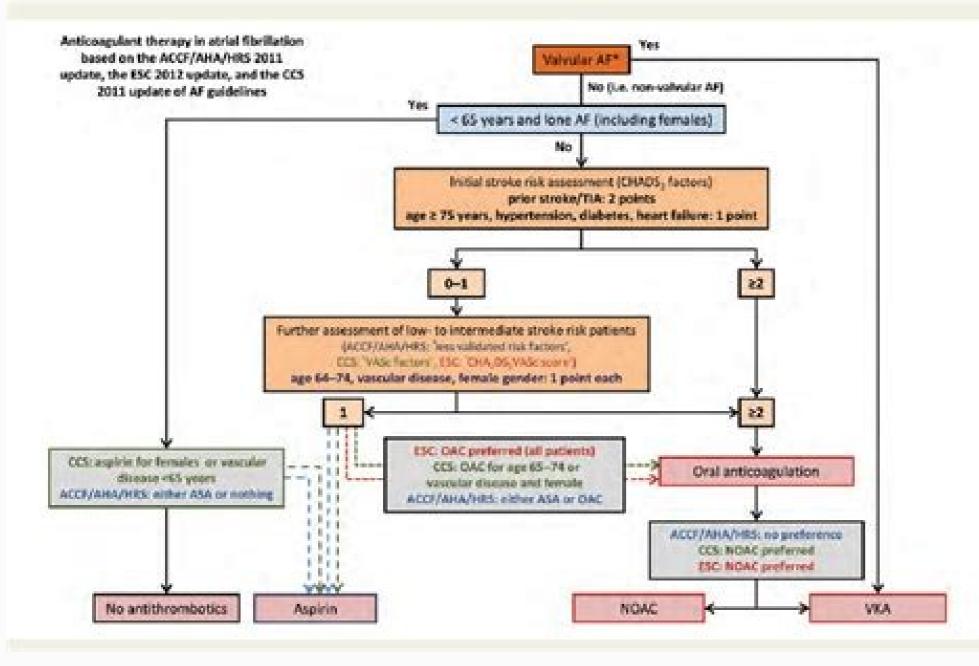
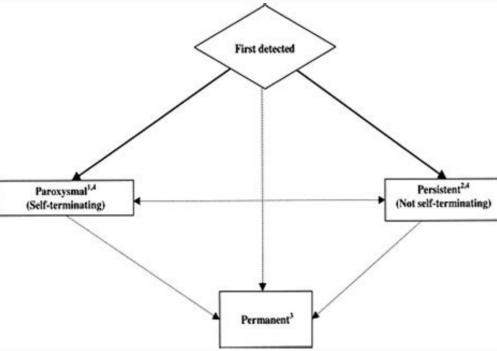
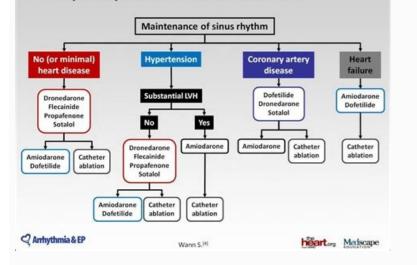
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ACCF/AHA/HRS: AF Guideline 2011



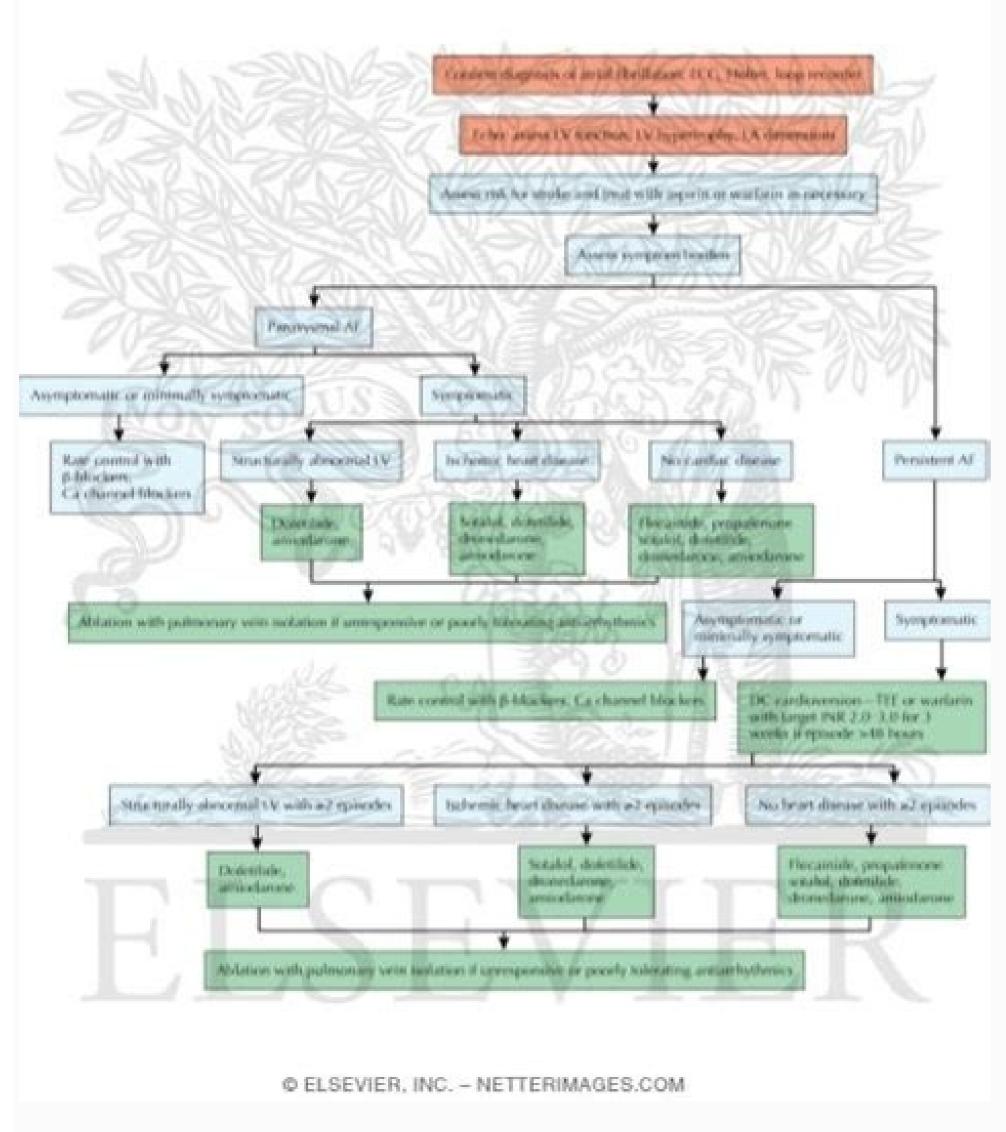
Patient Care

2011 ACCF/AHA/HRS Guidelines

Antithrombotic Therapy for Patients with Atrial Fibrillation

	Risk Category ¹	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 > 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

Less Validated / Weaker Risk Factors	Moderate Risk Factors	High Risk Factors	isk Factors	
Female gender	Age ≥75 years	Previous stroke, TIA or embolism		
Age 65 to 74 years	Hypertension	Mitral stenosis		
Coronary artery disease	Heart failure	Prosthetic heart valve* * If mechanical valve, target international normalized ratio (INR) > 2.5		
Thyrotoxicosis	LV ejection fraction ≤35%			
	Diabetes mellitus			
2011 Focused Update Recom	1 Focused Update Recommendation Class I ²			
thromboembolism in patients will systemic embolization who do n	ative to warfarin for the prevention of th paroxysmal to permanent AF and of have a prosthetic heart valve or h re (creatinine clearance <15 mL/min ion), (Level of Evidence: 8)	risk factors for stroke or emodynamically significant	New Recommendation	
	ar 15:123(10): Pub Med PMID: 2138 diol. 2011 Mar 15:57(11):1330-7. Pt		3	



Aha/acc/hrs guidelines for atrial fibrillation. 2011 accf/aha/hrs guidelines for the management of patients with atrial fibrillation. 2019 aha/acc/hrs guidelines for atrial fibrillation. 2014 aha/acc/hrs guidelines for atrial fibrillation.

