AV node (such as digitalis, verapamil, or diltiazem) do not block conduction over the accessory pathway and may accelerate the ventricular rate. Hence, these agents are contraindicated in this situation (62). 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 in patients with AF associated with preexcitation.

C. Myocardial and Hemodynamic Consequences of Atrial Fibrillation

Among factors that affect 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, HCM, or restrictive cardiomyopathy. Myocardial contractility is not constant during AF because of force–interval relationships associated with variations in cycle length (63). In patients with persistent AF, mean LA and RA volumes increase over time (64) and restoration and maintenance of sinus rhythm decrease these volumes (65). Moreover, TEE has demonstrated that contractile function and blood flow velocity in the LAA recover after cardioversion, consistent with a reversible atrial cardiomyopathy in patients with AF (66). Although one might expect restoration of sinus rhythm to improve the other hemodynamic characteristics associated with AF, this is not always the case (67).

Beyond its effects on atrial function, a persistently elevated ventricular rate during AF may adversely increase mitral regurgitation and produce dilated ventricular cardiomyopathy (tachycardia-induced cardiomyopathy) (2,68). It is important to recognize this cause of cardiomyopathy, in which HF is a consequence rather than the cause of AF, because control of the ventricular rate may lead to reversal of the myopathic process. A variety of hypotheses have been proposed to explain tachycardia-mediated cardiomyopathy on the basis of myocardial energy depletion, ischemia, abnormal calcium regulation, and remodeling, but the actual mechanisms are still unclear (69).

D. Thromboembolism

Although ischemic stroke and systemic arterial occlusion in AF are generally attributed to embolism of thrombus from the LA, the pathogenesis of thromboembolism is complex (70). 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 (71,72). The annual risk of stroke in patients with AF is in the range of 3% to 8% per year, depending on associated stroke risk factors (23). About half of all elderly AF patients have hypertension (a major risk factor for cerebrovascular disease), and approximately 12% have carotid artery stenosis (73). Carotid atherosclerosis is not substantially more prevalent in AF patients with stroke than in patients without AF, however, and is probably a relatively minor contributing epidemiological factor (74).

1. Pathophysiology of Thrombus Formation

Thrombus formation as a result of stasis in the LAA is thought to represent the main source of disabling cardioembolic ischemic strokes in patients with AF. These thrombi cannot be regularly examined by precordial (transthoracic) echocardiography (75), and TEE is a more sensitive and specific method to assess LAA function (76) and detect thrombus formation. Serial TEE studies of the LA (77) and LAA (78) during conversion of AF to sinus rhythm demon-

strated reduced LAA flow velocities related to loss of organized mechanical contraction during AF. Thrombi are more often encountered in AF patients with ischemic stroke than in those without stroke (79). 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 (80,81).

After successful cardioversion, regardless of whether the method is electrical, pharmacological, or spontaneous (82), stunning of the LAA may account for an increased risk of thromboembolic events. Atrial stunning is at a maximum immediately after cardioversion; progressive improvement of atrial transport function usually occurs within a few days but sometimes takes as long as 3 to 4 wk, depending on the duration of AF (82,83). This corroborates the clinical observation that following cardioversion, more than 80% of thromboembolic events occur during the first 3 d and almost all occur within 10 d (84). TEE studies have verified resolution of thrombus in the majority of patients (85). 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. Although stunning may be milder with certain associated conditions or a short duration of AF, anticoagulation is recommended during cardioversion and for at least 4 wk afterward in all patients with AF lasting longer than 48 h or of unknown duration, including lone AF, except when contraindicated.

Decreased flow within the LA/LAA during AF has been associated with spontaneous echo contrast (SEC), thrombus formation, and embolic events (86,87). Specifically, SEC, or "smoke," a swirling haze of variable density, may be detected by transthoracic echocardiography or TEE imaging under low-flow conditions (88). There is evidence that SEC is a marker of stasis caused by AF (89,90), but the utility of SEC for prospective thromboembolic risk stratification beyond that achieved by clinical assessment alone has not been confirmed.

LAA flow velocities are lower in patients with atrial flutter than is 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 (91) and anticoagulation is recommended similarly. (See Section 8.1.4.1.3 in the full-text guidelines, Therapeutic Implications.)

2. Clinical Implications

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. The strong association between hypertension and stroke in AF is probably mediated primarily by embolism originating in the LAA (72), but hypertension also increases the risk of noncardioembolic strokes in patients with AF (92). Whether control of hypertension lowers the risk for cardioembolic stroke in patients with AF is a vital question.

The increasing stroke risk in patients with AF with advancing age is also multifactorial. Aging is a risk factor for atherosclerosis, and plaques in the aortic arch are associated with stroke independent of AF (93). Age is a more potent risk factor when combined with other risk factors such as hypertension or female gender, and women over age 75 y with AF are at particular risk for stroke (94).

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 (95) but not in moderate-risk patients given aspirin (96,97). LV systolic dysfunction has been associated both with LA thrombus and with noncardioembolic strokes in patients with AF (72,98).

VI. Causes, Associated Conditions, Clinical Manifestations, and Quality of Life

A. Causes and Associated Conditions

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. In the setting of acute MI, the development of AF portends an adverse prognosis compared with preinfarct AF or sinus rhythm (99,100). When AF is associated with atrial flutter, WPW syndrome, or AV nodal reentrant tachycardia, treatment of the primary arrhythmia reduces or eliminates the incidence of recurrent AF (101). AF is a common early postoperative complication of cardiac and thoracic surgery.

2. Atrial Fibrillation Without Associated Heart Disease

Approximately 30% to 45% of cases of paroxysmal AF and 20% to 25% of cases of persistent AF occur in young patients without demonstrable underlying disease ("lone AF") (12). AF can present as an isolated or familial arrhythmia, although a causal underlying disease may appear over time (102). Although AF may occur in the elderly without underlying heart disease, the changes in cardiac structure and function that accompany aging, such as increased myocardial stiffness, may be associated with AF, just as heart disease in older patients may be coincidental and unrelated to AF.

3. Medical Conditions Associated With Atrial Fibrillation

Obesity is an important risk factor for the development of AF (103). After adjustment for clinical risk factors, the excess risk of AF appears related to LA dilation. There is a graded increase in LA size as body mass index increases from normal to the overweight and obese categories, and weight has been linked to regression of LA enlargement (104). These findings suggest a physiological link between obesity, AF, and stroke and raise the intriguing possibility that weight reduction may decrease the risk associated with AF.

4. Atrial Fibrillation With Associated Heart Disease

Specific cardiovascular conditions associated with AF include valvular heart disease (most often mitral valve disease), HF, coronary artery disease (CAD), and hypertension, particularly when LV hypertrophy (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.

5. Familial 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 the offspring of parents with 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 with a family history of hypertension, diabetes, or HF (105). The molecular defects responsible for familial AF are largely unknown. Specific chromosomal loci linked to AF in some families (106) suggest distinct genetic mutations (107).

6. Autonomic Influences in Atrial Fibrillation

Autonomic influences play an important role in the initiation of AF. Measurement of heart rate variability (HRV) reflects changes in relative autonomic modulation rather than the absolute level of sympathetic or parasympathetic tone. It appears, however, that the balance between sympathetic and vagal influences is important as a predictor of AF. Vagal predominance has been observed in the minutes preceding the onset of AF in some patients with structurally normal hearts, while in others there is a shift toward sympathetic predominance (108,109). Although certain patients can be characterized in terms of a vagal or an adrenergic form of AF, these cases likely represent the extremes of either influence (110). In general, vagally mediated AF occurs at night or after meals, while adrenergically induced AF typically occurs during the daytime (111). In patients with vagally mediated AF, the more common form, adrenergic blocking drugs or digitalis sometimes worsen symptoms. For AF of the adrenergic type, beta blockers are the initial treatment of choice.

B. Clinical Manifestations

AF may cause a sensation of palpitations, have distinct hemodynamic or thromboembolic consequences, or follow an asymptomatic period of unknown duration. Ambulatory ECG recordings and device-based monitoring reveal that individuals may experience periods of both symptomatic and asymptomatic AF (112–114). Over time, palpitation may disappear, such that patients in whom the arrhythmia has become permanent 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, underlying functional status, duration of AF, and individual patient factors (115).

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 that can occur upon conversion in patients with sinus node dysfunction or because of rapid ventricular rates in patients with HCM, valvular aortic stenosis, or an accessory pathway.

C. Quality of Life

Available data suggest that quality of life is considerably impaired in patients with AF compared to 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 (116). In a typical study, a majority of patients with paroxysmal AF considered the arrhythmia disruptive of lifestyle, but this perception was not associated with either the frequency or duration of symptomatic episodes (117).

VII. Clinical Evaluation

A. Basic Evaluation of the Patient With Atrial Fibrillation

1. Clinical History and Physical Examination

The diagnosis of AF requires confirmation by ECG recording, sometimes in the form of bedside telemetry or ambulatory Holter recordings. The initial evaluation of a patient with suspected or proven 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 management. The work-up and therapy can usually be accomplished in a single outpatient encounter (Table 3), unless the rhythm has not been specifically documented and additional monitoring is necessary.

Physical examination may suggest AF on the basis of irregular pulse, irregular jugular venous pulsations, variation in the intensity of the first heart sound, or absence of a fourth sound heard previously during sinus rhythm. 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.

2. Investigations

The diagnosis of AF requires ECG documentation by at least a single-lead recording during the arrhythmia. In patients with implanted pacemakers or defibrillators, the diagnostic and memory functions may allow accurate and automatic detection (118). A chest radiograph is valuable mostly to detect intrinsic pulmonary pathology and evaluate the pulmonary vasculature. It is important that thyroid, renal, and hepatic

TABLE 3. 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 14).

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

TABLE 4. Trials Comparing Rate Control and Rhythm Control Strategies in Patients With AF

							Clinical Events (n)			
							Stroke/Embolism		Death	
Trial	Reference	Patients (n)	AF Duration	Follow-Up (y)	Age (mean y ±SD)	Patients in SR*	Rate	Rhythm	Rate	Rhythm
AFFIRM (2002)	128	4060	†/NR	3.5	70±9	35% vs. 63% (at 5 y)	88/2027	93/2033	310/2027	356/2033
RACE (2002)	124	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)	130	252	7 to 360 d	1	61±10	10% vs. 56% (at 1 y)	0/125	2/127	2/125	2/127
STAF (2003)	126	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)	127	205	7 to 730 d	1.7	61±11	NR vs. 64%	1/101	3/104	1/101	3/104

*Comparison between rate and rhythm control groups.

†Approximately one third of patients were enrolled with first episode of atrial fibrillation (AF).

AFFIRM indicates Atrial Fibrillation Follow-Up Investigation of Rhythm Management; ECV, internal or external electrical cardioversion; HOT CAFÉ, How to Treat Chronic Atrial Fibrillation; IA, quinidine, procainamide; IC, propafenone and/or flecainide; 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; and TE, thromboembolism.

functions, serum electrolytes, and the hemogram be measured at least once in the course of evaluation (119). All patients with AF should also have 2-dimensional, Doppler echocardiography to assess LA and LV dimensions, LV wall thickness, and function and to exclude occult valvular or pericardial disease and HCM. Thrombus in the LA or LAA is seldom detected without TEE. Among the TEE features associated with thromboembolism in patients with nonvalvular AF are thrombus, SEC, reduced LAA flow velocity, and aortic atheromatous abnormalities (120), but 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 (81).

VIII. Management

A. Strategic Objectives

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.

B. Pharmacological and Nonpharmacological Treatment 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 persons 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 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. Because the LAA is the site of greater than 95% of detected thrombi, this structure is commonly removed from the circulation during cardiac surgery in patients at risk of developing postoperative AF, although this has not been proved to prevent stroke (121).

1. Heart Rate Control Versus Rhythm Control

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. 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.

Randomized trials comparing outcomes of rhythm versus rate control strategies in patients with AF are summarized in Tables 4, 5, and 6. 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 antiar-

TABLE 5. 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)		
							Rate Control	Rhythm Control	*p*
PIAF (2000)	130	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)	124	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)	126	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)	128	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)	127	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; and STAF, Strategies of Treatment of Atrial Fibrillation.

rhythmic 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 (122). While secondary analyses support this notion, the stroke rate in patients assigned to rhythm control who stopped warfarin is uncertain, and additional research is needed to address this important question.