Smith Sidney C., MD, FACC, FAHA, FESCChair, ACC/AHA Task Force on Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committee for Practice GuidelinesPriori Silvia G., MD, PhD, FESCChair, ESC Committees 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 or update or update

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 persona 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. with industry that might be perceived as relevant to guideline staff in writing committee member develops a new relationship with industry during their tenure, they are required to notify guideline staff in writing. The continued participation of the writing committee member will be reviewed. These statements are reviewed by the parent Task Force, reported orally to all members of the writing committee at each meeting, and updated and reviewed by the writing committee as changes occur. Please refer to the methodology manuals for further description of the policies used in guideline development, including relationships with industry, available online at the ACC, AHA, and ESC World Wide Web sites (and . 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 guidelines attempt to define practices that meet the needs of most patients in most circumstances. 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. 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 reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are updated, revised, or sunsetted and withdrawn from distribution. and recommendations are published in the August 15, 2006, issues of the Journal of the American College of Cardiology and Circulation and the August 15, 2006, issues of the Journal of the American College of Cardiology and Circulation and the August 16, 2006, issues of the Journal of the American College of Cardiology and Circulation and the August 16, 2006, issues of the Journal of the September 2006 issue of Europace, as well as posted on the ACC (www.acc.org), AHA (www.americanheart.org), and ESC (www.acc.org), AHA (www.americanheart.org), and ESC (www.acc.org), AHA (www.americanheart.org), and ESC (www.acc.org), and ESC (www new or updated text, view the 2011 Focused Update and the 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated. Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF 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 College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) created a committee to establish guidelines for optimum management of this frequent and complex arrhythmia. The committee was composed of members representing the ACC, AHA, and ESC, as well as the European Heart RhythmAssociation (EHRA) and the Heart RhythmAssoc ACC, 2 official reviewers nominated by the AHA, and 2 official reviewers nominated by the ESC, as well as by the ACCF Clinical Electrophysiology Committee, the AHA Stroke Review Committee, the AHA S approved for publication by the governing bodies of the ACC, AHA, and ESC and officially endorsed by the EHRA and the HRS. The ACC/AHA/ESC Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation conducted a comprehensive review of the relevant literature from 2001 to 2006. Literature searches were conducted in the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Database of Systematic Reviews and the Cochrane Library (including the Cochrane Database). information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Major search terms included atrial fibrillation, age, atrial remodeling, atrioventricular conduction, atrioventricular conduction, atrioventricular conduction, atrial fibrillation, age, atrial remodeling, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, experimental, heart failure (HF), hemodynamics, human, hyperthyroidism, meta-analysis, myocardial infarction, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, risks, sinus rhythm, symptoms and tachycardia-mediated cardiomyopathy. The complete list of search terms is beyond the scope of this section. Classification of Recommendations are evidence based and derived primarily from published data. Table 1. Applying Classification of Recommendations and Level of Evidence† (UPDATED) (see the 2011 Focused Update and the 2011 Focus there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy. Class IIa: Weight of 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 A: Data derived from multiple random ized trials or meta-analyses.Level of Evidence B: Data derived from a single random ized trial, or nonrandomized studies. Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care. 1.2. Contents of These Guidelines first present a comprehensive review of the latest information about the definition, classification, epidemiology, pathophysiological mechanisms, and clinical characteristics of AF. The management of this complex and potentially dangerous arrhythmia is then reviewed. This includes prevention of AF, control of heart rate, prevention of thromboembolism, and conversion to and maintenance of sinus rhythm. The treatment algorithms include pharmacological antiarrhythmic approaches, as well as antithrombotic strategies most appropriate for particular clinical conditions. Overall, this is a consensus document that attempts to reconcile evidence and opinion from both sides of the Atlantic Ocean. The pharmacological antiarrhythmic approaches may include some drugs and devices that do not have the approval of all government regulatory agencies. Additional informa-tion may be obtained from the package inserts when the drug or device has been approved for the stated indication. Because atrial flutter can precede or coexist with AF, special consideration is given to this arrhythmia in each section. There are important differences in the mechanisms of AF and atrial flutter, and the body of evidence available to support therapeutic recommendations is distinct for the 2 arrhythmias. Atrial flutter is not addressed in the ACC/AHA/ESC Guidelines on the Management of Patients with Supraventricular Arrhythmias. 11.3. Changes Since the Initial Publication of These Guidelines in 2001 In developing this revision of the guidelines, the Writing Committee considered evidence published since 2001 and drafted revised recommendations where appropriate to incorporate results from major clinical trials such as those that compared rhythm-control and rate-control approaches to long-term management. The text has been reorganized to reflect the implications for patient care, beginning with recognition of AF and
its pathogenesis and the general priorities of rate control, prevention of thromboembolism, and maintain normal sinus rhythm. Advances in catheter-based ablation technologies have been incorporated into expanded sections and recommendations, with the recognition that such vital details as patient selection, optimum catheter positioning, absolute rates of treatment success, and the frequency of complications remain incompletely defined. human studies with compounds that have been approved for clinical use in North America and/or Europe. Accumulating evidence from clinical studies on the emerging role of angiotensin inhibition to reduce the occur-rence and complications of AF and information on approaches to the primary prevention of AF are addressed comprehensively in the text, as these may evolve further in the years ahead to form the basis for recommendations affecting patient care. Finally, data on specific aspects of management of patients who are prone to develop AF in special circumstances have become more robust, allowing formulation of recommendations based on a higher level of evidence than in the first edition of these guidelines. An example is the completion of a relatively large randomized trial addressing prophylactic administration of antiarrhythmic medication for patients undergoing cardiac surgery. In developing the updated recommendations, every effort was made to maintain consistency with other ACC/AHA and ESC practice guidelines addressing, for example, the management of patients undergoing myocardial revascularization procedures.2. Definition2.1. Atrial FibrillationAF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial mechanical function. On the electrocardiogram (ECG), AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response to AF depends on electrophysiological (EP) properties of the AV node and other conducting tissues, the level of vagal and sympathetic tone, the presence of AV block or ventricular or AV junctional tachycardia. In patients with implanted pacemakers, diagnosis of AF may require temporary inhibition of the pacemaker to expose atrial fibrillatory activity.4 A rapid, irregular, sustained, wide-QRS-complex tachycardia strongly suggests AF with underlying bundle-branch block. Extremely rapid rates (over 200 beats per minute) suggest the presence of an accessory pathway or AF with underlying bundle-branch block. ventricular tachycardia. Figure 1. Electrocardiogram showing atrial fibrillation with a controlled rate of ventricular response. P waves are replaced by fibrillatory waves and the ventricular response is completely irregular. 2.2. Related Arrhythmias most commonly atrial flutter or tachycardia. Atrial flutter may arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF. Atrial flutter (f) waves on the ECG, particularly visible in leads II, III, aVF, and V1 (Fig. 2). In the untreated state, the atrial rate in atrial flutter typically ranges from 240 to 320 beats per minute, with f waves inverted in ECG leads II, III, and aVF and upright in lead V1. The direction of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and inverted in ECG leads II, III, and aVF and upright in lead V1. The direction of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and inverted in ECG leads II, III, and aVF and upright in lead V1. The direction of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and inverted in ECG leads II, III, and aVF and upright in lead V1. The direction of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF atrium (RA) m in a regular or irregular ventricular rate of 120 to 160 beats per minute (most characteristically about 150 beats per minute). Atrial flutter and AF, reflecting changing activation of the atria. Atrial flutter is usually readily distinguished from AF, but when atrial activity is prominent on the ECG in more than 1 lead, AF may be misdiagnosed as atrial flutter.5Figure 2. Electrocardiogram showing typical atrial flutter.5Figure 2. Electrocardiogram showing typical atrial flutter.5Figure 2. deflections.Focal atrial tachycardias, AV reentrant tachycardias, and AV nodal reentrant tachycardias may also trigger AF. In other atrial tachycardias, P waves may be readily identified and are separated by an isoelectric baseline in 1 or more ECG leads. The morphology of the P waves may help localize the origin of the tachycardias.3. ClassificationVarious classification systems have been proposed for AF. One is based on the ECG presentation.2-4 Another is based on epicardial6 or endocavitary recordings or non-contact mapping of atrial electrical activity. Several clinical classification systems have been proposed, but none fully accounts for all aspects of AF.7-10 To be clinically useful, a classification system must be based on a sufficient number of features and carry specific therapeutic implications. Assorted labels have been used to describe the pattern of AF, including acute, chronic, paroxysmal, intermittent, constant, persistent, and permanent, but the vagaries of definitions make it difficult to compare studies of AF or the effectiveness of therapeutic strategies based on these designations. Although the pattern of the arrhythmia can change over time, it may be of clinical value to characterize the arrhythmia at a given moment. The classification scheme recommended in this document represents a consensus driven by a desire for simplicity and clinical relevance. The clinician should distinguish a first-detected episode of AF, whether or not it is symptomatic or self-limited, recognizing that there may be uncertainty about the duration of the episode and about previous undetected episodes (Fig. 3). When a patient has had 2 or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recur- rent AF is designated paroxysmal; when sustained beyond 7 d, AF is designated persistent. Termination with pharmacological therapy or direct-current cardioversion does not change the designated persistent. Termination with pharmacological therapy or direct-current cardioversion does not change the designated persistent. AF (eg, greater than 1 y), usually leading to permanent AF, in which cardioversion has failed or has not been attempted. Figure 3. Patterns of atrial fibrillation (AF). 1, Episodes that usually last 7 d or less (most less than 24 h); 2, episodes that usually last 7 d or less (most less than 24 h); 2, episodes that usually last 7 d or less (most less than 24 h); 2, episodes that usually last 10 permanent AF, in which cardioversion has failed or has not been attempted. Figure 3. Patterns of atrial fibrillation (AF). AF may be recurrent. These categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal and persistent AF, it is practical to categorize a given patient by the most frequent presentation. The definition of permanent AF is often arbitrary. The duration of AF refers both to individual episodes and to how long the patient has been affected by the arrhythmia. Thus, a patient with paroxysmal AF may have episodes that last seconds to hours occurring repeatedly for years. Episodes of AF briefer than 30 s may be important in certain clinical situations involving symptomatic patients, pre-excitation or in assessing the effectiveness of therapeutic interventions. This terminology applies to episodes of AF that last more than 30 s without a reversible cause. Secondary AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, myocardit or other acute pulmonary disease is considered separately. In these settings, AF is not the primary problem, and treatment of the underlying disorder like well-controlled hypothyroidism, and then the general principles for management of the arrhythmia apply. The term "lone AF" has been variously defined but generally applies to young individuals (under 60 y of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. 11 These patients have a favorable prognosis with respect to thromboembolism and mortality. Over time, patients may move out of the lone AF category due to aging or development of the left atrium (LA. Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term "nonvalvular AF" is restricted to cases in which
the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.4. Epidemiology and PrognosisAF is the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. Most data regarding the epidemiology, prognosis, and quality of life in AF have been obtained in the United States and western Europe. It has been estimated that 2.2 million people in America and 4.5 million in the European Union have paroxysmal or persistent AF.12 During the past 20 y, there has been a 66% increase in hospital admissions for AF13-15 due to a combination of factors including the aging of the population, a rising prevalence of chronic heart disease, and more frequent diagnosis through use of ambulatory monitoring devices. AF is an extremely costly public health problem, 16, 17 with hospitalizations as the primary cost driver (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%). Globally, the annual cost per patient is close to €3000 (approximately U.S. \$3600).16 Considering the prevalence of AF is 0.4% to 1% in the general population, increasing with age.18,19 Cross-sectional studies have found a lower prevalence in those below the age of 60 y, increasing to 8% in those older than 80 y (Fig. 4).20-22 The age-adjusted prevalence of AF is higher in men,22,23 in whom the prevalence has more than doubled from the 1970s to the 1990s, while the prevalence in women has remained unchanged.24 The median age of AF patients is about 75 y. Approximately 60% of AF patients over 75 y are female. Based on limited data, the age-adjusted risk of developing AF in blacks seems less than half that in whites.18,25,26 AF is less common among African-American than Caucasian patients with heart failure (HF). Figure 4. Estimated age-specific prevalence, age, distribution, and gender of patients with AF analysis and implications. Modified with permission from Feinberg WM, Blacks-hear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995;155:469-73.19 Copyright © 1995, American Medical Association. All rights reserved. In population-based studies, patients with no history of cardiopulmonary disease account for fewer than 12% of all cases of AF.11,22,27,28 In some series, however, the observed proportion of lone AF was over 30%.29,30 These differences may depend on selection bias when recruiting patients seen in clinical practice compared with population-based observations. In the Euro Heart Survey on AF,31 the prevalence of idiopathic AF amounted to 10%, with an expected highest value of 15% in paroxysmal AF, 14% in first-detected AF, 10% in persistent AF, and only 4% in permanent AF. Essential hypertension, ischemic heart disease, HF (Table 2), valvular heart disease, and diabetes are the most prominent conditions associated with AF.14Table 2. Prevalence of AF in Patients With Heart Failure as Reflected in Several Heart Failure TrialsPredominant NYHA ClassPrevalence of AF (%)StudyI4SOLVD-Prevention (1992)14aII-III10 to 26SOLVD-Treatment (1991)14bCHF-STAT (1995)14cMERIT-HF (1999)501II-IV12 to 27CHARM (2003) Val-HeFT (2003)848III-IV20 to 29Middlekauff (1991)14eStevenson (1996) GESICA (1994)14fIV50CONSENSUS (1987)14g4.2. Incidence In prospective studies, the incidence of AF increases from less than 0.1% per year in those under 40 y old to exceed 1.5% per y implications for the future impact of AF.34 During 38 y of follow-up in the Framingham Study, 20.6% of men who developed AF had HF at inclusion versus 3.2% of those without AF; the corresponding incidences in women were 26.0% and 2.9%.35 In patients referred for treatment of HF, the 2- to 3-y incidence of AF was 5% to 10%.25,36,37 Theorem 4.5%. incidence of AF may be lower in HF patients treated with angiotensin inhibitors.38-40 Similarly, angiotensin inhibition may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be confined to those with left ventricular hypertrophy (LVH).43-45Figure 5. Incidence of AF in patients with hypertension, 41,42 although this may be confined to those with left ventricular hypertension, 41,42 although this may be confined to those with left ventricular hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients with hypertension, 41,42 although this may be associated with a reduced incidence of AF in patients. epidemio-logical studies. Framingham indicates the Framingham Meart Study. Data are from Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Data are from Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455-61;25 and Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in older adults. Circulation 1997;96:2455-61;25 and Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in older adults. attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-54.464.3. PrognosisAF is associated with AF is about double that of patients in normal sinus rhythm and linked to the severity of underlying heart disease 20,23,33 (Fig. 6). About two-thirds of the 3.7% mortality over 8.6 mo in the Etude en Activité Libérale sur la Fibrillation Auriculaire Study (ALFA) was attributed to cardiovascular causes.29Table 3 shows a list of associated heart diseases in the population of the ALFA study.29Figure 6. Relative risk of stroke and mortality in patients with atrial fibrillation (AF) compared with patients without AF. Source data from the Framingham Heart Study (Kannel WB, Abbott RD, Savage DD, et al. Coronary heart J 1983;106:389-96),23 the Regional Heart Study and the Whitehall study (Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation), and the Manitoba study (Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476-84).33 Table 3. Demographics and Associated Conditions Among Patients With Atrial Fibrillation in the Coronary artery disease17121819 ALFA StudyTotal PopulationParoxysmal AFChronic AFRecent-Onset AFNo. of patients756167389200Age, y69667068Male/female ratio1121Time from first episode of AF (mo)473966NAUnderlying heart disease (%) Hypertensive heart disease21172225 Valvular (rheumatic)15102012 Bronchopulmonary disease11101310 Hypertrophic cardiomyopathy5349 Other91497 None294623280ther predisposing or associated factors (%) Hyperthyroidism3425 Hypertension39353846 Diabetes117139 Dilated cardiomyopathy92139 Congestive HF30144318 events88114Left atrial size (mm)44404742Left ventricular ejection fraction (%)59635758Mortality in the Veterans Administration Heart Failure Trials (V-HeFT) was not increased among patients with concomitant AF,49 whereas in the Studies of Left Ventricular Dysfunction (SOLVD), mortality was 34% for those with AF versus 23% for patients in sinus rhythm (P less than 0.001).50 The difference was attributed mainly to deaths due to HF rather than to thromboembolism. AF was a strong
independent risk factor for mortality in those with AF at entry but mortality increased in those who developed AF during follow-up.51 In the Val-HeFT cohort of patients with chronic HF, and individuals with either condition who develop the alternate condition share a poor prognosis.52 Thus, managing the association is a major challenge 53 and the need for randomized trials to investigate the impact of AF on the prognosis in HF is apparent. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of people without AF20, 21, 29, 32, 33, 47 (Fig. 6). One of every 6 strokes occurs in a patient with AF.54 matched controls, 59 and attributable risk was 5 times greater than that in those with nonrheumatic AF.21 In the Manitoba Follow-up Study, AF doubled the risk for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study, AF doubled the risk for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall and the relative risks for stroke in nonrheumatic AF.21 In the Manitoba Follow-up Study and 2.3% in the Whitehall AF patients from general practices in France, the Etude en Activité Libérale sur le Fibrillation Auriculaire (ALFA) study found a 2.4% incidence of thromboembolism over a mean of 8.6 mo of follow-up.29 The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF was 1.5% in participants 50 to 59 y old and 23.5% in those aged 80 to 89 y.215. Pathophysiological Mechanisms5.1. Atrial Factors5.1.1. Atrial Factors5.1.1. Atrial FibrillationThe most frequent pathoanatomic changes in AF are atrial fibrosis juxtaposed with normal atrial fibers, which may account for nonhomogeneity of conduction.60-62 The sinoatrial (SA) and AV nodes may also be involved, accounting for the sick sinus syndrome and AV block. It is difficult to distinguish between changes due to associated heart disease, but fibrosis may precede the onset of AF.63Biopsy of the LA posterior wall during mitral valve surgery revealed mild to moderate fibrosis in specimens obtained from patients with sinus rhythm or AF of relatively short duration, compared with severe fibrosis responded more successfully to cardioversion than did those with severe fibrosis, which was thought to contribute to persistent AF in cases of valvular heart disease.64 In atrial tissue specimens from 53 explanted hearts from transplantation recipients with dilated cardiomyopathy, 19 of whom had permanent, 18 persistent, and 16 no documented AF, extracellular matrix remodeling including selective downregulation of atrial insulin-like growth factor II mRNA-binding protein 2 (IMP-2) and upregulation of matrix metalloproteinase 2 (MMP-2) and type 1 collagen volume fraction (CVF-1) were associated with sustained AF.65Atrial biopsies from patients undergoing cardiac surgery revealed apoptosis66 that may lead to replacement of atrial myocytes by interstitial fibrosis, loss of myofibrils, accumu-lation of glycogen granules, disruption of cell coupling at gap junctions,67 and organelle aggregates.68 The concentration of membrane-bound glycoproteins that regulate cell-cell and cell-matrix interactions (disintegrin and metalloproteinases) in human atrial myocardium has been reported to double during AF. Increased disintegrin and metalloproteinase activity may contribute to atrial dilation in patients with long-standing AF. Atrial fibrosis may be caused by genetic defects like lamin AC gene mutations.69 Other triggers of fibrosis include inflammation70 as seen in cardiac sarcoidosis71 and autoimmune disorders.72 In one study, histological changes consistent with myocarditis were reported in 66% of atrial biopsy specimens from patients with lone AF,62 but it is uncertain whether these inflammatory changes were a cause or consequence of AF. Autoimmune activity is suggested by high serum levels of antibodies against myosin heavy changes were a cause or consequence of AF. chains in patients with paroxysmal AF who have no identified heart disease.72 Apart from fibrosis, atrial pathological findings in patients with AF, including valvular disease, 73,74 hemochromatosis, 75,76 Fibrosis is also triggered by atrial dilation in any type of heart disease associated with AF, including valvular disease, 72,76 Fibrosis is also triggered by atrial dilation in any type of heart disease associated with AF, including valvular disease, 72,76 hypertension, HF, or coronary atherosclerosis.77 Stretch activates several molecular pathways, including the renin-angiotensin-aldosterone system (RAAS). Both angiotensin II and transforming growth factor (CTGF).70. Atrial tissue from patients with persistent AF undergoing open-heart surgery demonstrated increased amounts of extracellular signal-regulated kinase messenger RNA (ERK-2-mRNA), and expression of angiotensin-converting enzyme (ACE) was increased 3-fold during persistent AF.78 A study of 250 patients with AF and an equal number of controls demonstrated the association of RAAS gene polymorphisms with this type of AF.79Several RAAS pathways are activated in experimental78,80-84 as well as human AF,78,85 and ACE inhibition and interstitial fibrosis facilitates sustained AF.86-92 The regional electrical silence (suggesting scar), voltage reduction, and conduction and dispersion of the atrial refractory period.94 Thus, AF seems in the atrial refractory period.94 Thus, AF seems in the atrial refractory period.94 Thus, AF seems a consequence of aging. AF is associated with delayed interatrial conduction and dispersion of the atrial refractory period.94 Thus, AF seems a consequence of aging. AF is associated with delayed interatrial conduction and dispersion of the atrial refractory period.94 Thus, AF seems a consequence of aging. AF is associated with delayed interatrial conduction and dispersion of the atrial refractory period.94 Thus, AF seems a consequence of aging. AF is associated with delayed interatrial conduction and dispersion of the atrial conduction at the attrial conduction at the attrial conducting at the attrial conduction to cause a variety of alterations in the atrial architecture and function that contribute to remodeling and perpetuation of the pulmonary veins (PVs) will prevent AF in many such patients with paroxysmal AF.5.1.1.1. Pathological Changes Caused by Atrial FibrillationJust as atrial stretch may cause AF, AF can cause atrial dilation through loss of contractility and increased compliance.61 Stretch-related growth mechanisms and fibrosis is not the primary feature of AF-induced structural remodeling,95,96 although accumulation of extracellular matrix and fibrosis are associated with more pronounced myocytes in the hibernating myocardium associated with chronic ischemia.98 Among these features are an increase in cell size perinuclear glycogen accumulation, loss of sarcoplasmic reticulum and sarcomeres (myolysis). Changes in gap junction distribution and expression are inconsistent, 61,99 and may be less important than fibrosis or shortened refractoriness in promoting AF. Loss of sarcomeres and contractility seems to protect myocytes against the high metabolic stress associated with rapid rates. In fact, in the absence of other pathophysiological factors, the high atrial tissues. Aside from changes in atrial dimensions that occur over time, data on human atrial structural remodeling are limited 96,100 and difficult to distinguish from degenerative changes related to aging and associated heart disease.96 One study that compared atrial tissue specimens from patients with either pattern of AF, while myolysis and mitochondria hibernation were limited to those with persistent AF. The activity of calpain I, a proteolytic enzyme activated in response to cytosolic calcium overload, was upregulated in both groups and correlated with ion channel protein and structural and electrical remodeling. Hence, calpain activation may link calcium overload to cellular adaptation in patients with AF.3415.1.2. Mechanisms of Atrial FibrillationThe onset and maintenance of a tachyarrhythmia require both an initiating event and an anatomical substrate. With respect to AF, the situation is often complex, and available data support a "focal" mechanism involving automaticity or multiple reentrant wavelets. times coexist in the same patient (Fig. 7). Figure 7. Posterior view of