Information about the effects of antiarrhythmic and chronotropic therapies on quality of life is inconsistent (116,130,131). Neither the AFFIRM (132), RACE (124), PIAF (Pharmacologic Intervention in Atrial Fibrillation) (125), nor STAF (Strategies of Treatment of Atrial Fibrillation) (126) studies found differences in quality of life with rhythm control compared with rate control. Rhythm control in the PIAF and HOT CAFÉ (How to Treat Chronic Atrial Fibrillation) (127) studies resulted in better exercise tolerance than rate control, but this did not translate into improved quality of life. Symptomatic improvement has been reported after the maze procedure in patients with AF (133). Clinicians must exercise judgment, however, in translating shifts in quality of life in these selected populations to the sense of well-being experienced by individual patients. Patients with similar health status may experience an 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.

Depending on 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 (134).

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

TABLE 6. 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	Thromboembolic		Bleeding
					Stroke	Events	
RACE (2002)	124	36	18/18	ND	ND	14/21	12/9
PIAF (2000)	130	4	1/1	1*	ND	ND	ND
STAF (2003)	126	12 (8/4)	8/3	0/1	1/5	ND	8/11
AFFIRM (2002)	128	666 (310/356)	167/164	113/165	77/80	ND	107/96
HOT CAFÉ (2004)	127	4 (1/3)	0/2	1/1	0/3	ND	5/8

*Total number of patients not reported.

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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; and STAF, Strategies of Treatment of Atrial Fibrillation.

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 use of 24-h Holter recording). The definition of adequate rate control has been based primarily on short-term hemodynamic benefits and not well studied with respect to regularity or irregularity of the ventricular response to AF, quality of life, symptoms, or development of cardiomyopathy. No standard method for assessment of heart rate control has been established to guide the 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.

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) that improves with adequate rate control. 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 (137).

a. Pharmacological Rate Control During Atrial Fibrillation

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. 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 7). Combinations may be necessary to achieve rate control in both acute and chronic situations. Some patients develop symptomatic bradycardia that requires permanent pacing. Nonpharmacological therapy should be considered when pharmacological measures fail.

Special considerations in patients with the Wolff-Parkinson-White syndrome.

Intravenous administration of beta blockers, digitalis, adenosine, lidocaine, and nondihydropyridine calcium channel antagonists, all of which slow conduction across the AV node, is 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 (2), resulting in acceleration of the ventricular rate, hypotension, or ventricular fibrillation (62). 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 maintenance therapy (138).

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.

b. 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 (139). 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 right ventricular pacing.

c. Atrioventricular 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 (140–143). 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-analyses 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 (143). Catheter ablation of inferior atrial inputs to the AV node slows the ventricular rate during AF and improves symptoms without pacemaker implantation (144,145). 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. Thus, AV nodal modification without pacemaker implantation is only rarely used.

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 (146). Patients with abnormal-

TABLE 7. 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					
Heart rate control in patients without accessory pathway					
Esmolol*†	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†	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†	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
Heart rate control in patients with accessory pathway§					
Amiodarone‡‖	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
Heart rate control in patients with heart failure and without accessory pathway					
Digoxin	Class I, LOE B	0.25 mg IV each 2 h, up to 1.5 mg	60 min or more§	0.125 to 0.375 mg daily IV or orally	Digitalis toxicity, HB, ↓ HR
Amiodarone‡	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¶					
Heart rate control					
Metoprolol†	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†	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
Heart rate control in patients with heart failure and without accessory pathway					
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‡	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

*Onset is variable and some effect occurs earlier.

†Only representative members of the type of beta-adrenergic antagonist drugs are included in the table, but other, similar agents could be used for this indication in appropriate doses. Beta blockers are grouped in an order preceding the alphabetical listing of drugs.

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

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

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

¶Adequacy of heart rate control should be assessed during physical activity as well as at rest.

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

ities of diastolic ventricular compliance who depend on AV synchrony to maintain cardiac output, such as those with HCM 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.

Patients with normal LV function or reversible LV dysfunction undergoing AV nodal ablation are most likely to

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TABLE 8. 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 (17). 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.

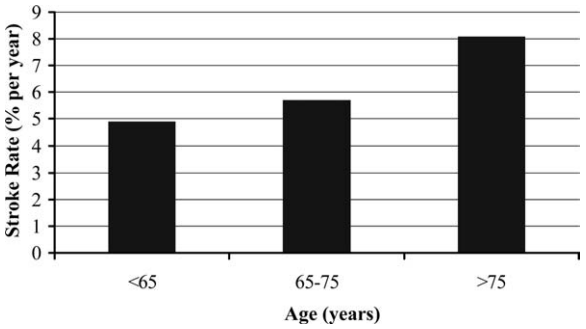

Figure 3. Stroke rates in relation to age among patients in untreated control groups of randomized trials of antithrombotic therapy. Data are from the Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–1457 (17).

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 a right ventricular pacing system who have undergone AV node ablation (147).

2. Preventing Thromboembolism

a. Risk Stratification

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% (5). In the SPAF (Stroke Prevention in Atrial Fibrillation III) studies, the annualized rate of ischemic stroke during aspirin treatment was similar in those with paroxysmal (3.2%) and permanent (3.3%) AF (148). 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 (149). 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 (96). Other factors, such as female gender, systolic blood pressure over 160 mm Hg, and LV dysfunction, have been variably linked to stroke (96). 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 8. 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). All patients with prior stroke or TIA require anticoagulation unless contraindications exist in a given patient. Patient age is a consistent independent predictor of stroke (Fig. 3), but older people are also at increased risk for anticoagulant-related bleeding (150). Special consideration of these older patients is therefore a critical aspect of effective stroke prophylaxis (151).

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 spontaneous echo contrast 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.

Several clinical schemes have been proposed to stratify the risk of ischemic stroke in patients with AF, based on analyses of prospectively monitored cohorts of participants in clinical trials in which antithrombotic therapy was controlled. Other criteria have been developed by expert consensus to classify patients into low-, intermediate-, and high-risk groups. Still others have used recursive partitioning and other techniques to identify low-risk patients. The $CHADS_2$ (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) integrates elements from several of these schemes and 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 and a history of hypertension, diabetes, or recent HF (Table 9) (152,153). 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.

Although these 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). Some advocate the routine use of anticoagulation in those with stroke rates in this range (154), whereas others favor selective anticoagulation of patients at intermediate risk, with weight given to individual bleeding risks and patient preferences (24), The threshold of benefit at which AF patients choose anticoagulation varies; some at intermediate risk elect

TABLE 9. Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ 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)* (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

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. 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;163:936–43 (153); 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 (152).

AF indicates atrial fibrillation; $CHADS_2$, Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; and TIA, transient ischemic attack.

anticoagulation, whereas others do not (155). Our recommendations for antithrombotic therapy in patients with AF are summarized in Table 10.

The risk of thromboembolism is not as well established for atrial flutter 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. Although the overall thromboembolic risk associated with atrial flutter may be somewhat lower than with AF (156), it seems prudent to estimate risk by the use of similar stratification criteria for both arrhythmias until more robust data become available.

b. 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 (23). 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.

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 (157–163) (Fig. 4). A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or cerebral TIA (164). Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 61% (95% CI 47% to 71%) versus placebo (165) (Fig. 4). 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 (166–169). Trial participants, at an average age of 69 y, were 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.

The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of

TABLE 10. 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)*	
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*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

*If mechanical valve, target international normalized ratio (INR) greater than 2.5.

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

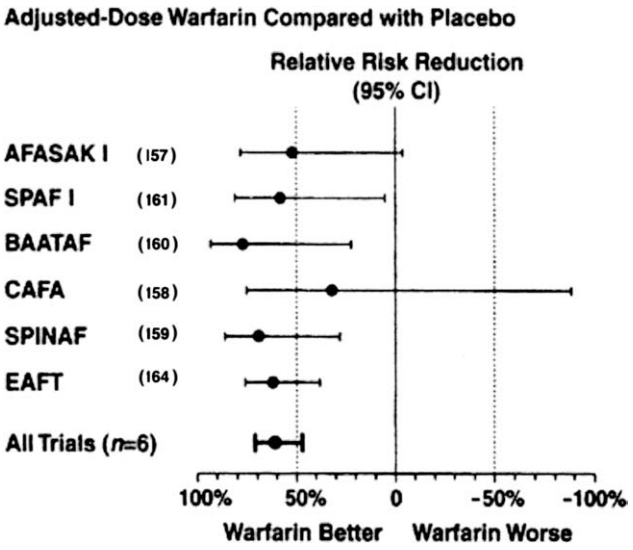

Figure 4. Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation. Adjusted-dose warfarin compared with placebo (six random trials). Modified with permission from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501 (165). AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

hemorrhagic complications (Fig. 5). Targeting the lowest adequate intensity of anticoagulation to minimize the risk of bleeding is particularly important for elderly AF patients. Maximum protection against ischemic stroke in AF is probably achieved at an INR range of 2.0 to 3.0 (170). 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 (171–173).

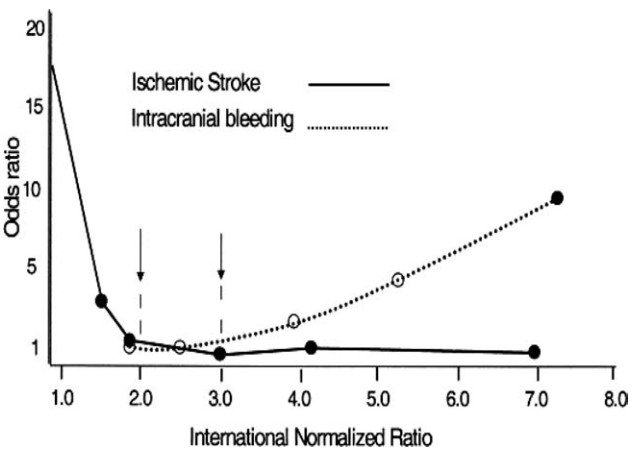

Figure 5. Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897–902 (166). Data from Odén A, Fahlén M, Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res* 2006;117:493–9 (167).

Aspirin for antithrombotic therapy in patients with atrial fibrillation.

Aspirin offers only modest protection against stroke for patients with AF (157,161,164,174–180) (Fig. 6). Meta-analysis of 5 randomized trials showed a stroke reduction of 19% (95% CI=2% to 34%) (165). Aspirin may be more efficacious for AF patients with hypertension or diabetes (181) and for reduction of noncardioembolic versus cardioembolic ischemic strokes in AF patients (72). Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes (92). Aspirin appears to prevent nondisabling strokes more than disabling strokes (165). Thus, the greater the risk of disabling cardioembolic stroke in a population of patients with AF, the less protection is afforded by aspirin (92).

Combining anticoagulant and platelet-inhibitor therapy. Combinations of oral anticoagulants plus antiplatelet agents have not generally shown reduced risks of hemorrhage or augmented efficacy over adjusted-dose anticoagulation alone. Combining aspirin with an oral anticoagulant at higher intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients (183). 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.

Platelet-inhibitor drugs are particularly valuable for prevention of recurrent myocardial ischemia 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, after which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.

Low-molecular-weight heparins.

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 (184). 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%

TABLE 11. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Up to 7-d Duration

Drug*	Route of Administration	Class of Recommendation	Level of Evidence	References
Agents with proven efficacy				
Dofetilide	Oral	I	A	197–202
Flecainide	Oral or intravenous	I	A	191, 203–210
Ibutilide	Intravenous	I	A	211–216
Propafenone	Oral or intravenous	I	A	191, 193, 195, 207, 210, 217–227, 255
Amiodarone	Oral or intravenous	IIa	A	194, 206, 217, 228–235
Less effective or incompletely studied agents				
Disopyramide	Intravenous	IIb	B	247
Procainamide	Intravenous	IIb	B	211, 213, 239
Quinidine	Oral	IIb	B	195, 203, 225, 230, 236–238, 273
Should not be administered				
Digoxin	Oral or intravenous	III	A	195, 207, 227, 231, 241, 245
Sotalol	Oral or intravenous	III	A	214, 237, 238, 242, 246

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

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 (185). 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 (186).