principal electro-physiological mechanisms of atrial fibrillation. A, Focal activation. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. B, Multiple wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. B, Multiple wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. wavelet reentry. Wavelets (indicated by arrows) randomly reenter tissue previously activated by the same or another wavelets travel vary. Reproduced with permission from Konings KT, Kirchhof CJ, Smeets JR, et al. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89:1665-80.101 LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium.5.1.2.1. Automatic Focus Theory focal origin of AF is supported by experimental models of aconitine and pacing-induced AF102,103 in which the arrhythmia persists only in isolated regions of atrial myocardium. This theory received minimal attention until the important observation that a focal source for AF could be identified in humans and ablation of this source could extinguish AF.104 While PVs are the most frequent source of these rapidly atrial impulses, foci have also been found in the superior vena cava, ligament of Marshall, left posterior free wall, crista terminalis, and coronary sinus.79,104-110In histological studies, cardiac muscle with preserved electrical properties of AF has prompted substantial research into the anatomical and EP properties of these structures. Atrial tissue on the PV of patients with AF has shorter refractory periods than in control patients or other parts of the atria in patients with AF.117,118 The refractory period is shorter in atrial tissue in the PV-LA junction. Decremental conduction may active a conduction may active a controls, and AF is more frequent in AF patients than in controls, and AF is more frequent in AF patients than in controls, and AF is more frequent in AF patients than in controls, and AF is more frequent in AF patients than in controls, and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than in controls and AF is more frequent in AF patients than a controls and AF is more frequent in AF patients than a control and the PV-LA patients than a control a promote reentry and form a substrate for sustained AF.119 Programmed electrical stimulation in PV isolated by catheter ablation initiated sustained pulmonary venous tachycardia, probably as a consequence of reentry.120 Rapidly firing atrial automatic foci may be responsible for these PV triggers, with an anatomical substrate for reentry vested within the PV.Whether the source for AF is an automatic focus or a microreentrant circuit, rapid local activation in the LA with decreasing frequency as activation progressed to the RA. A similar phenomenon has been shown in patients with paroxysmal AF.121 Such variation in conduction leads to disorganized atrial activation, which could explain the ECG appearance of a chaotic atrial rhythm.122 The existence of triggers for AF does not negate the role of substrate modification. In some patients with persistent AF, disruption of the muscular connections between the PV and the LA may terminate the arrhythmia. In others, AF persists following isolation of the supposed triggers, sustained AF may depend on an appropriate anatomical substrate.5.1.2.2. Multiple-Wavelet HypothesisThe multiple-wavelet hypothesis as the mechanism of reentrant AF was advanced by Moe and colleagues, 123 who proposed that fractionation of wavefronts propagating through the atria results in self-perpetuating "daughter wave-lets." 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 wavelet hypothesis in human subjects.127For many years, the multiple-wavelet hypothesis was the dominant theory explaining the mechanism of AF, but the data presented above and from experimental127a and clinical127b,127c mapping studies challenge this notion. Even so, a number of other observations support the importance of an abnormal atrial substrate in the maintenance of AF. For over 25 y, EP studies in humans have implicated atrial vulnerability in the pathogenesis of AF.128-132 In one study of 43 patients with a history of AF, the arrhythmia was induced with a single extrastimulus, while a more aggressive pacing protocol was required in 23 of 25 control patients without previously documented AF. In patients with idiopathic paroxysmal AF, widespread distribution of abnormal electrograms in the RA predicted development of persistent AF, suggesting an abnormal substrate.132 In patients with persistent AF who had undergone conversion to sinus rhythm, there was significant prolongation of intra-atrial conduction compared with a history of paroxysmal AF, even those with lone AF, have abnormal atrial refractoriness and conduction compared with patients without AF. An abnormal signal-averaged P-wave ECG reflects slowed intra-atrial conduction and shorter wavelengths of reentrant impulses. The resulting increase in wavelet density promotes the onset and maintenance of AF. Among patients with HF, prolongation of the P wave was more frequent in those prone to paroxysmal AF.133 Irreduction and shorter wavelengths of reentrant impulses. specimens of RA appendage tissue obtained from patients undergoing open-heart surgery, P-wave duration was correlated with amyloid deposition.73 Because many of these observations were made prior to the onset of clinical AF, the findings cannot be ascribed to atrial remodeling that occurs as a consequence of AF. Atrial refractoriness increases with age in both men and women, but concurrent age-related fibrosis lengthens effective intra-atrial conduction pathways. This, coupled with the shorter wavelengths of reentrant impulses, increases the likelihood that AF will develop.134,135 Nonuniform alterations of refractoriness and conduction throughout the atria may provide a milieu for the maintenance of AF. However, the degree to which changes in the atrial architecture contribute to the initiation and maintenance of AF is not known. Isolation of the PV may prevent recurrent AF even in patients with substantial abnormalities in atrial refractoriness and shortening of the AF cycle length, attesting to the importance of electrical remodeling in the maintenance of AF.136 The anatomical and electrophysiological Substrates Promoting the Initiation and/or Maintenance of Atrial FibrillationDiseasesAnatomicalSubstrates*CellularElectrophysiologicalPart A. Substrate develops during sinus rhythm (remodeling related to stretch and dilatation. The main pathways involve the RAAS, TGF-beta, and CTGF. HypertensionAtrial dilatationMyolysisConduction abnormalities Heart failurePV dilatationApoptosis Valvular diseasePart B. Substrate develops due to tachycardia (tachycardia-related remodeling, downregulation of calcium channel and calcium handling. Coronary diseaseFibrosisChannel expression changeEctopic activity Focal AFNone or†None or†Ectopic activity Atrial flutterAtrial dilatationCalcium channel downregulationMicroreentryPV dilatationMyolysisShort ERP‡Large PV sleevesConnexin downregulationERP dispersion§Reduced contractility Adrenergic supersensitivitySlowed conductionFibrosisChanged sympathetic innervation5.1.3. Atrial Electrical RemodelingPharmacological or direct-current cardioversion of AF has a higher success rate when AF has been present for less than 24 h,137 whereas more prolonged AF makes restoring and maintaining sinus rhythm less likely. These observations gave rise to the adage "atrial fibrillation." The notion that AF is self-perpetuating takes experimental support from a goat model using an automatic atrial fibrillator that detected spontaneous termination of AF and reinduced the arrhythmia by electrical stimulation.138 Initially, electrical stimulation.138 was related to progressive shortening of effective refractory periods with increasing episode duration, a phenomenon known as EP remodeling. These measurements support clinical observations139 that the short atrial effective refractory period in patients with paroxysmal AF fails to adapt to rate, particularly during bradycardia. Confirmation came from recordings of action potentials in isolated fibrillating atrial tissue and from patients after cardioversion.140 The duration of atrial monophasic action potentials was shorter after cardioversion.140 The duration of atrial tachycardia or atrial flutter.142-144 After a period of rapid atrial rate, electrical remodeling stimulates progressive intracellular calcium current in turn shortens the action potential duration and atrial refractory period, which may promote sustained AF. The role of potassium currents in this situation is less clear.145 Electrical remodeling has also been demonstrated in PV myocytes subjected to sustained rapid atrial pacing, resulting in shorter action potential durations and both early and delayed afterdepolarizations.147In addition to remodeling has also been demonstrated in PV myocytes subjected to sustained rapid atrial pacing, resulting in shorter action potential durations.147In addition to remodeling and changes in electrical refractoriness, prolonged AF disturbs atrial contractile function. With persistent AF, recovery of atrial contraction can be delayed for days or weeks
following the restoration of sinus rhythm, which has important implications for the duration of sinus rhythm, which has important implications for the duration of sinus rhythm.) Both canine and preliminary human data suggest that prolonged AF may also lengthen sinus node recovery time.148,149 The implication is that AF may be partly responsible for sinus node dysfunction in some patients with the tachycardia-bradycardia syndrome. Reversal of electrical remodeling in human atria may occur at different rates depending on the region of the atrium studied.150 When tested at various times after cardioversion, the effective refractory period of the lateral RA increased within 1 h after cardioversion, while that in the coronary sinus was delayed for 1 wk. In another study, recovery of normal atrial refractoriness after cardioversion, while that in the coronary sinus was delayed for 1 wk. In another study, recovery of normal atrial refractoriness after cardioversion, while that in the coronary sinus was delayed for 1 wk. refractoriness between the RA appendage and the distal coronary sinus. The disparities between studies may reflect patient factors or the duration or pattern of AF before cardioversion.5.1.4. Counteracting Atrial Electrical RemodelingData are accumulating on the importance of the RAAS in the genesis of AF.145 Irbesartan plus amiodarone was associated with a lower incidence of recurrent AF after catheter ablation of atrial flutter.152 Amiodarone may reverse electrical remodeling even when AF is ongoing,153 and this explains how amiodarone can convert persistent AF to sinus rhythm. Inhibition of the RAAS, alone or in combination with other therapies, may therefore prevent the onset or maintenance of AF43 through several mechanisms. These include hemodynamic changes (lower atrial pressure and wall stress), prevention of structural remodeling (fibrosis, dilation, and hypertrophy) in both the LA and left ventricle (LV), inhibition of neurohumoral activation, reduced blood pressure, prevention or amelioration of HF, and avoidance of AF in patients with LV dysfunction following acute MI,36 but it remains to be clarified whether the antiarrhythmic effect of these agents is related to reversal of structural or electrical remodeling in the atria or to these other mechanisms. 