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 (187). 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 Group 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.

c. Nonpharmacological Approaches to Prevention of Thromboembolism

An emerging option for patients with AF who cannot safely undergo anticoagulation, not yet sufficiently investigated to

TABLE 12. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation Present for More Than 7 d

Drug*	Route of Administration	Recommendation Class	Level of Evidence	References
Agents with proven efficacy				
Dofetilide	Oral	I	A	197–202
Amiodarone	Oral or intravenous	IIa	A	194, 206, 217, 228–235
Ibutilide	Intravenous	IIa	A	211–216
Less effective or incompletely studied agents				
Disopyramide	Intravenous	IIb	B	247
Flecainide	Oral	IIb	B	191, 203–210
Procainamide	Intravenous	IIb	C	211, 213, 239
Propafenone	Oral or intravenous	IIb	B	191, 193, 195, 207, 210, 217–227, 248, 255
Quinidine	Oral	IIb	B	195, 203, 225, 230, 236–238, 273
Should not be administered				
Digoxin	Oral or intravenous	III	B	195, 207, 227, 231, 241–243, 245
Sotalol	Oral or intravenous	III	B	214, 237, 238, 242, 246

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

TABLE 13. Recommended Doses of Drugs Proven Effective for Pharmacological Cardioversion of Atrial Fibrillation

Drug*	Route of Administration	Dosage†	Potential Adverse Effects	References
Amiodarone	Oral	Inpatient: 1.2 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 Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)	194, 206, 217, 228–236, 250
	Intravenous/oral	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): More than 60 — 500 40 to 60 — 250 20 to 40 — 125 Less than 20 — Contraindicated	QT prolongation, torsades de pointes; adjust dose for renal function, body size and age	197–202
Flecainide	Oral	200 to 300 mg‡	Hypotension, atrial flutter with high ventricular rate	191, 203–210
	Intravenous	1.5 to 3.0 mg/kg over 10 to 20 min‡		
Ibutilide	Intravenous	1 mg over 10 min; repeat 1 mg when necessary	QT prolongation, torsades de pointes	211–216
Propafenone	Oral	600 mg	Hypotension, atrial flutter with high ventricular rate	191, 193, 195, 207, 210, 217–227, 248, 255
	Intravenous	1.5 to 2.0 mg/kg over 10 to 20 min‡		
Quinidine§	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	195, 203, 225, 230, 236–238

*Drugs are listed alphabetically.

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

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

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

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

allow general clinical application, is obliteration of the LAA to remove a principal nidus of thrombus formation (188). In addition to direct surgical amputation or truncation of appendage, several methods are under development to achieve this with intravascular catheters or transpericardial approaches (189). 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 comparably effective and safer than anticoagulation for some patients remains to be established (190).

3. 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 more than 48 h.

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 anticoagula-

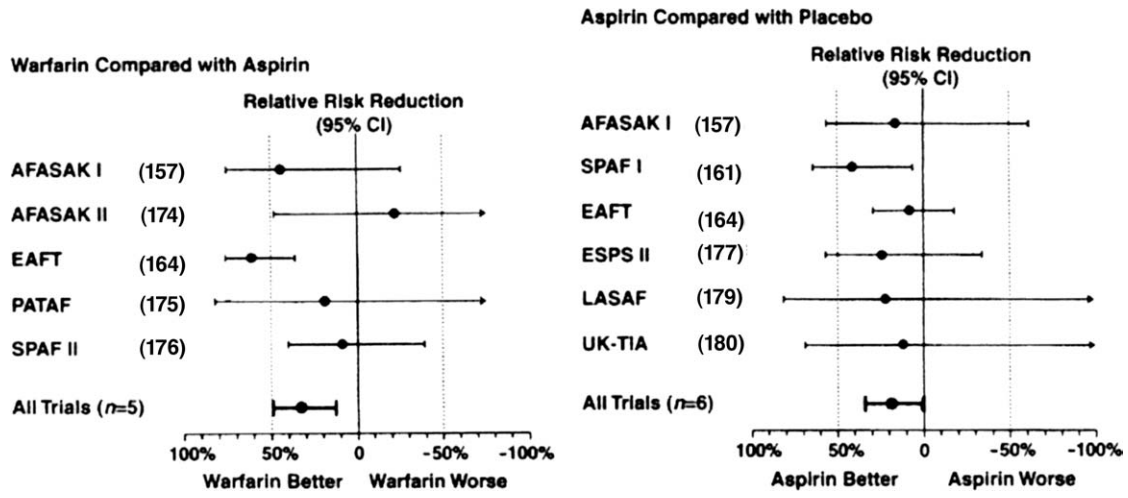

Figure 6. Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation: warfarin compared with aspirin and aspirin compared with placebo. Modified with permission from Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501 (165). AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, United Kingdom Transient Ischaemic Attack Aspirin Trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

tion are therefore the same for both methods, as outlined in Section I.C.2, Preventing Thromboembolism. Cardioversion in patients with AF following recent heart surgery or MI is addressed later (see Section I.C.5, Special Considerations).

a. 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 (191,192). 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 III, Classification.) A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 h (193). 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 (194). 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 (195). 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 for cardioversion of AF is presented in Tables 11, 12, and 13. Algorithms for pharmacological management of AF are given in Figures 7, 8, 9, and 10. Throughout this document, reference is made to the Vaughan Williams classification of antiarrhythmic drugs (196), modified to include drugs that became available after the original classification was developed (Table 14). The recommendations given in this document are based on published data and do not necessarily adhere to the regulations and labeling requirements of governmental agencies. These antiarrhythmic drugs 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.

4. Pharmacological Agents to Maintain Sinus Rhythm

a. 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 parox-

TABLE 14. 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
Bretylium
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 (196). © 1984 by Sage Publications Inc.

ysmal 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 and doses for maintenance of sinus rhythm are given in Table 15. It should be noted that any membrane active agent may cause proarrhythmia.

b. 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. With the exception of those involving low-dose oral amiodarone (234), virtually all studies of pharmacological cardioversion have involved hospitalized patients. However, 1 study (251) provided a clinically useful approach with out-of-hospital patient-controlled conversion using class IC drugs.

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 (252). 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 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) (253–255). 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 (256,257). Unless AV node conduction is impaired, a short-acting beta blocker or nondihydropyridine

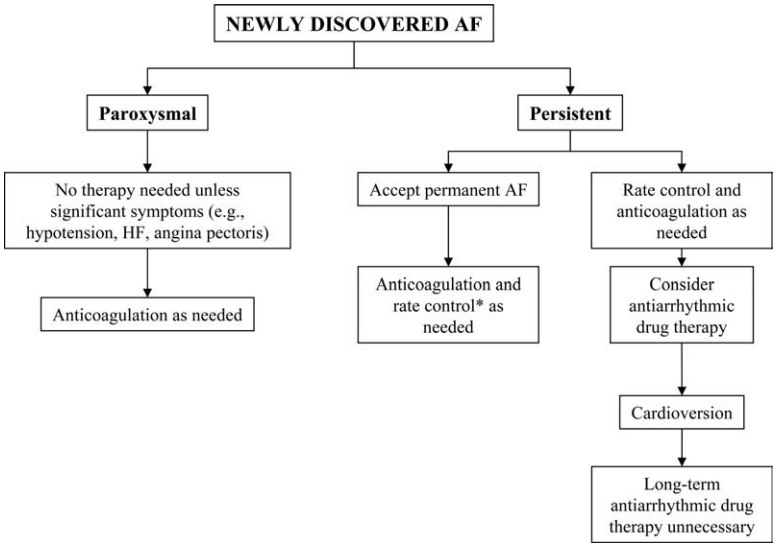

Figure 7. Pharmacological management of patients with newly discovered atrial fibrillation (AF). *See Figure 9. HF indicates heart failure.

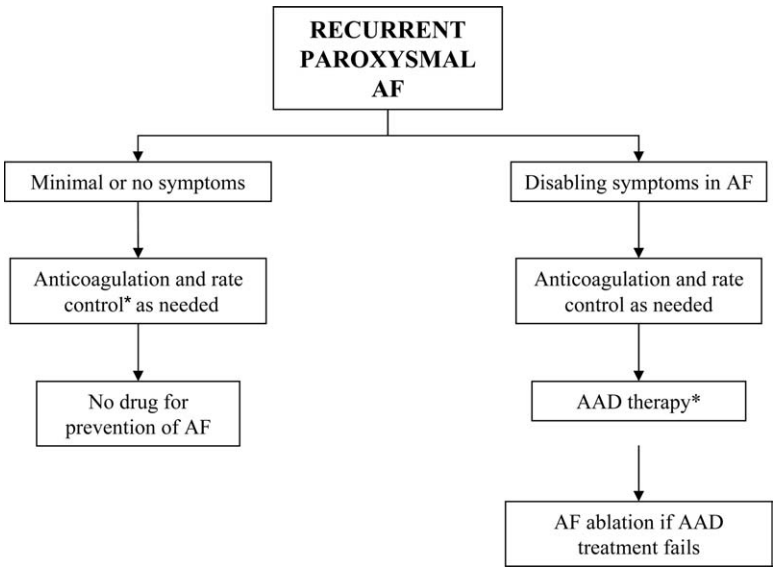

Figure 8. Pharmacological management of patients with recurrent paroxysmal atrial fibrillation (AF). *See Figure 9. AAD indicates antiarrhythmic drug.

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. 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 16 lists other factors associated with proarrhythmic toxicity to class IC agents. It should be noted that these 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 "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 460 ms, serum electrolytes are normal, and risk factors associated with class III drug–related proarrhythmia are considered (Table 16), sotalol may be initiated in outpatients with little or no heart disease. It is safest to start sotalol when the patient is in

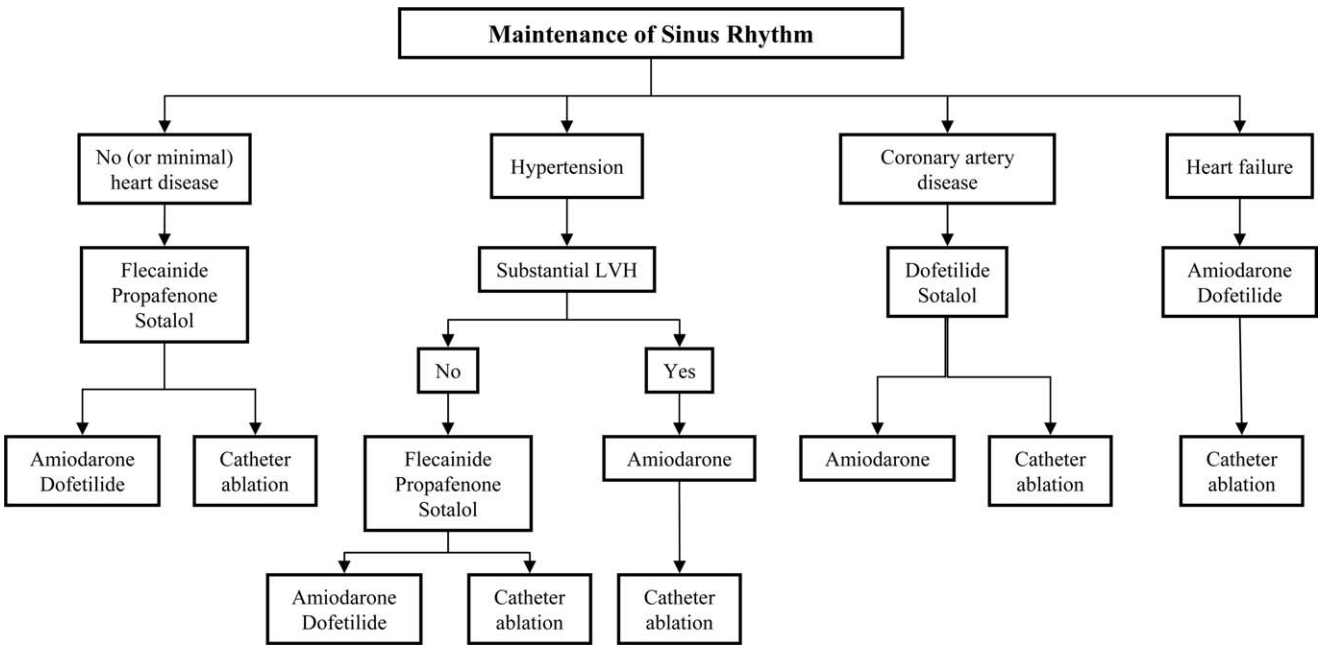

Figure 9. Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness 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 in the full-text guidelines for details. LVH indicates left ventricular hypertrophy.