5.1.5. Other Factors Contributing to Atrial Fibrillation. autonomic nervous system activity, atrial ischemia, 154 atrial dilation, 155 anisotropic conduction, 156 and structural changes associated with aging.3 It has been postulated that oxidative stress and inflammation, were higher in patients with atrial arrhythmias than in those without rhythm disturbances, 159 and those with persistent AF had higher CRP levels than those with paroxysmal AF. In a population-based cohort of nearly 6000 patients, AF was more prevalent among patients without AF at baseline, CRP levels were associated with the future development of AF.158The effects of HMG CoA-reductase inhibitors ("statins"), which have both anti-inflammatory and antioxidant properties, on electrical remodeling was suppressed by pretreatment with simvastatin but not by the antioxidant vitamins C and E. The mechanism responsible for the salutary effect of simvastatin requires further investigation, and the utility of drugs in the statin class to prevent clinical AF has not yet been established. Increased sympathetic or parasympathetic tone has been implicated in the initiation of AF. Autonomic ganglia containing parasympathetic and sympathetic fibers are present on the epicardial surface of both the RA and LA, clustered on the posterior wall near the ostia of the PV, superior vena cava (SVC), and coronary sinus. In animal models, parasympathetic stimulation shortens atrial and PV refractory periods, potentiating initiation and maintenance of AF,161,162 and vagal denervation of the atria prevents induction of AF.163 In 297 patients with paroxysmal AF, vagal denervation concomitant with extensive endocardial catheter ablation was associated with significant reduction in subsequent AF in a third of cases.162 Pure autonomic initiation of clinical AF is uncommon and seen only in situations of high sympathetic or high vagal tone, but recordings of heart rate variability (HRV) disclose autonomic perturbations in some patients that precede the onset of AF.164-169There is a strong association between obstructive sleep apnea, hypertension, and AF.170 It is likely that LV diastolic dysfunction plays a role in the genesisted of AF.164-169There is a strong association between obstructive sleep apnea, hypertension, and AF.170 It is likely that LV diastolic dysfunction plays a role in the genesisted of AF.164-169There is a strong association between obstructive sleep apnea, hypertension, and AF.170 It is likely that LV diastolic dysfunction plays a role in the genesisted of A of AF, either by increasing pressure that affects stretch receptors in PV triggers and other areas of the atria or by inducing direct structural changes in atrial myocardium.171,172 Familial factors are discussed in Section 6.1.5.5.2. Atrioventricular Conduction5.2.1. General AspectsIn the absence of an accessory pathway or His-Purkinje dysfunction, the AV node limits conduction during AF.144 Multiple atrial inputs to the AV node have been identified, 2 of which seem dominant: one directed posteriorly via the interatrial septum. Other factors affecting AV conduction are the intrinsic refractoriness of the AV node, concealed conduction, and autonomic tone. Concealed conduction, which occurs when atrial impulses traverse part of the AV node but are not conducted to the ventricles, plays a prominent role in determining the ventricular response during AF.173,174 These impulses alter AV nodel refractoriness, slowing or blocking subsequent atrial impulses, and may explain the irregularity of ventricular response during AF.125 When the atrial rate is relatively slow during AF, the ventricular rate tends to rise. Conversely, a higher atrial rate is associated with slower ventricular rate tends to rise. in states of decreased parasympathetic and increased sympathetic tone.173,175,176 Vagal tone also enhances the negative chronotropic effects of concealed conduction in the AV node.175,176 Fluctuations in autonomic tone can produce disparate ventricular responses to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in a given patient as exemplified by a slow ventricular response to AF in accelerated ventricular response during exercise. Digitalis, which slows the ventricular rate during activity. Wide swings in rate due to variations in autonomic tone may create a therapeutic challenge. Conducted QRS complexes are narrow during AF unless there is fixed or rate-related bundle-branch block or accessory pathway. Aberrant conducted (Ashman phenomenon).1775.2.2. Atrioventricular Conduction in Patients With Preexcitation SyndromesConduction across an accessory pathway during AF can result in a dangerously rapid ventricular response, alterations in vagal tone have little effect on conduction over accessory pathways. Transition of AV reentry into AF in patients with the Wolff-Parkinson-White (WPW) syndrome can produce a rapid ventricular response that degenerates into ventricular fibrillation, leading to death. 178, 180 Intravenous administration of drugs such as digitalis, verapamil, or diltiazem, which lengthen refractoriness and slow conduction across the AV node, does not block conduction over the accessory pathway and may accelerate the ventricular rate. Hence, these agents are contraindicated in this situation.181 Although the potential for beta blockers to potentiate conduction across the accessory pathway is controversial, caution should be exercised in the use of these agents as well as in patients with AF associated with preexcitation.5.3. Myocardial and Hemodynamic 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, hypert model with complete heart block, in which cardiac output fell by approximately 9% during irregular ventricular pacing at the same
mean cycle length as a regularly paced rhythm.182 In patients undergoing AV nodal ablation, irregular right ventricular pacing at the same mean cycle length as a regularly paced rhythm.182 In patients undergoing AV nodal ablation, irregular right ventricular pacing at the same mean cycle length as a regularly paced rhythm.182 In patients undergoing AV nodal ablation, irregular right ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular pacing at the same mean cycle length as a regular ventricular ventricular pacing at the same mean cycle length as a regular ventricular ventricula output.183 Myocardial contractility is not constant during AF because of force-interval relationships associated with variations in cycle length.184 Although one might expect restoration of sinus rhythm to improve these hemodynamic characteristics, this is not always the case.185,186 Myocardial blood flow is determined by the presence or absence of coronary obstructive disease, the difference between aortic diastolic pressure and LV end-diastolic pressure (myocardial perfusion pressure), coronary vascular resistance, and the duration of diastole. AF may adversely impact all of these factors. An irregular rhythm is associated with a regular rhythm is associated at the same average rate. 186 Animal studies have consistently shown that the decrease in coronary flow caused by experimentally induced AF relates to an increase in coronary vascular resistance mediated by sympathetic activation of alpha-adrenergic receptors that is less pronounced than during regular atrial pacing at the same ventricular rate.187 Similarly, coronary blood flow is lower during AF than during regular atrial pacing in patients with angiographically normal coronary arteries.188 The reduced coronary to sodilation is limited. These findings may explain why patients without previous angina sometimes develop chest discomfort with the onset of AF.In patients with persistent AF, mean LA volume increased from 49 to 66 cm3.189 Restoration and maintenance of sinus rhythm decreased atrial volumes.190 Moreover, transesophageal echocardiography (TEE) has demonstrated that contractile function and blood flow velocity in the LA appendage (LAA) recover after cardioversion, consistent with AF.191,192Beyond its effects on atrial function, a persistently elevated ventricular rate during AF—greater than or equal to 130 beats per minute in one study193—can produce dilated ventricular cardiomyopathy, in which HF is a consequence rather than the cause of AF. Control of the ventricular rate may lead to reversal of the myopathic process. In one study, the median LV ejection fraction increased with rate control from 25% to 52%.194 This phenomenon also has implications for timing measurements of ventricular performance in patients with AF. A reduced ejection fraction during or in the weeks following tachycardia may not reliably predict ventricular function once the rate has been consistently controlled. A variety of hypotheses have been proposed to explain tachycardia-mediated cardiomyopathy: myocardial energy depletion, ischemia, abnormal calcium regulation, and remodeling, but the actual mechanisms are still unclear.197Because of the relationship between LA and LV pressure, a rapid ventricular rate during AF may adversely impact mitral valve function, increasing mitral regurgitation. In addition, tachycardia may be associated with rate-related intraventricular conduction delay (including left bundle-branch block), which further compromises the synchrony of LV wall motion and reduces cardiac output. Such conduction disturbances may exacerbate mitral regurgitation and limit ventricular filling. Controlling the ventricular rate may reverse these effects 5.4. Thromboembolism Although ischemic arterial occlusion in AF are generally attributed to embolism of thrombus from the LA, the pathogenesis of thromboembolism is complex.198 Up to 25% of strokes in patients with AF may be due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or atheromatous pathology in the proximal aorta.199,200 In patients 80 to 89 y old, 36% of strokes occur in those with AF. The annual risk of stroke for octogenarians with AF is in the range of 3% to 8% per year, depending on associated stroke risk factors.21 About half of all elderly AF patients have hypertension (a major risk factor for cerebrovascular disease, 47 and approximately 12% harbor carotid atherosclerosis is not substantially more prevalent in AF patients with stroke than in patients without AF and is probably a relatively minor contributing epidemiological factor. 2025.4.1. Pathophysiology of Thrombus FormationThrombotic material associated with AF arises most frequently in the LAA, which cannot be regularly examined by precordial (transthoracic) echocardiography.203 Doppler TEE is a more sensitive and specific method to assess LAA function204 and to detect thrombus formation. Thrombi are more often encountered in AF patients with ischemic stroke than in those without stroke.205 Although clinical management is based on the presumption that thrombus formation begins with Virchow's triad of stasis, endothelial dysfunction, and a hypercoagulable state. Serial TEE studies of the LA208 and LAA209 during conversion of AF to sinus rhythm demonstrated reduced LAA flow velocities related to loss of organized mechanical contraction during AF. Stunning of the LA210 seems responsible for an increased risk of thromboembolic events after successful cardioversion, regardless of whether the method is electrical, pharmacological, or spontaneous.210 Atrial stunning is at a maximum immediately after cardioversion, with progressive improvement of atrial transport function within a few days but sometimes as long as 3 to 4 wk, depending on the duration of AF.210,211 This corroborates the observation that following cardioversion, more than 80% of thromboembolic events occur during the first 3 d and almost all occur within 10 d.212 Atrial stunning is more pronounced in patients with AF associated with ischemic heart disease than in those with hypertensive heart disease than a line of the hypertensive heart disease theart disease theart disease theart disease the hypert certain associated conditions or a short duration of AF, anticoagulation is recommended during cardioversion in all patients with AF lasting longer than 48 h or of unknown duration, including lone AF except when anticoagulation is contraindicated. Decreased flow within the LA/LAA during AF has been associated with spontaneous echo contrast (SEC), thrombus formation, and embolic events.213-218 Specifically, SEC, or "smoke," a swirling haze of variable density, may be detected by transthoracic or transesophageal echocardio-graphic imaging of the cardiac chambers and great vessels under low-flow conditions.219 This phenomenon relates to fibrinogen-mediated erythrocyte aggregation220 and is not resolved by anticoagulation.221 There is evidence that SEC is a marker of stasis caused by AF.222-224 Independent predictors of SEC in patients with AF include LA enlargement, reduced LAA flow velocity.213,225 LV dysfunction, fibrinogen level,218 and hematocrit.217,218 The utility of SEC for prospective thromboembolic risk stratification beyond that achieved by clinical assessment alone has, however, not been confirmed.LAA flow velocities are lower in patients with atrial flutter than are usually seen during sinus rhythm but higher than in AF. atrial flutter is uncertain. As in AF, atrial flutter is associated with low appendage emptying velocities following cardioversion with the potential for thromboembolism226,227 and anticoagulation is similarly recommended. (See Section 8.1.4.1.3, Therapeutic Implications.) Although endothelial dysfunction has been difficult to demonstrate as distinctly contributing to thrombus formation in AF, it may, along with stasis, contribute to a hypercoagulable state. Systemic and/or atrial tissue levels of P-selectin and von Willebrand factor are elevated in some patients, 228-233 and AF has been associated with biochemical markers of coagulation and platelet activation that reflect a systemic hypercoagulable state.228,234-236 Persistent and paroxysmal AF have been associated with increased systemic fibrinogen and fibrin D-dimer levels, indicate platelet factor 4 levels in selected patients with AF indicate platelet activation,235,238,239 but these data are less robust, in line with the lower efficacy of platelet-inhibitor drugs for prevention of thromboembolism in clinical trials. Fibrin D-dimer levels are higher in patients with AF than in patients in sinus rhythm, irrespective of underlying heart disease.240 The levels of some markers of coagulation fall to normal during anticoagulation therapy,234 and some increase immediately after conversion to sinus rhythm and then normalize.241 These biochemical markers do not, however, distinguish a secondary reaction to intravascular coagulation from a primary hypercoagulable state. C-reactive protein (CRP) is increased in patients with AF compared with controls159,242 and correlates with clinical and
echocardiographic stroke risk factors.243 Although these findings do not imply a causal relationship, the association may indicate that a thromboembolic milieu in the LA may involve mechanisms linked to inflammation.243In patients with rheumatic mitral stenosis undergoing trans-septal catheterization for balloon valvuloplasty, levels of fibrinopeptide A, thrombin-antithrombin III complex, and prothrombin fragment F1.2 are increased in the LA compared with the RA and femoral vein, indicating regional activation of the coagulation system. 244, 245 Whether such elevations are related to AF, for example, through atrial pressure overload or due to another mechanism has not been determined. Regional coagulopathy is associated with SEC in the LA and hence with atrial stasis.245 Contrary to the prevalent concept that systemic anticoagulation for 4 wk results in organization and endocardial adherence of LAA thrombus, TEE studies have verified resolution of thrombus in the majority of patients.246 Similar observations have defined the dynamic nature of LA/LAA dysfunction following conversion of AF, providing a mechanistic rationale for anticoagulation for several weeks before and after successful cardioversion. Conversely, increased flow within the LA in patients with mitral regurgitation has been associated with less prevalent LA SEC247.248 and fewer thromboembolic events, even in the presence of LA enlargement.2495.4.2. Clinical ImplicationsBecause the pathophysiology of thromboembolism in patients with AF are incompletely defined. The strong association between hypertension and stroke in AF is probably mediated primarily by embolism originating in the LAA,200 but hypertension also increases the risk of noncardioembolic strokes in patients with AF is associated with reduced LAA flow velocity, SEC, and thrombus formation.225,251,252 Ventricular diastolic dysfunction might underlie the effect of hypertension on LA dynamics, but this relationship is still speculative.253,254 Whether control of hypertension lowers the risk for cardioembolic stroke in patients with AF is a vital question, because LV diastolic abnormalities associated with hypertension in the elderly are often multifactorial and difficult to reverse.254,255The increasing stroke risk in patients with AF with advancing age is also multifactorial. In patients with AF, aging is associated with LA enlargement, reduced LAA flow velocity, and SEC, all of which predispose to LA thrombus formation.225,251,256 Aging is associated with stroke independent of AF.257 Levels of prothrombin activation fragment F1.2, an index of thrombin generation, increase with age in the general population 258-260 as well as in those with AF,12,261 suggesting an age-related prothrombotic diathesis. In the Stroke Prevention in Atrial Fibrillation (SPAF) studies, age was a more potent risk factor when combined with other risk factors such as hypertension or female gender, 261, 262 placing women over age 75 y with AF at particular risk for cardioembolic strokes. 263LV systolic dysfunction, as indicated by a history of HF or echocardiographic assessment, predicts ischemic stroke in patients with AF who receive no antithrombotic therapy 264–267 but not in moderate-risk patients given aspirin.261,268 Mechanistic inferences are contradictory; LV systolic dysfunction has been associated both with LA thrombus and with noncardioembolic mechanisms are operative in AF and involve the interplay of risk factors related to atrial stasis, endothelial dysfunction, and systemic and possibly local hypercoagulability.6. Causes, Associated Conditions, Clinical Manifestations, and Quality of Life6.1. Causes and Associated Conditions.1.1. Reversible Causes of Atrial FibrillationAF may be related to acute, temporary causes, including alcohol intake ("holiday heart syndrome"), surgery, electrocution, MI, pericarditis, myocarditis, pulmonary embolism or other pulmonary diseases, hyperthyroidism, and other metabolic disorders. In such cases, successful treatment of the underlying condition often eliminates AF. AF that develops in the setting of acute MI portends an adverse prognosis compared with preinfarct AF or sinus rhythm.270,271 AF may be associated with atrial flutter, the WPW syndrome, or AV nodal reentrant tachycardias, and treatment of the primary arrhythmias reduces or eliminates the incidence of recurrent AF.172 AF is a common early postoperative complication of cardiac or thoracic surgery.6.1.2. Atrial Fibrillation Without Associated Heart DiseaseAF is often an electrical manifestation of underlying cardiac disease. Nonetheless, approximately 30% to 45% of cases of paroxysmal AF and 20% to 25% of cases of paroxysmal AF and 20% to over time.272 Although AF may occur without underlying heart disease in the elderly, the changes in cardiac structure and function that accompany aging, such as an increase in myocardial stiffness, may be associated with AF, just as heart disease in older patients may be coincidental and unrelated to AF.6.1.3. Medical Conditions Associated With Atrial FibrillationObesity is an important risk factor for development of AF.273-275 After adjusting for clinical risk factors, the excess risk of AF appears mediated by LA dilation, because there is a graded increase from normal to the overweight and obese categories.273 Weight reduction has been linked to regression of LA enlargement.273,276 These findings suggest a physiological link between obesity, AF, and stroke and raise the intriguing possibility that weight reduction may decrease the risk of AF.6.1.4. Atrial Fibrillation With Associated Heart DiseaseSpecific cardiovascular conditions associated with AF include valvular heart disease (most often, mitral valve) disease), HF, CAD, and hypertension, particularly when LVH is present. In addition, AF may be associated with HCM, dilated cardiomyopathy, or congenital heart disease, especially atrial septal defect in adults. Potential etiologies also include restrictive cardiomyopathy, or congenital heart disease, especially atrial septal defect in adults. tumors, and constrictive pericarditis. Other heart diseases, such as mitral valve prolapse with or without mitral regurgitation, calcification of the RA, have been associated with a high incidence of AF. AF is commonly encountered in patients with sleep apnea syndrome, but whether the arrhythmia is provoked by hypoxia, another biochemical abnormality, changes in pulmonary dynamics or RA factors, changes in autonomic tone, or systemic hypertension has not been determined. Table 5. Etiologies and factors predisposing patients to AF. (For a list of associated heart diseases in the ALFA study, see Table 3.) Table 5. Etiologies and factors predisposing patients to AF. 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) and Factors Predisposing Patients to AFElectrophysiological abnormalities Semilunar valvular Systemic or pulmonary hypertension (pulmonary embolism) Coronary artery diseaseInflammatory or infiltrative atrial disease abnormalities (causing ventricular hypertrophy) Intracardiac tumors or thrombiAtrial ischemia Pericarditis Amvloidosis Mvocarditis Age-induced atrial fibrotic Increased sympathetic activityPrimary or metastatic disease in or adjacent to the atrial wallPostoperative Alcohol CaffeineEndocrine disorders Hyperthyroidism PheochromocytomaChanges in autonomic tone Increased parasympathetic activity Cardiac, pulmonary, or changesDrugs esophagealCongenital heart diseaseNeurogenic Subarachnoid hemorrhage Nonhemorrhagic, major strokeIdiopathic (lone AF)Familial AF6.1.5. Familial (Genetic) Atrial FibrillationFamilial AF, defined as lone AF running in a family, is more common than previously recognized but should be distin-guished from AF secondary to other

genetic diseases like familial cardiomyopathies. The likelihood of developing AF is increased among those whose parents had AF, suggesting a familial susceptibility to the arrhythmia, but the mechanisms associated with transmission are not necessarily electrical, because the relationship has also been seen in patients who have a family history of hypertension, diabetes, or HF.277The molecular defects responsible for familial AF are largely unknown. Specific chromosomal loci278 have been linked to AF in some families, suggesting distinct genetic mutations.279 Two mutations associated with gain of function leading to short atrial refractoriness have been discovered in several Chinese families.280,2816.1.6. Autonomic Influences in Atrial FibrillationAutonomic tone in humans has been augmented by measures of HRV,282 which reflect changes in the relative autonomic modulation of heart rate rather than the absolute level of sympathetic or parasympathetic tone. It appears that the balance between sympathetic and vagal influences is as important as absolute sympathetic tone as measured by HRV occur prior to the development of AF. Fluctuations in autonomic tone as measured by HRV occur prior to the development of AF. has been observed in some patients with structurally normal hearts, while in others there is a shift toward sympathetic predominance.283,284 Although Coumel285 recognized that certain patients could be characterized in terms of a vagal or adrenergic form of AF, these cases likely represent the extremes of either influence. In general, vagally mediated AF occurs at night or after meals, while adrenergically induced AF typically occurs during the daytime in patients with organic heart disease. 286 Vagally mediated AF is the more common form, and in such cases adrenergic blocking drugs or digitalis sometimes worsens symptoms and anticholinergic agents such as disopyramide are sometimes helpful to prevent recurrent AF. Classification of AF as of either the vagal or adrenergic form has only limited impact on management. For AF of the adrenergic type, beta blockers are the initial treatment of choice.6.2. Clinical ManifestationsAF has a heterogeneous clinical presentation, occurring in the presence or absence of detectable heart disease. An episode of AF may be self-limited or require medical intervention, frequency, mode of onset, triggers, and response to therapy, but these features may be impossible to discern when AF is first encountered in an individual patient.AF may be immediately recognized by sensation of palpitations or by its hemodynamic or thromboembolic consequences or follow an asymptomatic AF.287-290 Patients in whom the arrhythmia has become permanent often notice that palpitation decreases with time and may become asymptomatic. This is particularly common among the elderly. Some patients experience symptoms only during paroxysmal AF or only intermittently during sustained AF. When present, symptoms of AF vary with the irregularity and rate of ventricular response, 291 underlying functional status, duration of AF, and individual patients complain of palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope. Polyuria may be associated with the release of atrial natriuretic peptide, particularly as episodes of AF begin or terminate. AF associated with a sustained, rapid ventricular response can lead to tachycardia-mediated cardiomyopathy, especially in patients unaware of the arrhythmia.Syncope is an uncommon complication of AF that can occur upon conversion in patients with sinus node dysfunction or because of rapid ventricular rates in patients with HCM, in patients with valvular aortic stenosis, or when an accessory pathway is present.6.3. Quality of LifeAlthough stroke certainly accounts for much of the functional impairment associated with AF, available data suggest that quality of life is considerably impaired in patients with AF compared with age-matched controls. Sustained sinus rhythm is associated with improved quality of life and better exercise performance than AF in some studies but not others.292-296 In the SPAF study cohort, Ganiats et al297 found the New York Heart Association functional classification, originally developed for HF, an insensitive index of quality of life in patients with AF. In another study,298 47 of 69 patients (68%) with paroxysmal AF considered the arrhythmia disruptive of lifestyle, but this perception was not associated with either the frequency or duration of symptomatic episodes.7. Clinical History and Physical ExaminationThe diagnosis of AF is based on history and clinical examination and confirmed by ECG recording, sometimes in the form of bedside telemetry or ambulatory Holter recordings. The initial evaluation of a patient with suspected or proved AF involves characterizing the pattern of the arrhythmia as paroxysmal or persistent, determining its cause, and defining associated cardiac and extracardiac factors pertinent to the etiology, tolerability, and history of prior management (Table 6). A thorough history will result in a well-planned, focused workup that serves as an effective guide to therapy.3 The workup of a patient with AF can usually take place and therapy initiated in a single outpatient encounter. Delay occurs when the rhythm has not been specifically documented and additional monitoring is necessary. Table 6. Clinical Evaluation in Patients With AFClinical type of AF (first episode, paroxysmal, persistent, or permanent)Onset of the first symptomatic attack or date of discovery of AFFrequency, duration, precipitating factors, and modes of termination of AFResponse to any pharmacological agents that have been administeredPresence of any underlying heart disease or other reversible conditions (eg, hyperthyroidism or alcohol consumption)Electrocardiogram, to identifyRhythm (verify AF)LV hypertrophyP-wave duration and morphology or fibrillatory wavesPreexcitationBundle-branch blockPrior MIOther atrial arrhythmics for measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapyTransthoracic echocardiogram, to identifyValvular heart diseaseLA and RA sizeLV size and functionPeak RV pressure (pulmonary hypertension)LV hypertrophyLA thrombus (low sensitivity)Pericardial diseaseBlood tests of thyroid, renal, and hepatic functionFor a first episode of AF, when the ventricular rate is difficult to controlAdditional testingOne or several tests may be necessary. Six-minute walk testIf the adequacy of rate control is in questionExercise testingIf the adequacy of rate control is in questionAs a means are a means are a means are a means and the type of arrhythmic drugHolter monitoring or event recordingIf diagnosis of the type of arrhythmic are a means are a of evaluating rate controlTransesophageal echocardiographyTo identify LA thrombus (in the LA appendage)To guide cardioversionElectrophysiological studyTo clarify the mechanism of wide-QRS-complex tachycardiaTo identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardiaTo seek sites for curative ablation or AV conduction block/modificationChest radiograph, to evaluateLung parenchyma, when clinical findings suggest an abnormalityTypically, AF occurs in patients with underlying heart disease, such as hypertensive heart disease.33,299 (See Section 6, Causes, Associated Conditions, Clinical Manifestations, and Quality of Life.) Atherosclerotic or valvular heart diseases are also common substrates, whereas pulmonary pathology, preexcitation syndromes, and thyroid disease are less frequent causes. 