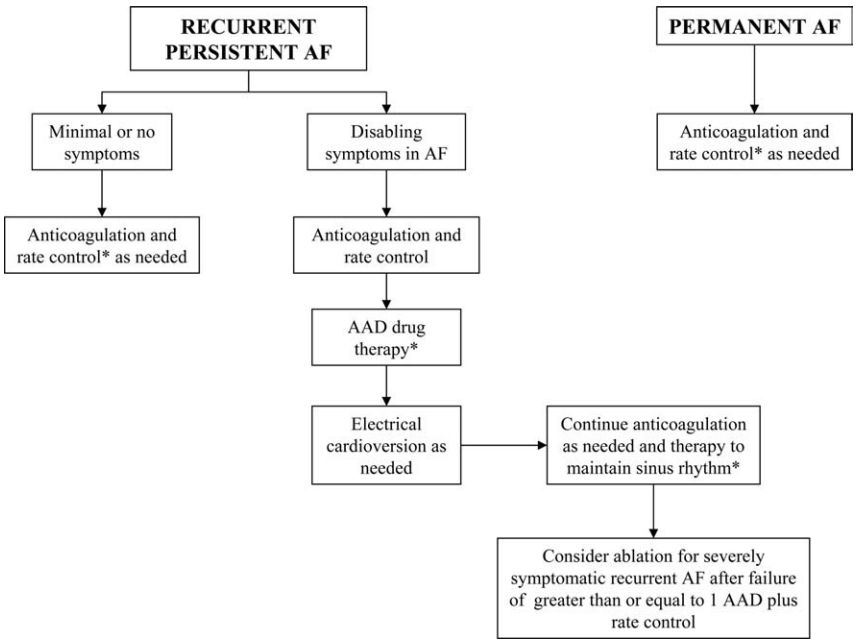

Figure 10. Pharmacological management of patients with recurrent persistent or permanent atrial fibrillation (AF). *See Figure 9. Initiate drug therapy before cardioversion to reduce the likelihood of early recurrence of AF. AAD indicates antiarrhythmic drug.

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 (258), 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 wk (258) or 1 g daily for 1 wk (232), followed by lower maintenance doses. Amiodarone, class IA or IC agents, or sotalol can be associated with bradycardia requiring permanent pacemaker implantation (259); 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 and out-of-hospital initiation of dofetilide is not currently 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, amiodarone, or disopyramide) 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 should be reassessed after each dose change. The heart rate should be monitored at approximately weekly intervals, either by checking the pulse rate, by use of an event recorder, or by ECG tracings obtained in 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 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.

TABLE 15. Typical Doses of Drugs Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation*

Drug†	Daily Dosage	Potential Adverse Effects
Amiodarone‡	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§	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§	160 to 320 mg	Torsades de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

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

5. Direct-Current Cardioversion of Atrial Fibrillation and Atrial Flutter

a. Technical and Procedural Aspects

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 (136), 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.

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 (135,260).

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 (261). The electric

TABLE 17. Types of Proarrhythmia During Treatment With Various Antiarrhythmic Drugs for AF or Atrial Flutter According to the Vaughan Williams Classification

A. Ventricular proarrhythmia
Torsades de pointes (VW types IA and III drugs*)
Sustained monomorphic ventricular tachycardia (usually VW type IC drugs)
Sustained polymorphic ventricular tachycardia/VF without long QT (VW types IA, IC, and III drugs)
B. Atrial proarrhythmia
Provocation of recurrence (probably VW types IA, IC, and III drugs)
Conversion of AF to flutter (usually VW type IC drugs)
Increase of defibrillation threshold (a potential problem with VW type IC drugs)
C. Abnormalities of conduction or impulse formation
Acceleration of ventricular rate during AF (VW types IA and IC drugs)
Accelerated conduction over accessory pathway (digoxin, intravenous verapamil, or diltiazem†)
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 (196).

*This complication is rare with amiodarone.

†Although 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 atrial fibrillation (AF) associated with preexcitation.

VF indicates ventricular fibrillation.

TABLE 16. 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*	Depressed LV function*
Hypokalemia/hypomagnesemia*	
Female gender	
Renal dysfunction*	
Bradycardia*	Rapid ventricular response rate*
1. (Drug-induced) sinus node disease or AV block	1. During exercise
2. (Drug-induced) conversion of AF to sinus rhythm	2. During rapid AV conduction
3. Ectopy producing short-long R-R sequences	
Rapid dose increase	Rapid dose increase
High dose (sotalol, dofetilide), drug accumulation*	High dose, drug accumulation*
Addition of drugs*	Addition of drugs*
1. Diuretics	1. Negative inotropic drugs
2. Other QT-prolonging antiarrhythmic drugs	
3. Nonantiarrhythmic drugs listed in http://www.torsades.org/	
Previous proarrhythmia	
After initiation of drug	
Excessive QT lengthening	Excessive (more than 150%) QRS widening

*Some of these factors may develop later after initiation of drug treatment. See Section 8.3.3.3 in the full-text guidelines for details. 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 (196).

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

TABLE 18. Pharmacological Treatment Before Cardioversion in Patients With Persistent AF: Effectiveness of Various Antiarrhythmic Drugs on Acute and Subacute Outcome of Transthoracic DC Shock

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

All 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; and SRAF, subacute recurrence of atrial fibrillation.

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. 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, 39% with 200, and 95% with 360 J, respectively), resulting in fewer shocks and less cumulative energy when 360 J was delivered initially (262). 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 (263).

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.

b. 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 (264,265). Prophylactic antithrombotic therapy is discussed in Section VIII.B.5.c, Pharmacological Enhancement of Direct-Current Cardioversion.

c. Pharmacological Enhancement of Direct-Current Cardioversion

Although most recurrences of AF occur within the first month after direct-current cardioversion, research with internal atrial cardioversion (270) and postconversion studies using transthoracic shocks (271) have established several patterns of AF recurrence (Fig. 7). 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 (272), and recurrence after cardioversion is sometimes delayed for days or weeks (271). 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 (273).

Restoration and maintenance of sinus rhythm are less likely when AF has been present for more 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 (262,274–276) is partly explained by differences in patient characteristics and the waveform used but also depends on the definition of success, because the interval at which the result is evaluated ranges from moments to several days. In general, it appears that 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 therapy.

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. Antiarrhythmic medications may be initiated out of hospital or in hospital immediately prior to direct-current cardioversion. (see Section 8.1.7 in the full-text guidelines, Out-of-Hospital Initiation of Antiarrhythmic Drugs in Patients). The risks of pharmacological treatment include the possibility of paradoxically increasing the defibrillation threshold, as described with flecainide (277), accelerating the ventricular rate when class IA or IC drugs are given without an AV nodal blocking agent (256,257,278,279), and inducing ventricular arrhythmias (Table 17).

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, but infrequently repeated cardioversions may be acceptable in patients who are highly symptomatic upon relapse to AF.

Available data suggest that starting pharmacological therapy and establishing therapeutic plasma drug concentrations before direct-current cardioversion enhances immediate success and suppresses 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 (Table 18).

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 (280,281).

d. Prevention of Thromboembolism in Patients With Atrial Fibrillation Undergoing Conversion

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% (265,282). 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 (62,269). It is common practice to administer anticoagulant drugs when preparing patients with AF of more than 2-d duration for cardioversion. Manning et al (283) suggested that TEE might be used to identify patients without LAA thrombus who do not require anticoagulation, but a subsequent investigation (284) and meta-analysis found this approach unreliable (285).

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. 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 LAA (286) ("stunning"), which can occur after spontaneous, pharmacological (287,288), or electrical (288–290) conversion of AF or after radiofrequency catheter ablation of atrial flutter (91). Recovery of mechanical function may be delayed, depending in part on the duration of AF before conversion (291–293). This could explain why some patients without demonstrable LA thrombus on TEE before cardioversion subsequently experience thromboembolic events (284). 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 (84).

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 AF (294) 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 longer 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. Stroke or systemic embolism has been reported in patients with atrial flutter undergoing cardioversion (295–297), 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.

6. Maintenance of Sinus Rhythm

a. Pharmacological Therapy

Whether paroxysmal or persistent, AF is a chronic disorder, and recurrence at some point is likely in most patients (299–301). 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. Trials in which rate versus rhythm control strategies were compared in patients with persistent and paroxysmal AF (124,126,127,130,132) found no reduction in death, disabling stroke, hospitalizations, new arrhythmias, or thromboembolic complications in the rhythm control group.

b. Predictors of Recurrent Atrial Fibrillation

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 (302). In 1 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 (300). Predictors of recurrences within that interval included hypertension, age over 55 y, and AF duration of longer than 3 mo. Serial cardioversions and prophylactic drug therapy resulted in freedom from recurrent AF in approximately 30% of patients (300), and with this approach predictors of recurrence included age over 70 y, AF duration beyond 3 mo, and HF (300). Other risk factors for recurrent AF include LA enlargement and rheumatic heart disease.

Various benign arrhythmias, especially ventricular and supraventricular premature beats, bradycardia, and short periods of sinus arrest, may arise after cardioversion and commonly subside spontaneously (266). More dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may arise in the face of hypokalemia, digitalis intoxication, or improper synchronization (267,268). Serum potassium levels should be in the normal range for safe, effective cardioversion. Cardioversion is contraindicated in cases of digitalis toxicity because resulting ventricular tachyarrhythmia may be difficult to terminate.

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 (269).

c. 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 AF 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 (303).

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.

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.

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. 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.

d. Selection of Antiarrhythmic Agents in Patients With Cardiac Diseases

Pharmacological management algorithms to maintain sinus rhythm in patients with AF (see Figs. 7, 8, 9, and 10) and applications in specific cardiac disease states are based on available evidence and extrapolated from experience with these agents in other situations.

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 (200,304), and these are the recommended drugs for maintenance of sinus rhythm in patients with AF in the presence of HF (Fig. 9). 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 (305–308).

Coronary artery disease.

In stable patients with CAD, beta blockers may be considered first, although their use is supported by only 2 studies (309,310) and data on efficacy for maintenance of sinus rhythm in patients with persistent AF after cardioversion are not convincing (310). 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 MI (311) but may be preferred over sotalol in patients with HF (312,313). 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 DIAMOND-MI (Danish Investigations of Arrhythmias and Mortality on Dofetilide in Myocardial Infarction) trial (314) 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 for such patients (Fig. 9).

Hypertensive heart disease.

Hypertension is the most prevalent and potentially modifiable independent risk factor for the development of AF and its complications, including thromboembolism (315,316). Blood pressure control may become an opportune strategy for the prevention of AF. Patients with LVH may face an increased risk of torsades de pointes related to early ventricular afterdepolarizations (303,317). 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, both propafenone and flecainide are reasonable choices. Proarrhythmia with 1 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 to 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 (318). Drugs modulating the RAAS reduce structural cardiac changes (319), 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 (320). In patients at increased risk of cardiovascular events, therapy with either the ACE inhibitor ramipril (321–323) or angiotensin receptor antagonist, losartan (324,325) 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 (326). New-onset AF and stroke were significantly reduced by losartan as compared to atenolol in hypertensive patients with ECG-documented LVH, despite a similar reduction of blood pressure (16). The benefit of losartan was greater in patients with AF than in those with sinus rhythm for the primary composite endpoint (cardiovascular mortality, stroke, and MI) and for cardiovascular mortality alone (327). Presumably, the beneficial effects of beta blockers and drugs modulating the RAAS are at least partly related to lower blood pressure.

7. 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.

a. Surgical Ablation

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 (328), 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 (329).

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 macroentrant rhythms—atrial flutter or AF—from becoming sustained (330). Success rates of around 95% over 15 y of follow-up have been reported in patients undergoing mitral valve surgery (331). Other studies suggest success rates around 70% (332). 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 re-operation, impaired atrial transport function, delayed atrial arrhythmias (especially atrial flutter), and atrioesophageal fistula.

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 (332). 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.

b. Catheter Ablation

Early radiofrequency catheter ablation techniques emulated the surgical maze procedure by introducing linear scars in the atrial endocardium (333). While the success rate was approximately 40% to 50%, a relatively high complication rate diminished enthusiasm for this approach (38). 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 (38). 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 (38). In another study, the success rate was 86% over a 6-mo follow-up (334). 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 (335), and modification of the procedures has incorporated linear LA ablation, mitral isthmus ablation, or both for selected patients (336).

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 (337). 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 (338), but success rates were lower in patients with cardiac dysfunction (339). Still another approach (340,341) 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 (341), with approximately 90% success in cases of paroxysmal AF and 80% in cases of persistent AF (339,342,343).

Another anatomic approach to radiofrequency catheter ablation targets complex fractionated electrograms (344) 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 (345). 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 (346).

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 (140–142,347–349). A meta-analysis of 10 studies of patients with AF (143) 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.

Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrate 1 or more y free from recurrent AF in most (albeit carefully selected) patients (350–352). 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 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.

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, atrioesophageal fistula, and LA flutter (343). The initial ablation approach targeting PV ectopy was associated with an unacceptably high rate of PV stenosis (334,353), 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 (338).

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 (354). Based on limited data from dose-comparison studies, it seems likely that more aggressive anticoagulation may reduce the incidence of thromboembolism associated with catheter-based ablation of AF.

Atrioesophageal fistula has been reported with both the circumferential Pappone approach (355,356) and the Haissaguerre PV ablation techniques (356) 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 (357), and this is amenable to further ablation (358).