300 Because of reports of genetic transmission of AF, the family history is important as well.272,301 Although various environmental triggers can initiate episodes of AF, this aspect may not emerge from the history given spontaneously by the patient and often requires specific inquiry. Commonly mentioned triggers include alcohol, sleep deprivation, and emotional stress, but vagally mediated AF may occur during sleep or after a large meal and is more likely to arise during a period of rest succeeded by a period of stress. Stimulants such as caffeine or exercise may also precipitate AF. The physical examination in the intensity of the first heart sound or absence of a fourth sound heard previously during sinus rhythm. Examination may also disclose associated valvular heart disease, myocardial abnormalities, or HF. The findings are similar in patients with atrial flutter, except that the rhythm may be regular and rapid venous oscillations may occasionally be visible in the jugular pulse. 7.1.2. Investigations The diagnosis of AF requires ECG documentation by at least a single-lead recording during the arrhythmia, which may be facilitated by review of emergency department records, Holter monitoring, or transtelephonic or telemetric recordings. A portable ECG record of the arrhythmia. In patients with implanted pacemakers or defibrillators, the diagnostic and memory functions may allow accurate and automatic detection of AF.302 A chest radiograph may detect enlargement of the cardiac chambers and HF but is valuable mostly to detect intrinsic pulmonary pathology and evaluate the pulmonary vasculature. It is less important than echocardiography for routine evaluation of patients with AF. As part of the initial evaluation, all patients with AF should have 2-dimensional, Doppler echocardiography to assess LA and LV wall thickness and function and to exclude occult valvular or pericardial disease and HCM. LV systolic and diastolic performance helps guide decisions regarding antiar-rhythmic and antithrombotic therapy. Thrombus should be sought in the LA but is seldom detected without TEE.203,303,304Blood tests are routine but can be abbreviated. It is important that thyroid, renal, and hepatic function, serum electrolytes, and the hemogram be measured at least once in the course of evaluating a patient with AF.3057.2. Additional
Investigation of Selected Patients With Atrial FibrillationAbnormalities in P-wave duration detected by signal-averaged ECG during sinus rhythm that reflect slow intra-atrial conduction are associated with an increased risk of developing AF.133,306–308 The sensitivity and negative predictive value of signalaveraged P-wave ECG are high, but specificity and positive predictive value are low, limiting the usefulness of this technique.309 Measurement of HRV has failed to provide useful information for risk stratification.309Both B-type natriuretic peptide (assessed by measuring BNP or N-terminal pro-BNP), which is produced mainly in the ventricles, and atrial naturetic peptide (ANP), which is produced primarily in the atria, are associated with AF. Plasma levels of both peptides. In atrial naturetic peptide (ANP), which is produced primarily in the atria, are associated with AF. Plasma levels of these peptides. In the absence of HF, there is an inverse correlation between LA volume and ANP/BNP levels;251 spontaneous conversion to sinus rhythm is associated with higher ANP levels may be related to degeneration of atrial myocytes.314 High levels of BNP may be predictive of thromboembolism315 and recurrent AF,40,316 but further studies are needed to evaluate the utility of BNP as a prognostic marker.7.2.1. Electrocardiogram Monitoring and Exercise TestingProlonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF, which may be a cause of cryptogenic stroke. Ambulatory ECG (eg, Holter) monitoring is also useful to judge the adequacy of rate control. This technology may provide valuable information to guide drug dosage for rate control or rhythm management.317Exercise testing should be performed if myocardial ischemia is suspected and prior to initiating type IC antiarrhythmic drug therapy. Another reason for exercise testing is to study the adequacy of rate control across a full spectrum of activity, not only at rest, in patients with AF. By placing a high-frequency ultrasound transducer close to the heart, however, TEE provides high-quality images of cardiac structure318 and function.319 It is the most sensitive and specific technique to detect sources and potential mechanisms for cardiogenic embolism.320 The technology has been used to stratify stroke risk in patients with AF and to guide cardioversion. (See Section 8.1.4, Preventing Thromboembolism.) Several TEE features have been associated with thromboembolism in patients with nonvalvular AF, including LA/LAA SEC, reduced LAA flow velocity, and aortic atheromatous abnormalities.252 Although these features are associated with cardiogenic embolism, 268,321 prospective investigations are needed to compare these TEE findings with clinical and transthoracic echocardiographic predictors of thromboembolism. Detection of LA/LAA thrombus in the setting of stroke or systemic embolism is convincing evidence of a cardiogenic mechanism.207TEE of patients with AF before cardioversion has shown LA or LAA thrombus in 5% to 15%,304,321-323 but thromboembolism after conversion to sinus rhythm has been reported even when TEE did not show thrombus.324 These events typically occur relatively soon after cardioversion in patients with AF undergoing cardioversion even when no thrombus is identified. For patients with AF of greater than 48-h duration, a TEE-guided strategy of anticoagulation for 4 wk before and 4 wk after elective cardioversion resulted in similar rates of thromboembolism (less than 1% during the 8 wk).325 Contrast-enhanced magnetic resonance imaging is an emerging technique for detection of intracardiac thrombi that appears more sensitive than precordial echocardiography and comparable to TEE.3267.2.3. Electrophysiological StudyAn EP study can be helpful when AF is a consequence of reentrant tachycardia such as atrial flutter, intra-atrial reentry, or AV reentry involving an accessory pathway. Detection of a delta wave on the surface ECG in a patient with a history of AF or syncope is a firm indication of flutter also have AF, and ablation of flutter can eliminate the possibility and ablation of flutter also have AF, and ablation of flutter also hav of developing AF in the future.327 AF associated with rapid ventricular rates and wide-complex QRS morphology may sometimes be mislabeled as ventricular tachycardia, and an EP study will differentiate the 2 arrhythmias. In short, EP testing is indi- cated when ablative therapy of arrhythmias that trigger AF or ablation of AF is planned. In patients with AF who are candidates for ablation, an EP study is critical to define the targeted site or sites of ablation in the LA and/or right-sided structures. Evolving strategies in the ablation of AF are discussed in Section 8.0.8. Management (UPDATED)For new or updated text, view the 2011 Focused Update and the 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated. 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 also requires attention to rate control. Depending on the patient's course, the strategy initially chosen may prove unsuccessful and the alternate strategy is then adopted. Regardless of whether the rate-control or rhythm-control strategy is pursued, attention must also be directed to antithrombotic therapy for prevention of thromboembolism. At the initial encounter, an overall management strategy should be discussed with the patient, considering several factors: 1 type and duration of AF,2 severity and type of symptoms,3 associated cardiovascular disease,4 patient age,5 associated medical conditions,6 short-term and long-term treatment goals, and7 pharmacological therapeutic options. A patient with a first-documented episode of AF in whom rate control is achieved does not require hospitalization. Duration And Pattern Of Atrial Fibrillation. As defined in Section 3, AF may be categorized as paroxysmal (self-terminating), persistent (requiring electrical or pharmacological termination), or permanent (cardioversion impossible or futile). The duration since onset may be known or unknown in an individual patient depending upon the presence or absence of specific symptoms or ECG documentation of the arrhythmia. Type And Severity Of Symptoms. As described in Section 6.2, few arrhythmias present with such protean manifestations, some of which are subtle. is restored. In contrast, other patients have no or minimal symptoms during AF and restoration of sinus rhythm would not change their functional status. Before deciding on whether the patient is truly asymptomatic, it may be helpful to ask whether the patient has noticed a decline in activity over time, especially when there is no other obvious explanation. Associated Cardiovascular Disease. The presence of cardiovascular disease. face difficulties in the future if left in AF until it becomes difficult to restore sinus rhythm because of atrial remodeling. Potential For Changes In Cardiac Function Related. To Age. Before choosing rate control as a long-term strategy, the clinician should consider how permanent AF is likely to affect the patient in the future. In a patient with asymptomatic persistent AF, attempts to restore sinus rhythm may not be needed. Prospective studies like Rate Control vs Electrical cardioversion for persistent atrial fibrillation (RACE) and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) showed that patients who could tolerate rate-controlled AF had outcomes similar to those randomized to rhythm control. However, these studies enrolled predominantly older patients (average 70 y), most of whom had persistent AF and heart disease, and follow-up extended over just a few years. Thus, the trial data do not necessarily apply to younger patients without heart disease or to patients whose dependency upon sinus rhythm is likely to change appreciably over time. Among the latter may be patients in HF, who are prone to deteriorate over time if left in AF. The problem with allowing AF to persist for years is that it may then be impossible to restore sinus rhythm as a consequence of electrical and structural remodeling, which preclude successful restoration or maintenance of sinus rhythm and favor permanent AF. This makes it important to ensure that a window of opportunity to maintain sinus rhythm is not overlooked early in the course of management of a patient with AF.8.1. Pharmacological and Nonpharmacological Therapeutic OptionsDrugs and ablation are effective for both rate and rhythm control and in special circumstances surgery may be the preferred option. Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is maintained. For rhythm control, drugs are typically the first choice and LA ablation is a second-line choice, especially in patients with symptomatic lone AF. In some patients, especially young ones with very symptomatic AF who need sinus rhythm, radiofrequency ablation may be preferred over years of drug therapy. Patients are candidates for a stand-alone surgical procedure to cure AF using the maze or LA ablation techniques, these approaches can be an effective adjunct to coronary bypass or valve repair surgery to prevent recurrent postoperative AF. Applied in this way, AF may be eliminated without significant additional risk. Because the LAA is the site of over 95% of detected thrombi, this structure should be removed from the circulation when possible during cardiac surgery in patients at risk of devel- oping postoperative AF, although this has not been proved to prevent