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.

c. Suppression of Atrial Fibrillation Through Pacing

Several studies have examined the role of atrial pacing, either in the RA alone or in more than 1 atrial location, to prevent recurrent paroxysmal AF. In patients with symptomatic bradycardia, the risk of AF is lower with atrial than with ventricular pacing (359). 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 (360–363). 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, which 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. Although atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, the value of pacing as a primary therapy for prevention of recurrent AF has not been proven.

d. Internal Atrial Defibrillators

There has been an interest in internal cardioversion of AF for the past 10 y (135). Intense basic and clinical research to find 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 (135). 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.

An important limitation of atrial defibrillators, unrelated to efficacy, is that most patients find discharge energies over 1 J uncomfortable. 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.

C. 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 (359,360). On the other hand, studies in patients with intermittent atrial tachyarrhythmias failed to illustrate a general benefit of atrial pacing (360,365,366). Another potential avenue for primary prevention has been suggested following secondary analysis of placebo-controlled trials of treatment with ACE inhibitors (56,367). In the LIFE (Losartan Intervention For End Point Reduction in Hypertension) (16) and CHARM (Candesartan in Heart Failure As-

sessment of Reduction in Mortality and Morbidity) (368) trials, the angiotensin receptor antagonists losartan and candesartan reduced the incidence of AF in hypertensive patients with LVH (16) and symptomatic HF (21,368), respectively. These results, together with their favorable safety profile compared with antiarrhythmic agents, suggest a role for ACE inhibitor 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 (55).

Yet inadequately explored, the use of statins has also been suggested to protect against AF (369,370), and dietary lipid components may influence the propensity of patients to develop AF (371). 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 (369). 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.

IX. Proposed Management Strategies

A. 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 Figs. 7, 8, 9, and 10).

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 study (132) 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 to a rhythm control strategies (132). Other trials that addressed this issue reached similar conclusions (124,126,127,130). 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 longer 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).

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 (Fig. 9). For individuals with no or minimal heart disease, flecainide, propafenone, or sotalol is recommended as initial antiarrhythmic therapy because they 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 algorithms presented here have been developed by consensus and are subject to revision as additional evidence emerges.

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, or AV nodal ablation and pacing.

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.

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. James E. Lowe	None	None	None	None	None
Dr. G. Neal Kay	None	None	None	None	None
Dr. S. Bertil Olsson	AstraZeneca L.P.	None	AstraZeneca L.P. Upjohn	None	AstraZeneca L.P. Boeringer-Ingelheim
Dr. Eric N. Prystowsky	Sanofi-Aventis	Reliant	CardioNet	CardioNet	Bard Guidant Sanofi-Aventis Stereotaxis
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)	Sanofi-Aventis
Dr. Juan 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 Proctor and Gamble Pharmaceuticals	None	None	AstraZeneca Berlex Laboratories Cardiome Hewlett Packard Proctor 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 Pfizer Sunol	None	None	None	Aventis
Dr. Dan Atar	Content—ESC	None	None	None	None	None
Dr. Martin Borggrefe	Content—ESC, VA SCD Guideline Writing Committee	Medtronic	None	None	None	Proctor and Gamble Syncor
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 loyalties)		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

APPENDIX II: Continued

Peer Reviewer	Representation	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/Advisory Member
Dr. Larry Goldstein	Content—Stroke Review Committee	AGA Corp Boehringer Ingleheim CDC/UNC-Chapel Hill NIH Pfizer-Parke-Davis Veteran's 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			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
Dr. Bradley Knight	Content—ACC ECA Committee, ACCP 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 Commitee	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 Dronedarone 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 naturetic 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
EAFT	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 Dronedarone 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 Insufficienca 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

APPENDIX III: Continued

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	Metropolol 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

References

1. Bellet S. Clinical Disorders of the Heart Beat. 3rd ed. Philadelphia: Lea & Febiger, 1971.
2. Prystowsky EN, Katz AM. Atrial Fibrillation in Textbook of Cardiovascular Medicine. Philadelphia: Lippincott-Raven, 1998:1661.
3. Knight BP, Michaud GF, Strickberger SA, et al. Electrocardiographic differentiation of atrial flutter from atrial fibrillation by physicians. J Electrocardiol 1999;32:315–9.
4. Allessie MA, Konings KT, Kirchhof CJ. Mapping of atrial fibrillation. In: Olsson SB, Allessie MA, Campbell RW, editors. Atrial Fibrillation: Mechanisms and Therapeutic Strategies. Armonk, NY: Futura, 1994: 37–49.
5. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. N Engl J Med 1987;317:669–74.
6. Deleted in proof.
7. Friberg J, Buch P, Scharling H, et al. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14:666–72.
8. Le Heuzey JY, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J 2004;147:121–6.
9. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5.
10. 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.
11. Friberg J, Scharling H, Gadsboll N, et al. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). Am J Cardiol 2003;92:1419–23.
12. 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.
13. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455–61.
14. Crijns HJ, Tjeerdsma G, De Kam PJ, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. Eur Heart J 2000;21:1238–45.
15. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation 2002;106:331–6.
16. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:712–9.
17. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials [published erratum appears in Arch Intern Med 1994;154:2254]. Arch Intern Med 1994;154:1449–57.
18. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.
19. 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.
20. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.
21. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005;149: 548–57.
22. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920–5.
23. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
24. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. Ann Intern Med 1999;131: 688–95.
25. Wolf PA, Dawber TR, Thomas HE Jr, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–7.
26. Bharti S, Lev M. Histology of the normal and diseased atrium. In: Fall RH, Podrid PJ, editors. Atrial Fibrillation: Mechanism and Management. New York: Raven Press, 1992:15–39.
27. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230–46.
28. Aime-Sempe C, Folliguet T, Rucker-Martin C, et al. Myocardial cell death in fibrillating and dilated human right atria. J Am Coll Cardiol 1999;34:1577–86.
29. Polontchouk L, Haefliger JA, Ebelt B, et al. Effects of chronic atrial fibrillation on gap junction distribution in human and rat atria. J Am Coll Cardiol 2001;38:883–91.
30. Mary-Rabine L, Albert A, Pham TD, et al. The relationship of human atrial cellular electrophysiology to clinical function and ultrastructure. Circ Res 1983;52:188–99.
31. Bailey GW, Braniff BA, Hancock EW, et al. Relation of left atrial pathology to atrial fibrillation in mitral valvular disease. Ann Intern Med 1968;69:13–20.
32. Pokharel S, van Geel PP, Sharma UC, et al. Increased myocardial collagen content in transgenic rats overexpressing cardiac angiotensin-converting enzyme is related to enhanced breakdown of N-acetyl-Ser-Asp-Lys-Pro and increased phosphorylation of Smad2/3. Circulation 2004;110:3129–35.
33. Goette A, Staack T, Rocken C, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol 2000;35: 1669–77.
34. Kumagai K, Nakashima H, Urata H, et al. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003;41:2197–204.
35. Verheule S, Wilson E, Everett T, et al. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003;107:2615–22.
36. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003;108:1461–8.
37. Jais P, Haissaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95: 572–6.
38. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.
39. Schwartzman D, Bazaz R, Nosbisch J. Common left pulmonary vein: a consistent source of arrhythmogenic atrial ectopy. J Cardiovasc Electrophysiol 2004;15:560–6.
40. Hsu LF, Jais P, Keane D, et al. Atrial fibrillation originating from persistent left superior vena cava. Circulation 2004;109:828–32.
41. Chen SA, Tai CT, Yu WC, et al. Right atrial focal atrial fibrillation: electrophysiologic characteristics and radiofrequency catheter ablation. J Cardiovasc Electrophysiol 1999;10:328–35.
42. Jais P, Hocini M, Macle L, et al. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. Circulation 2002;106:2479–85.
43. Shah D, Haissaguerre M, Jais P, et al. Nonpulmonary vein foci: do they exist? Pacing Clin Electrophysiol 2003;26:1631–5.
44. Ortiz J, Niwano S, Abe H, et al. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter: insights into mechanism. Circ Res 1994;74:882–894.
45. Konings KT, Kirchof CJ, Smeets JR, et al. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89: 1665–80.
46. Moe GK, Abildskov JA. Atrial fibrillation as a self sustaining arrhythmia independent of focal discharge. Am Heart J 1959;58:59–70.
47. Cox JL, Canavan TE, Schuessler RB, et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg 1991;101:406–26.

47a. Mandapati R, Skanes A, Chen J, et al. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000;101:194–199.

47b. Lazar S, Dixit S, Marchlinski FE, et al. Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. Circulation 2004;110:3181–3186.

47c. Sanders P, Berenfeld O, Hocini M, et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005;112:789–797.

48. Nakao K, Seto S, Ueyama C, et al. Extended distribution of prolonged and fractionated right atrial electrograms predicts development of chronic atrial fibrillation in patients with idiopathic paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:996–1002.
49. Akyurek O, Sayin T, Dincer I, et al. Lengthening of intraatrial conduction time in atrial fibrillation and its relation with early recurrence of atrial fibrillation. Jpn Heart J 2001;42:575–84.
50. Yamada T, Fukunami M, Shimonagata T, et al. Prediction of paroxysmal atrial fibrillation in patients with congestive heart failure: a prospective study. J Am Coll Cardiol 2000;35:405–13.
51. Ricard P, Levy S, Trigano J, et al. Prospective assessment of the minimum energy needed for external electrical cardioversion of atrial fibrillation. Am J Cardiol 1997;79:815–6.
52. Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
53. Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002; 415:219–26.
54. Anne W, Willems R, Van der MN, et al. Atrial fibrillation after radiofrequency ablation of atrial flutter: preventive effect of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics. Heart 2004;90:1025–30.
55. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005;45:1832–9.
56. Pedersen OD, Bagger H, Kober L, et al. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999;100:376–80.
57. Prystowsky EN. Atrioventricular node reentry: physiology and radiofrequency ablation. Pacing Clin Electrophysiol 1997;20:552–71.
58. Page RL, Wharton JM, Prystowsky EN. Effect of continuous vagal enhancement on concealed conduction and refractoriness within the atrioventricular node. Am J Cardiol 1996;77:260–5.
59. Moe GK, Abildskov JA. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. Circ Res 1964;4: 447–60.
60. Van Den Berg MP, Crijns HJ, Haaksma J, et al. Analysis of vagal effects on ventricular rhythm in patients with atrial fibrillation. Clin Sci (Colch) 1994;86:531–5.
61. Klein GJ, Bashore TM, Sellers TD, et al. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. N Engl J Med 1979;301:1080–5.
62. Prystowsky EN, Benson DW Jr, Fuster V, et al. Management of patients with atrial fibrillation. A statement for healthcare professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. Circulation 1996;93:1262–77.
63. Brookes CI, White PA, Staples M, et al. Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. Circulation 1998;98:1762–8.
64. Sanfilippo AJ, Abascal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990;82:792–7.
65. Gosselink AT, Crijns HJ, Hamer HP, et al. Changes in left and right atrial size after cardioversion of atrial fibrillation: role of mitral valve disease. J Am Coll Cardiol 1993;22:1666–72.
66. Manning WJ, Silverman DI, Katz SE, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994;23:1535–40.
67. Van Den Berg MP, Tuinenburg AE, van Veldhuisen DJ, et al. Cardioversion of atrial fibrillation in the setting of mild to moderate heart failure. Int J Cardiol 1998;63:63–70.
68. Packer DL, Bardy GH, Worley SJ, et al. Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. Am J Cardiol 1986;57:563–70.
69. Shinbane JS, Wood MA, Jensen DN, et al. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997;29:709–15.
70. Halperin JL, Hart RG. Atrial fibrillation and stroke: new ideas, persisting dilemmas. Stroke 1988;19:937–41.
71. Bogousslavsky J, Van Melle G, Regli F, et al. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. Neurology 1990;40:1046–50.
72. Miller VT, Rothrock JF, Pearce LA, et al. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. Neurology 1993; 43:32–6.
73. Kanter MC, Tegeler CH, Pearce LA, et al. Carotid stenosis in patients with atrial fibrillation. Prevalence, risk factors, and relationship to stroke in the Stroke Prevention in Atrial Fibrillation Study. Arch Intern Med 1994;154:1372–7.
74. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. Stroke 2001;32:803–8.
75. Aschenberg W, Schluter M, Kremer P, et al. Transesophageal twodimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol 1986;7:163–6.
76. Mugge A, Kuhn H, Nikutta P, et al. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. J Am Coll Cardiol 1994;23:599–607.
77. Manning WJ, Leeman DE, Gotch PJ, et al. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. J Am Coll Cardiol 1989;13:617–23.
78. Grimm RA, Stewart WJ, Maloney JD, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993;22:1359–66.
79. Chimowitz MI, DeGeorgia MA, Poole RM, et al. Left atrial spontaneous echo contrast is highly associated with previous stroke in patients with atrial fibrillation or mitral stenosis. Stroke 1993;24:1015–9.
80. Stoddard MF, Dawkins PR, Prince CR, et al. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol 1995;25:452–9.
81. Manning WJ, Silverman DI, Waksmonski CA, et al. Prevalence of residual left atrial thrombi among patients with acute thromboembolism and newly recognized atrial fibrillation. Arch Intern Med 1995;155: 2193–8.
82. Khan IA. Atrial stunning: determinants and cellular mechanisms. Am Heart J 2003;145:787–94.
83. Dunn MI, Marcum JL. Atrial mechanical performance following internal and external cardioversion of atrial fibrillation: its relationship to peripheral embolization and acute cerebrovascular accident. Chest 2002;121:1–3.
84. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. Am J Cardiol 1998;82:1545–7, A8.
85. Collins LJ, Silverman DI, Douglas PS, et al. Cardioversion of nonrheumatic atrial fibrillation. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. Circulation 1995;92:160–3.
86. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994;23:961–9.
87. Black IW, Chesterman CN, Hopkins AP, et al. Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 1993;21:451–7.
88. Yang Y, Grosset DG, Li Q, et al. Identification of echocardiographic "smoke" in a bench model with transcranial Doppler ultrasound. Stroke 2000;31:907–14.
89. Agarwal AK, Venugopalan P. Left atrial spontaneous echo contrast in patients with rheumatic mitral valve stenosis in sinus rhythm: relationship to mitral valve and left atrial measurements. Int J Cardiol 2001;77:63–8.
90. Black IW. Spontaneous echo contrast: where there's smoke there's fire. Echocardiography 2000;17:373–82.
91. Sparks PB, Jayaprakash S, Vohra JK, et al. Left atrial "stunning" following radiofrequency catheter ablation of chronic atrial flutter. J Am Coll Cardiol 1998;32:468–75.
92. Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. Cerebrovasc Dis 2000;10:39–43.
93. Blackshear JL, Pearce LA, Hart RG, et al. Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. Stroke 1999;30:834–40.
94. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. Circulation 2005;112:1687–91.

95. Yoshida M, Nakamura Y, Higashikawa M, Kinoshita M. Predictors of ischemic stroke in non-rheumatic atrial fibrillation. Int J Cardiol 1996; 56:61–70.
96. Hart RG, Pearce LA, McBride R, et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke 1999;30:1223–9.
97. Stollberger C, Chnupa P, Kronik G, et al. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group. Embolism in Left Atrial Thrombi. Ann Intern Med 1998; 128:630–8.
98. Tsai LM, Lin LJ, Teng JK, et al. Prevalence and clinical significance of left atrial thrombus in nonrheumatic atrial fibrillation. Int J Cardiol 1997;58:163–9.
99. Rathore SS, Berger AK, Weinfurt KP, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. Circulation 2000;101:969–74.
100. Goldberg RJ, Yarzebski J, Lessard D, et al. Recent trends in the incidence rates of and death rates from atrial fibrillation complicating initial acute myocardial infarction: a community-wide perspective. Am Heart J 2002;143:519–27.
101. Prystowsky EN. Tachycardia-induced-tachycardia: a mechanism of initiation of atrial fibrillation. In: DiMarco JP, Prystowsky EN, editors. Atrial Arrhythmias: State of the Art. Armonk, NY: Futura, 1995.
102. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med 1997;336: 905–11.
103. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118:489–95.
104. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471–7.
105. Fox CS, Parise H, D'Agostino RB Sr, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 2004;291:2851–5.
106. Ellinor PT, Shin JT, Moore RK, et al. Locus for atrial fibrillation maps to chromosome 6q14–16. Circulation 2003;107:2880–3.
107. Darbar D, Herron KJ, Ballew JD, et al. Familial atrial fibrillation is a genetically heterogeneous disorder. J Am Coll Cardiol 2003;41: 2185–92.
108. Fioranelli M, Piccoli M, Mileto GM, et al. Analysis of heart rate variability five minutes before the onset of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1999;22:743–9.
109. Herweg B, Dalal P, Nagy B, et al. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am J Cardiol 1998;82:869–74.
110. Coumel P. Neural aspects of paroxysmal atrial fibrillation. In: Falk RH, Podrid PJ, editors. Atrial Fibrillation: Mechanisms and Management. New York: Raven Press, 1992:109–25.
111. Maisel WH. Autonomic modulation preceding the onset of atrial fibrillation. J Am Coll Cardiol 2003;42:1269–70.
112. Fetsch T, Bauer P, Engberding R, et al. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. Eur Heart J 2004;25: 1385–94.
113. Israel CW, Gronefeld G, Ehrlich JR, et al. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol 2004;43:47–52.
114. Page RL, Wilkinson WE, Clair WK, et al. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation 1994;89:224–7.
115. Kerr CR, Boone J, Connolly SJ, et al. The Canadian Registry of Atrial Fibrillation: a noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. Am J Cardiol 1998;82:82N-5N.
116. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861–72.
117. Hamer ME, Blumenthal JA, McCarthy EA, et al. Quality-of-life assessment in patients with paroxysmal atrial fibrillation or paroxysmal supraventricular tachycardia. Am J Cardiol 1994;74:826–9.
118. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. J Interv Card Electrophysiol 2000;4:369–82.
119. Krahn AD, Klein GJ, Kerr CR, et al. How useful is thyroid function testing in patients with recent-onset atrial fibrillation? The Canadian Registry of Atrial Fibrillation Investigators. Arch Intern Med 1996;156: 2221–4.
120. Zabalgoitia M, Halperin JL, Pearce LA, et al. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol 1998;31:1622–6.
121. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J 2005;150:288–93.
122. Sherman DG, Kim SG, Boop BS, et al. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. Arch Intern Med 2005; 165:1185–91.
123. Deleted in proof.
124. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834–40.
125. Gronefeld GC, Lilienthal J, Kuck KH, et al. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J 2003; 24:1430–6.
126. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol 2003; 41:1690–6.
127. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs. rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. Chest 2004;126:476–86.
128. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–33.
129. Pelargonio G, Prystowsky EN. Rate versus rhythm control in the management of patients with atrial fibrillation. Nat Clin Pract Cardiovasc Med 2005;2:514–21.
130. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet 2000;356:1789–94.
131. Hagens VE, Ranchor AV, Van SE, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. J Am Coll Cardiol 2004;43:241–7.
132. Cooper HA, Bloomfield DA, Bush DE, et al. Relation between achieved heart rate and outcomes in patients with atrial fibrillation (from the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] Study). Am J Cardiol 2004;93:1247–53.
133. Lonnerholm S, Blomstrom P, Nilsson L, et al. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. Circulation 2000;101:2607–11.
134. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med 2006;354:934–41.
135. Levy S, Ricard P, Lau CP, et al. Multicenter low energy transvenous atrial defibrillation (XAD) trial results in different subsets of atrial fibrillation. J Am Coll Cardiol 1997;29:750–5.
136. Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias: use of synchronized capacitor discharge. JAMA 1962;182:548–55.
137. Nerheim P, Birger-Botkin S, Piracha L, et al. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. Circulation 2004;110:247–52.
138. Petri H, Kafka W, Rudolph W. [Discrepant effects of oral and intravenous verapamil on A-V conduction in patients with ventricular preexcitation and atrial fibrillation]. Herz 1983;8:144–52.
139. Wittkampf FH, de Jongste MJ, Lie HI, et al. Effect of right ventricular pacing on ventricular rhythm during atrial fibrillation. J Am Coll Cardiol 1988;11:539–45.
140. Brignole M, Menozzi C, Gianfranchi L, et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. Circulation 1998;98:953–60.
141. Kay GN, Ellenbogen KA, Giudici M, et al. The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. APT Investigators. J Interv Card Electrophysiol 1998;2:121–35.
142. Brignole M, Gianfranchi L, Menozzi C, et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus

pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. Circulation 1997;96:2617–24.
143. Wood MA, Brown-Mahoney C, Kay GN, et al. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. Circulation 2000;101:1138–44.
144. Williamson BD, Man KC, Daoud E, et al. Radiofrequency catheter modification of atrioventricular conduction to control the ventricular rate during atrial fibrillation [published erratum appears in N Engl J Med 1995;332:479]. N Engl J Med 1994;331:910–7.
145. Feld GK, Fleck RP, Fujimura O, et al. Control of rapid ventricular response by radiofrequency catheter modification of the atrioventricular node in patients with medically refractory atrial fibrillation. Circulation 1994;90:2299–307.
146. Evans GT Jr, Scheinman MM, Bardy G, et al. Predictors of in-hospital mortality after DC catheter ablation of atrioventricular junction. Results of a prospective, international, multicenter study. Circulation 1991;84:1924–37.
147. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002;39:1258–63.
148. Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol 2000;35:183–7.
149. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 1996;348:633–8.
150. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144–52.
151. Moulton AW, Singer DE, Haas JS. Risk factors for stroke in patients with nonrheumatic atrial fibrillation: a case-control study. Am J Med 1991;91:156–61.
152. 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.
153. 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;163:936–43.
154. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. JAMA 1998;279:1273–7.
155. Howitt A, Armstrong D. Implementing evidence based medicine in general practice: audit and qualitative study of antithrombotic treatment for atrial fibrillation. BMJ 1999;318:1324–7.
156. Biblo LA, Yuan Z, Quan KJ, et al. Risk of stroke in patients with atrial flutter. Am J Cardiol 2001;87:346–9, A9.
157. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;1:175–9.
158. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J Am Coll Cardiol 1991;18:349–55.
159. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators [published erratum appears in N Engl J Med 1993;328:148]. N Engl J Med 1992;327:1406–12.
160. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. N Engl J Med 1990;323:1505–11.
161. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527–39.
162. Deleted in proof.
163. Deleted in proof.
164. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet 1993;342:1255–62.
165. 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.
166. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897–902.
167. Odén A, Fahlén M, Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. Thromb Res 2006; 117:493–9
168. Fihn SD, Callahan CM, Martin DC, et al. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med 1996;124:970–9.
169. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med 2004;141:745–52.
170. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019–26.
171. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005;36:1588–93.
172. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690–8.
173. Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335:540–6.
174. Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial Fibrillation Aspirin and Anticoagulation. Arch Intern Med 1999;159:1322–8.
175. Hellemons BS, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. BMJ 1999;319:958–64.
176. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343:687–91.
177. Diener HC, Cunha L, Forbes C. et al. European Stroke Prevention Study-2 (ESPS-2). Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1–13.
178. European Stroke Prevention Study. ESPS Group. Stroke 1990;21:1122–30.
179. Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. LASAF Pilot Study Group. Am Heart J 1999;138:137–43.
180. 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.
181. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. The Atrial Fibrillation Investigators. Arch Intern Med 1997;157:1237–40.
182. Deleted in proof.
183. Hart RG, Benavente O, Pearce LA. Increased risk of intracranial hemorrhage when aspirin is combined with warfarin: a meta-analysis and hypothesis. Cerebrovasc Dis 1999;9:215–7.
184. Stellbrink C, Nixdorff U, Hofmann T, et al. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. Circulation 2004;109:997–1003.
185. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001;119:64S–94S.
186. Murray RD, Deitcher SR, Shah A, et al. Potential clinical efficacy and cost benefit of a transesophageal echocardiography-guided low-molecular-weight heparin (enoxaparin) approach to antithrombotic therapy in patients undergoing immediate cardioversion from atrial fibrillation. J Am Soc Echocardiogr 2001;14:200–8.
187. Stein PD, Alpert JS, Bussey HI, et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001;119:220S-7S.
188. Blackshear JL, Johnson WD, Odell JA, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. J Am Coll Cardiol 2003;42:1249–52.
189. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol 2005;46:9–14.

190. Halperin JL, Gomberg-Maitland M. Obliteration of the left atrial appendage for prevention of thromboembolism. J Am Coll Cardiol 2003;42:1259–61.
191. Suttorp MJ, Kingma JH, Jessurun ER, et al. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. J Am Coll Cardiol 1990;16:1722–7.
192. Platia EV, Michelson EL, Porterfield JK, et al. Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. Am J Cardiol 1989;63:925–9.
193. Azpitarte J, Alvarez M, Baun O, et al. Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation. Results of a randomized, double-blind, controlled study. Eur Heart J 1997;18:1649–54.
194. Kochiadakis GE, Igoumenidis NE, Solomou MC, et al. Efficacy of amiodarone for the termination of persistent atrial fibrillation. Am J Cardiol 1999;83:58–61.
195. Capucci A, Boriani G, Rubino I, et al. A controlled study on oral propafenone versus digoxin plus quinidine in converting recent onset atrial fibrillation to sinus rhythm. Int J Cardiol 1994;43:305–13.
196. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 1984;24:129–47.
197. Falk RH, Pollak A, Singh SN, et al. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators. J Am Coll Cardiol 1997; 29:385–90.
198. Norgaard BL, Wachtell K, Christensen PD, et al. Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled trial. Danish Dofetilide in Atrial Fibrillation and Flutter Study Group. Am Heart J 1999;137:1062–9.
199. Sedgwick ML, Lip G, Rae AP, et al. Chemical cardioversion of atrial fibrillation with intravenous dofetilide. Int J Cardiol 1995;49:159–66.
200. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N Engl J Med 1999;341:857–65.
201. Lindeboom JE, Kingma JH, Crijns HJ, et al. Efficacy and safety of intravenous dofetilide for rapid termination of atrial fibrillation and atrial flutter. Am J Cardiol 2000;85:1031–3.
202. Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. Circulation 2000;102:2385–90.
203. Borgeat A, Goy JJ, Maendly R, et al. Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1986;58: 496–8.
204. Suttorp MJ, Kingma JH, Lie AH, et al. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. Am J Cardiol 1989;63:693–6.
205. Capucci A, Lenzi T, Boriani G, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. Am J Cardiol 1992;70:69–72.
206. Donovan KD, Power BM, Hockings BE, et al. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. Am J Cardiol 1995;75:693–7.
207. Botto GL, Bonini W, Broffoni T, et al. Regular ventricular rhythms before conversion of recent onset atrial fibrillation to sinus rhythm. Pacing Clin Electrophysiol 1994;17:2114–7.
208. Donovan KD, Dobb GJ, Coombs LJ, et al. Reversion of recent-onset atrial fibrillation to sinus rhythm by intravenous flecainide. Am J Cardiol 1991;67:137–41.
209. Barranco F, Sanchez M, Rodriguez J, et al. Efficacy of flecainide in patients with supraventricular arrhythmias and respiratory insufficiency. Intensive Care Med 1994;20:42–4.
210. Baldi N, Russo VA, Lenti V, et al. Relation between plasma levels and efficacy of flecainide and propafenone for treatment of atrial fibrillation of recent onset. New Trends Arrhythmias 1993;9:899–906.
211. Stambler BS, Wood MA, Ellenbogen KA. Antiarrhythmic actions of intravenous ibutilide compared with procainamide during human atrial flutter and fibrillation: electrophysiological determinants of enhanced conversion efficacy. Circulation 1997;96:4298–306.
212. Guo GB, Ellenbogen KA, Wood MA, et al. Conversion of atrial flutter by ibutilide is associated with increased atrial cycle length variability. J Am Coll Cardiol 1996;27:1083–9.
213. Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J Am Coll Cardiol 1998;31: 1414–9.
214. Vos MA, Golitsyn SR, Stangl K, et al. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. The Ibutilide/Sotalol Comparator Study Group. Heart 1998;79:568–75.
215. Stambler BS, Wood MA, Ellenbogen KA, et al. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. Circulation 1996;94:1613–21.
216. Ellenbogen KA, Stambler BS, Wood MA, et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study [published erratum appears in J Am Coll Cardiol 1996;28:1082]. J Am Coll Cardiol 1996;28:130–6.
217. Bertini G, Conti A, Fradella G, et al. Propafenone versus amiodarone in field treatment of primary atrial tachydysrhythmias. J Emerg Med 1990; 8:15–20.
218. Boriani G, Capucci A, Lenzi T, et al. Propafenone for conversion of recent-onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. Chest 1995;108:355–8.
219. Boriani G, Biffi M, Capucci A, et al. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease. A randomized, controlled trial. Ann Intern Med 1997;126: 621–5.
220. Fresco C, Proclemer A, Pavan A, et al. Intravenous propafenone in paroxysmal atrial fibrillation: a randomized, placebo-controlled, double-blind, multicenter clinical trial. Paroxysmal Atrial Fibrillation Italian Trial (PAFIT)-2 Investigators. Clin Cardiol 1996;19:409–12.
221. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. Am J Cardiol 1997;79:418–23.
222. Bellandi F, Cantini F, Pedone T, et al. Effectiveness of intravenous propafenone for conversion of recent-onset atrial fibrillation: a placebo-controlled study. Clin Cardiol 1995;18:631–4.
223. Bianconi L, Mennuni M, Lukic V, et al. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. J Am Coll Cardiol 1996;28:700–6.
224. Weiner P, Ganam R, Ganem R, et al. Clinical course of recent-onset atrial fibrillation treated with oral propafenone. Chest 1994;105:1013–6.
225. Di Benedetto S. Quinidine versus propafenone for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1997;80:518–9.
226. Vita JA, Friedman PL, Cantillon C, et al. Efficacy of intravenous propafenone for the acute management of atrial fibrillation. Am J Cardiol 1989;63:1275–8.
227. Barroffio R, Tisi G, Guzzini F, et al. A randomised study comparing digoxin and propafenone in the treatment of recent onset atrial fibrillation. Clin Drug Invest 1995;9:277–83.
228. Galve E, Rius T, Ballester R, et al. Intravenous amiodarone in treatment of recent-onset atrial fibrillation: results of a randomized, controlled study. J Am Coll Cardiol 1996;27:1079–82.
229. Peuhkurinen K, Niemela M, Ylitalo A, et al. Effectiveness of amiodarone as a single oral dose for recent-onset atrial fibrillation. Am J Cardiol 2000;85:462–5.
230. Zehender M, Hohnloser S, Muller B, et al. Effects of amiodarone versus quinidine and verapamil in patients with chronic atrial fibrillation: results of a comparative study and a 2-year follow-up. J Am Coll Cardiol 1992;19:1054–9.
231. Hou ZY, Chang MS, Chen CY, et al. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. Eur Heart J 1995;16:521–8.
232. Opolski G, Stanislawska J, Gorecki A, et al. Amiodarone in restoration and maintenance of sinus rhythm in patients with chronic atrial fibrillation after unsuccessful direct-current cardioversion. Clin Cardiol 1997; 20:337–40.
233. Noc M, Stajer D, Horvat M. Intravenous amiodarone versus verapamil for acute conversion of paroxysmal atrial fibrillation to sinus rhythm. Am J Cardiol 1990;65:679–80.
234. Tieleman RG, Gosselink AT, Crijns HJ, et al. Efficacy, safety, and determinants of conversion of atrial fibrillation and flutter with oral amiodarone. Am J Cardiol 1997;79:53–7.
235. Vardas PE, Kochiadakis GE, Igoumenidis NE, et al. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. Chest 2000;117:1538–45.

236. Kerin NZ, Faitel K, Naini M. The efficacy of intravenous amiodarone for the conversion of chronic atrial fibrillation. Amiodarone vs. quinidine for conversion of atrial fibrillation. Arch Intern Med 1996; 156:49–53.
237. Hohnloser SH, van de LA, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. J Am Coll Cardiol 1995;26: 852–8.
238. Halinen MO, Huttunen M, Paakkinen S, et al. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). Am J Cardiol 1995;76: 495–8.
239. Madrid AH, Moro C, Marin-Huerta E, et al. Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. Eur Heart J 1993;14:1127–31.
240. Deleted in proof.
241. Falk RH, Knowlton AA, Bernard SA, et al. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. A randomized, double-blinded trial. Ann Intern Med 1987;106:503–6.
242. Singh S, Saini RK, DiMarco J, et al. Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation. The Sotalol Study Group. Am J Cardiol 1991;68:1227–30.
243. Jordaens L. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. Eur Heart J 1997;18:643–8.
244. Deleted in proof.
245. Intravenous digoxin in acute atrial fibrillation. Results of a randomized, placebo-controlled multicentre trial in 239 patients. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Eur Heart J 1997;18: 649–54.
246. Sung RJ, Tan HL, Karagounis L, et al. Intravenous sotalol for the termination of supraventricular tachycardia and atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled study. Sotalol Multicenter Study Group. Am Heart J 1995;129:739–48.
247. Nakazawa H, Lythall DA, Noh J, et al. Is there a place for the late cardioversion of atrial fibrillation? A long-term follow-up study of patients with post-thyrotoxic atrial fibrillation. Eur Heart J 2000;21:327–33.
248. Botto GL, Capucci A, Bonini W, et al. Conversion of recent onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenone: comparison of two regimens. Int J Cardiol 1997;58:55–61.
249. Deleted in proof.
250. Pilati G, Lenzi T, Trisolino G, et al. Amiodarone versus quinidine for conversion of recent onset atrial fibrillation to sinus rhythm. Curr Ther Res 1991;49:140–6.
251. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med 2004;351:2384–91.
252. Capucci A, Villani GQ, Piepoli MF, et al. The role of oral 1C antiarrhythmic drugs in terminating atrial fibrillation. Curr Opin Cardiol 1999;14:4–8.
253. Alboni P, Tomasi C, Menozzi C, et al. Efficacy and safety of out-of-hospital self-administered single-dose oral drug treatment in the management of infrequent, well-tolerated paroxysmal supraventricular tachycardia. J Am Coll Cardiol 2001;37:548–53.
254. Capucci A, Villani GQ, Piepoli MF. Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. Am J Cardiol 2003;92:1345–7.
255. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. J Am Coll Cardiol 2001;37:542–7.
256. Feld GK. Atrial fibrillation. Is there a safe and highly effective pharmacological treatment? Circulation 1990;82:2248–50.
257. Leitch JW, Klein GJ, Yee R, et al. Prognostic value of electrophysiology testing in asymptomatic patients with Wolff-Parkinson-White pattern [published erratum appears in Circulation 1991;83:1124]. Circulation 1990;82:1718–23.
258. Gosselink AT, Crijns HJ, Van Gelder IC, et al. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. JAMA 1992;267:3289–93.
259. Hauser TH, Pinto DS, Josephson ME, et al. Safety and feasibility of a clinical pathway for the outpatient initiation of antiarrhythmic medications in patients with atrial fibrillation or atrial flutter. Am J Cardiol 2003;91:1437–41.
260. Levy S, Ricard P, Gueunoun M, et al. Low-energy cardioversion of spontaneous atrial fibrillation. Immediate and long-term results. Circulation 1997;96:253–9.
261. Lesser MF. Safety and efficacy of in-office cardioversion for treatment of supraventricular arrhythmias. Am J Cardiol 1990;66:1267–8.
262. Joglar JA, Hamdan MH, Ramaswamy K, et al. Initial energy for elective external cardioversion of persistent atrial fibrillation. Am J Cardiol 2000;86:348–50.
263. Wozakowska-Kaplon B, Janion M, Sielski J, et al. Efficacy of biphasic shock for transthoracic cardioversion of persistent atrial fibrillation: can we predict energy requirements? Pacing Clin Electrophysiol 2004;27:764–8.
264. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. Am J Cardiol 1969;23:208–16.
265. Arnold AZ, Mick MJ, Mazurek RP, et al. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol 1992;19:851–5.
266. Rabbino MD, Likoff W, Dreifus LS. Complications and limitations of direct current countershock. JAMA 1964;190:417–20.
267. Lown B, Kleiger R, Williams J. Cardioversion and digitalis drugs: changed threshold to electric shock in digitalized animals. Circ Res 1965;17:519–31.
268. Aberg H, Cullhed I. Direct current countershock complications. Acta Med Scand 1968;183:415–21.
269. Mancini GB, Goldberger AL. Cardioversion of atrial fibrillation: consideration of embolization, anticoagulation, prophylactic pacemaker, and long-term success. Am Heart J 1982;104:617–21.
270. Timmermans C, Rodriguez LM, Ayers GM, et al. Effect of electrode length on atrial defibrillation thresholds. J Cardiovasc Electrophysiol 1998;9:582–7.
271. Tieleman RG, Van Gelder IC, Crijns HJ, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998;31:167–73.
272. Timmermans C, Rodriguez LM, Smeets JL, et al. Immediate reinitiation of atrial fibrillation following internal atrial defibrillation. J Cardiovasc Electrophysiol 1998;9:122–8.
273. Rossi M, Lown B. The use of quinidine in cardioversion. Am J Cardiol 1967;19:234–8.
274. Van Gelder IC, Crijns HJ, van Gilst WH, et al. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. Am J Cardiol 1991;68:41–6.
275. Lundstrom T, Ryden L. Chronic atrial fibrillation. Long-term results of direct current conversion. Acta Med Scand 1988;223:53–9.
276. Niebauer MJ, Brewer JE, Chung MK, et al. Comparison of the rectilinear biphasic waveform with the monophasic damped sine waveform for external cardioversion of atrial fibrillation and flutter. Am J Cardiol 2004;93:1495–9.
277. Van Gelder IC, Crijns HJ, van Gilst WH, et al. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. Am J Cardiol 1989;64:1317–21.
278. Crijns HJ, Van Gelder IC, Lie KI. Supraventricular tachycardia mimicking ventricular tachycardia during flecainide treatment. Am J Cardiol 1988;62:1303–6.
279. Van Gelder IC, Crijns HJ, van Gilst WH, et al. Effects of flecainide on the atrial defibrillation threshold. Am J Cardiol 1989;63:112–4.
280. Oral H, Souza JJ, Michaud GF, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. N Engl J Med 1999;340:1849–54.
281. Li H, Natale A, Tomassoni G, et al. Usefulness of ibutilide in facilitating successful external cardioversion of refractory atrial fibrillation. Am J Cardiol 1999;84:1096–8, A10.
282. Naccarelli GV, Dell'Orfano JT, Wolbrette DL, et al. Cost-effective management of acute atrial fibrillation: role of rate control, spontaneous conversion, medical and direct current cardioversion, transesophageal echocardiography, and antiembolic therapy. Am J Cardiol 2000;85: 36D–45D.
283. Manning WJ, Silverman DI, Gordon SP, et al. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. N Engl J Med 1993;328:750–5.
284. Black IW, Fatkin D, Sagar KB, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. A multicenter study. Circulation 1994;89:2509–13.
285. Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonantico-

agulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. Am Heart J 1995;129:71–5.
286. Fatkin D, Kuchar DL, Thorburn CW, et al. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardiol 1994;23:307–16.
287. Antonielli E, Pizzuti A, Bassignana A, et al. Transesophageal echocardiographic evidence of more pronounced left atrial stunning after chemical (propafenone) rather than electrical attempts at cardioversion from atrial fibrillation. Am J Cardiol 1999;84:1092–10.
288. Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. Am J Cardiol 1996;78:435–9.
289. Bellotti P, Spirito P, Lupi G, et al. Left atrial appendage function assessed by transesophageal echocardiography before and on the day after elective cardioversion for nonvalvular atrial fibrillation. Am J Cardiol 1998;81:1199–202.
290. Harjai K, Mobarek S, Abi-Samra F, et al. Mechanical dysfunction of the left atrium and the left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. Am J Cardiol 1998;81:1125–9.
291. Mitusch R, Garbe M, Schmucker G, et al. Relation of left atrial appendage function to the duration and reversibility of nonvalvular atrial fibrillation. Am J Cardiol 1995;75:944–7.
292. Manning WJ, Silverman DI, Katz SE, et al. Temporal dependence of the return of atrial mechanical function on the mode of cardioversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1995;75:624–6.
293. Grimm RA, Leung DY, Black IW, et al. Left atrial appendage "stunning" after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. Am Heart J 1995; 130:174–6.
294. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411–20.
295. Mehta D, Baruch L. Thromboembolism following cardioversion of "common" atrial flutter. Risk factors and limitations of transesophageal echocardiography. Chest 1996;110:1001–3.
296. Irani WN, Grayburn PA, Afridi I. Prevalence of thrombus, spontaneous echo contrast, and atrial stunning in patients undergoing cardioversion of atrial flutter. A prospective study using transesophageal echocardiography. Circulation 1997;95:962–6.
297. Lazzeroni E, Picano E, Morozzi L, et al. Dipyridamole-induced ischemia as a prognostic marker of future adverse cardiac events in adult patients with hypertrophic cardiomyopathy. Echo Persantine Italian Cooperative (EPIC) Study Group, Subproject Hypertrophic Cardiomyopathy. Circulation 1997;96:4268–72.
298. Deleted in proof.
299. Kerr CR, Humphries KH, Talajic M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. Am Heart J 2005;149:489–96.
300. Van Gelder IC, Crijns HJ, Tieleman RG, et al. Chronic atrial fibrillation. Success of serial cardioversion therapy and safety of oral anticoagulation. Arch Intern Med 1996;156:2585–92.
301. 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.
302. Suttorp MJ, Kingma JH, Koomen EM, et al. Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal left ventricular function. Am J Cardiol 1993;71:710–3.
303. Prystowsky EN. Management of atrial fibrillation: therapeutic options and clinical decisions. Am J Cardiol 2000;85:3–11.
304. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med 1995;333:77–82.
305. Ehrlich JR, Nattel S, Hohnloser SH. Atrial fibrillation and congestive heart failure: specific considerations at the intersection of two common and important cardiac disease sets. J Cardiovasc Electrophysiol 2002; 13:399–405.
306. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91:2D–8D.
307. Naccarelli GV, Hynes BJ, Wolbrette DL, et al. Atrial fibrillation in heart failure: prognostic significance and management. J Cardiovasc Electrophysiol 2003;14:S281–S286.
308. Meng F, Yoshikawa T, Baba A, et al. Beta-blockers are effective in congestive heart failure patients with atrial fibrillation. J Card Fail 2003;9:398–403.
309. Steeds RP, Birchall AS, Smith M, et al. An open label, randomised, crossover study comparing sotalol and atenolol in the treatment of symptomatic paroxysmal atrial fibrillation. Heart 1999;82:170–5.
310. Kuhlkamp V, Schirdewan A, Stangl K, et al. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 2000;36:139–46.
311. Essebag V, Hadjis T, Platt RW, et al. Amiodarone and the risk of bradyarrhythmia requiring permanent pacemaker in elderly patients with atrial fibrillation and prior myocardial infarction. J Am Coll Cardiol 2003;41:249–54.
312. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators [published errata appear in Lancet 1997;349:1180 and 1997;349:1776]. Lancet 1997;349:667–74.
313. Cairns JA, Connolly SJ, Roberts R, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators [published erratum appears in Lancet 1997 Jun 14;349(9067):1776]. Lancet 1997;349:675–82.
314. Kober L, Bloch Thomsen PE, Moller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. Lancet 2000;356:2052–8.
315. Peters NS, Schilling RJ, Kanagaratnam P, et al. Atrial fibrillation: strategies to control, combat, and cure. Lancet 2002;359:593–603.
316. Tsang TS, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:93–100.
317. Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 1988;31:115–72.
318. Van Noord T, Tieleman RG, Bosker HA, et al. Beta-blockers prevent subacute recurrences of persistent atrial fibrillation only in patients with hypertension. Europace 2004;6:343–50.
319. Klingbeil AU, Schneider M, Martus P, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003;115:41–6.
320. L'Allier PL, Ducharme A, Keller PF, et al. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J Am Coll Cardiol 2004;44:159–64.
321. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
322. Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial. BMJ 2002;324:699–702.
323. Chapman N, Huxley R, Anderson C, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke 2004;35:116–21.
324. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
325. Dahlof B, Zanchetti A, Diez J, et al. Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy. J Hypertens 2002;20:1855–64.
326. Arima H, Hart RG, Colman S, et al. Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke 2005;36:2164–9.
327. Wachtell K, Hornestam B, Lehto M, et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:705–11.
328. Cox JL, Schuessler RB, Lappas DG, et al. An 8 1/2-year clinical experience with surgery for atrial fibrillation. Ann Surg 1996;224:267–73.

329. Cox JL. Cardiac surgery for arrhythmias. J Cardiovasc Electrophysiol 2004;15:250–62.
330. Cox JL, Boineau JP, Schuessler RB, et al. Modification of the maze procedure for atrial flutter and atrial fibrillation. I. Rationale and surgical results. J Thorac Cardiovasc Surg 1995;110:473–84.
331. Damiano RJ Jr, Gaynor SL, Bailey M, et al. The long-term outcome of patients with coronary disease and atrial fibrillation undergoing the Cox maze procedure. J Thorac Cardiovasc Surg 2003;126:2016–21.
332. Gillinov AM, McCarthy PM. Advances in the surgical treatment of atrial fibrillation. Cardiol Clin 2004;22:147–57.
333. Packer DL, Asirvatham S, Munger TM. Progress in nonpharmacologic therapy of atrial fibrillation. J Cardiovasc Electrophysiol 2003;14:S296–S309.
334. Chen SA, Hsieh MH, Tai CT, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999;100:1879–86.
335. Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation 2003; 107:3176–83.
336. Hocini M, Sanders P, Jais P, et al. Techniques for curative treatment of atrial fibrillation. J Cardiovasc Electrophysiol 2004;15:1467–71.
337. Haissaguerre M, Shah DC, Jais P, et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. Circulation 2000; 102:2463–5.
338. Verma A, Marrouche NF, Natale A. Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. J Cardiovasc Electrophysiol 2004;15:1335–40.
339. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs. antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005;293:2634–40.
340. Pappone C, Rosanio S, Oreto G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000;102:2619–28.
341. Pappone C, Santinelli V. The who, what, why, and how-to guide for circumferential pulmonary vein ablation. J Cardiovasc Electrophysiol 2004;15:1226–30.
342. Oral H, Scharf C, Chugh A, et al. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation 2003;108:2355–60.
343. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100–5.
344. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044–53.
345. Hsu LF, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373–83.
346. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42:185–97.
347. Marshall HJ, Harris ZI, Griffith MJ, et al. Prospective randomized study of ablation and pacing versus medical therapy for paroxysmal atrial fibrillation: effects of pacing mode and mode-switch algorithm. Circulation 1999;99:1587–92.
348. Natale A, Zimerman L, Tomassoni G, et al. AV node ablation and pacemaker implantation after withdrawal of effective rate-control medications for chronic atrial fibrillation: effect on quality of life and exercise performance. Pacing Clin Electrophysiol 1999;22:1634–9.
349. Marshall HJ, Harris ZI, Griffith MJ, et al. Atrioventricular nodal ablation and implantation of mode switching dual chamber pacemakers: effective treatment for drug refractory paroxysmal atrial fibrillation. Heart 1998;79:543–7.
350. Hindricks G, Piorkowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation 2005;112:307–13.
351. Senatore G, Stabile G, Bertaglia E, et al. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. J Am Coll Cardiol 2005;45:873–6.
352. Karch MR, Zrenner B, Deisenhofer I, et al. Freedom from atrial tachyarrhythmias after catheter ablation of atrial fibrillation: a randomized comparison between 2 current ablation strategies. Circulation 2005;111:2875–80.
353. Haissaguerre M, Jais P, Shah DC, et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000;101:1409–17.
354. Ren JF, Marchlinski FE, Callans DJ, et al. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. J Cardiovasc Electrophysiol 2005;16:474–7.
355. Pappone C, Oral H, Santinelli V, et al. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. Circulation 2004;109:2724–6.
356. Scanavacca MI, D'avila A, Parga J, et al. Left atrial-esophageal fistula following radiofrequency catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2004;15:960–2.
357. Mesas CE, Pappone C, Lang CC, et al. Left atrial tachycardia after circumferential pulmonary vein ablation for atrial fibrillation: electroanatomic characterization and treatment. J Am Coll Cardiol 2004;44:1071–9.
358. Pappone C, Manguso F, Vicedomini G, et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. Circulation 2004;110:3036–42.
359. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;350:1210–6.
360. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000;342:1385–91.
361. Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med 1998;338:1097–104.
362. Lamas GA, Lee KL, Sweeney MO, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002;346: 1854–62.
363. Knight BP, Gersh BJ, Carlson MD, et al. Role of permanent pacing to prevent atrial fibrillation: science advisory from the American Heart Association Council on Clinical Cardiology (Subcommittee on Electrocardiography and Arrhythmias) and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. Circulation 2005;111:240–3.
364. Deleted in proof.
365. Blanc JJ, De Roy L, Mansourati J, et al. Atrial pacing for prevention of atrial fibrillation: assessment of simultaneously implemented algorithms. Europace 2004;6:371–9.
366. Friedman PA, Ip JH, Jazayeri M, et al. The impact of atrial prevention and termination therapies on atrial tachyarrhythmia burden in patients receiving a dual-chamber defibrillator for ventricular arrhythmias. J Interv Card Electrophysiol 2004;10:103–10.
367. Alsheikh-Ali AA, Wang PJ, Rand W, et al. Enalapril treatment and hospitalization with atrial tachyarrhythmias in patients with left ventricular dysfunction. Am Heart J 2004;147:1061–5.
368. Olsson LG, Swedberg K, Ducharme A, et al. on behalf of the CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction. Results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 2006;47:1997–2004.
369. Young-Xu Y, Jabbour S, Goldberg R, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. Am J Cardiol 2003;92:1379–83.
370. Siu CW, Lau CP, Tse HF. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. Am J Cardiol 2003;92:1343–5.
371. Mozaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk of incident atrial fibrillation. Circulation 2004;110:368–73.

KEY WORDS: ACC/AHA/ESC Guidelines ■ atrial fibrillation ■ arrhythmia ■ heart rate ■ anticoagulants ■ antiarrhythmia agents ■ electrophysiology ■ pharmacology