stroke.328Drugs are the primary treatment for rate control in most patients with AF. While ablation of the AV conduction system and permanent pacing (the "ablate and pace" strategy) is an option that often yields remarkable symptomatic relief, growing concern about the negative effect of long-term RV pacing, on the other hand, may overcome many of the adverse hemodynamic effects associated with RV pacing. 8.1.1. Pharmacological Therapy8.1.1.1. Drugs Modulating the Renin-Angiotensin-Aldosterone SystemExperimental and clinical studies have demonstrated that ACE inhibitors and angiotensin receptor antagonists may decrease atrial pressure, reduce the frequency of atrial premature beats, 329 reduce fibrosis, 86 and may lower the relapse rate after cardioversion39,330,331 in patients with AF. These drugs can reduce signal-averaged P-wave duration, the number of defibrillation attempts required to restore sinus rhythm, and the number of hospital readmissions for AF.332 Withdrawal of ACE-inhibitor medication is associated with postoperative AF in patients undergoing coronary bypass surgery,333 and concurrent therapy with ACE-inhibitor and antiarrhythmic agents enhances maintenance of sinus rhythm.334In patients with persistent AF and normal LV function, the combination of enalapril or irbesartan plus amiodarone resulted in lower rates of recurrent AF and normal LV function, the combination of enalapril or irbesartan plus amiodarone resulted in lower rates of recurrent AF and normal LV function, the combination of enalapril or irbesartan plus amiodarone resulted in lower rates of recurrent AF and normal LV function, the combination of enalapril or irbesartan plus amiodarone resulted in lower rates of recurrent AF and normal LV function. treatment with inhibitors of the RAAS in long-term maintenance of sinus rhythm in patients at risk of developing recurrent AF requires clarification in randomized trials before this approach can be routinely recommended.8.1.1.2. HMG CoA-Reductase Inhibitors (Statins)Available evidence supports the efficacy of statin-type cholesterol-lowering agents in maintaining sinus rhythm in patients with persistent lone AF. Statins decrease the risk of recurrences after successful direct-current cardioversion without affecting the defibrillation threshold.335 The mechanisms by which these drugs prevent AF recurrences after successful direct-current cardioversion without affecting the defibrillation threshold.335 The mechanisms by which these drugs prevent AF recurrences after successful direct-current cardioversion of CAD, pleiotropic (anti-inflammatory and antioxidant) effects, 336, 337 and direct antiarrhythmic effects involving alterations in transmembrane ion channels. 3388.1.2. Heart Rate Control Versus Rhythm Control 8.1.2.1. Distinguishing Short-Term and Long-Term Treatment GoalsThe initial and subsequent management of symptomatic AF may differ from one patient to another. For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control, while the long-term goal is to restore sinus rhythm. When cardioversion is contemplated and the duration of AF is unknown or exceeds 48 h, patients who do not require long-term anticoagulation may benefit from shortterm anticoagulation. If rate control offers inadequate symptomatic relief, restoration of sinus rhythm becomes a clear long-term goal. Early cardioversion may be necessary if AF causes hypotension or worsening HF, making the establishment of sinus rhythm a combined short- and long-term therapeutic goal. In contrast, amelioration of symptoms by rate control in older patients may steer the clinician away from attempts to restore sinus rhythm. In some circumstances, when the initiating pathophysiology of AF is reversible, as for instance in the setting of thyrotoxicosis or after cardiac surgery, no long-term therapy may be necessary.8.1.2.2. Clinical Trials Comparing Rate Control and Rhythm ControlRandomized trials comparing outcomes of rhythm- versus rate-control strategies in patients with AF are summarized in Tables 7 and 8. Among these, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) found no difference in mortality or stroke rate between patients assigned to one strategy or the other. The RACE (Rate Control vs. Electrical cardioversion for persistent atrial fibrillation) trial found rate control not inferior to rhythm control for prevention of death and morbidity. Clinically silent recurrences of AF in asymptomatic patients treated with antiar-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. While secondary analyses support this notion, 339 the stroke rate in patients assigned to rhythm control who stopped warfarin is uncertain, and additional research is needed to address this important question. Depending upon symptoms, rate control may be reasonable initial therapy in older patients with 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 and chrono-tropic therapies on quality of life is inconsistent.292,294, 295 The AFFIRM,293,296 RACE,293,295 PIAF (Pharmacologic Intervention in Atrial Fibrillation),342 and STAF (Strategies of Treatment of Atrial Fibrillation),343 studies found no differences in quality of life with rhythm control compared with rate control. Rhythm control in the PIAF and How to Treat Chronic Atrial symptom severity scale showed benefit of amiodarone over the other drugs. In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T),292 restoration and maintenance of sinus rhythm in patients with AF significantly improved quality of life in certain domains, but amiodarone was associated with a decrease in mental health function compared with sotalol or placebo.292 Symptomatic improvement has also been reported after the maze procedure in patients with AF.348In a substudy of AFFIRM, there was no significant association between achieved HR and quality-of-life measurements, New York Heart Association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AFFIRM, there was no significant association functional class, or 6-min walking distance in patients with AF.348In a substudy of AF.348In a compared with less well-controlled patients.345 On the whole, rate- and rhythm-control strategies do not affect quality of life significantly or differently. Even when sinus rhythm can be maintained, symptoms of associated cardiovascular conditions may obscure changes in quality of life related to AF. Clinicians must exercise judgment, however, in translating shifts in quality of life in these study populations to the sense of well-being experienced by individual patients. Patients with similar health status may experience entirely different quality, and frequency of symptoms, patient preferences, comorbid conditions, and the ongoing response to treatment. Long-term oral anticoagulant therapy with vitamin K antagonists involves multiple drug interactions and frequent blood testing, which influences quality of life in quantitative decision analysis. Some patients (16%) thought that their quality of life would be greater with aspirin than with oral anticoagulants, despite its lesser efficacy. Other investigators, using decision analysis to assess patient preferences, found that 61% of 97 patients preferences, found tha guidelines recommend treatment.350 In the future, these comparisons could be influenced by the development of more convenient approaches to antithrombotic therapy.8.1.2.4. Effects on Heart FailureHF may develop or deteriorate during either type of treatment for AF due to progression of underlying cardiac disease, inadequate control of the ventricular rate at the time of recurrent AF, or antiarrhythmic drug toxicity. Patients managed with rate compared with rhythm control did not, however, differ significantly in development or deterioration of HF. In the AFFIRM study, 2.1% of those in the rate-control group and 2.7% in
the rhythm-control group developed AF after an average followup of 3.5 y. In the RACE study, the incidence of hospitalization for HF was 3.5% during a management strategy directed at rate control and 4.5% with rhythm control, during an average follow-up of 2.3 y. Similarly, there were no differences in the STAF or HOT CAFE studies. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study53 is currently investigating this issue in a large number of patients.8.1.2.5. Effects on Thromboembolic ComplicationsThe majority of patients in the AFFIRM and RACE trials had 1 or more stroke risk factors in addition to AF, and the rhythm-control strategy did not lower the stroke rate more effectively than rate control and anticoagulation296,339, 351 (see Table 7). One methodological concern is that the success of rhythm control at maintaining sinus rhythm was assessed by intermittent ECG recordings, whereas longer-term monitoring might have identified patients at lower thromboembolic risk. Most strokes were diagnosed after discontinuation or at subtherapeutic intensity (International Normalized Ratio [INR] below 2.0). In addition, while recurrent AF was detected in only about one-third of those in the rate-control groups typically had AF. Long-term oral anticoagulation therefore seems appropriate for most patients with AF who have risk factors for thromboembolism, regardless of treatment strategy and of whether AF is documented at any given time. Table 7. Trials Comparing Rate Control Strategies in Patients With AFTrialReferencePatients (n)AF DurationFollow-Up (y)Age (mean y±SD)Patients in SR*Clinical Events (n)Stroke/EmbolismDeathRateRhythmAFFIRM (2002)2964060†/NR3.570±935% vs. 63% (at 5 y)88/202793/2033310/2027356/2033RACE (2002)2935221 to 399 d2.368±910% vs. 39% (at 2.3 y)7/25616/26618/25618/26618/26 mo1.666±811% vs. 26% (at 2 y)2/1005/1008/1004/100HOT CAFÉ (2004)3442057 to 730 d1.761±11NR vs. 64%1/1013/104 Primary Endpoint (n)PRate ControlRhythm ControlPIAF (2000)29425261.01.0Persistent AF (7 to 360 d)Symptomatic improvement76/125 (60.8%)70/127 (55.1%)0.317RACE (2002)29352268.02.3Persistent AF or flutter for less than 1 y and 1 to 2 cardioversions over 2 y and oral anticoagulationComposite: cardiovascular death, CHF, severe bleeding, PM implantation, thromboembolic events, severe adverse effects of antiarrhythmic drugs44/256 (17.2%)60/266 (22.6%)0.11STAF (2002)34320066.01.6Persistent AF (longer than 45 mm, CHF NYHA II-IV, LVEF less than 25% Composite: overall mortality, cerebrovascular complications, CPR, embolic eve nts10/100 (10.0%)9/100 (9.0%)0.99AFFIRM (2002)296406069.73.5Paroxysmal AF or persistent AF, age 65 y or older, or risk of stroke or deathAll-cause mortality310/2027 (25.9%)356/2033 (26.7%)0.08HOT CAFÉ (2004)34420560.81.7First clinically overt episode of persistent AF (7 d or more and less than 2 y), 50 to 75 y oldComposite; death, thromboembolic complications; intracranial or other major hemorrhage1/101 (1.0%)4/104 (3.9%)Greater than 0.718.1.2.6. Effects on Mortality was observed in patients treated for rhythm control compared with rate control after an average of 3.5 y (26.7% vs. 25.9%). P=0.08).296 The rhythm-control strategy was associated with excess mortality among older patients, those with HF, and those with CAD, but the tendency persisted after adjustment for these covariates. A substudy suggested that deleterious effects of antiarrhythmic drugs (mortality increase of 49%) may have offset the benefits of sinus rhythm (which was associated with a 53% reduction in mortality).352 Hospitalization was more frequent in the rhythm-control arms in all trials, mainly due to admissions for cardioversion. A substudy of RACE compared anticoagulated patients in the rhythm-control group who had permanent AF and found no benefit of rhythm control even in this selected subgroup.353 The implication that adverse drug effects in patients with underlying heart disease might exert an adverse of patient subgroups in these secondary analyses are not based on randomization (Table 9). Table 9. Comparison of Adverse Outcomes in Rhythm Control and Rate Control Trials in Patients With AFTrialReferenceDeaths From Noncardiovascular CausesStrokeThromboembolic EventsBleedingRACE rate control, yet a trend toward lower mortality was observed in the rate-control arm of the AFFIRM study and did not differ in the other trials from the outcome with the rhythm-control strategy. This might suggest that attempts to restore sinus rhythm with presently available antiarrhythmic drugs are obsolete. The RACE and AFFIRM trials did not address AF in younger, symptomatic patients with little underlying heart disease, in whom restoration of sinus rhythm by cardioversion antiarrhythmic drugs or nonpharmacological interventions still must be considered a useful therapeutic approach. One may conclude from these studies that rate control is a reasonable strategy in elderly patients with minimal symptoms related to AF. An effective method for maintaining sinus rhythm with fewer side effects would address a presently unmet need.8.1.3. Rate Control During Atrial Fibrillation (UPDATED)For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated. Criteria for Rate Control. In patients with AF, the ventricular rate may accelerate excessively during exercise even when it is well controlled at rest. In addition to allowing adequate time for ventricular filling and avoiding rate-related ischemia, enhancement of intraventricular conduction with rate reduction may result in improved hemodynamics. It may be useful to evaluate the heart rate response to submaximal or maximal exercise or to monitor the rate over an extended period (eg, by 24-h Holter recording). In addition, rate variability during AF provides information about the status of the autonomic nervous system that may have independent prognostic implications.356-359The definition of adequate rate control has been based primarily on short-term hemodynamic benefits and has not been well studied with respect to regularity of the ventricular response to AF, quality of life, or symptoms or development 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 either an average heart rate up to 80 beats per minute at rest and either an average rate up to 100 beats per minute over at least 18-h ambulatory Holter monitoring with no rate above 100% of the maximum age-adjusted predicted exercise heart rate or a maximum heart rate of 110 beats per minute at rest. Only about 5% of patients from these large clinical trials required AV ablation to achieve heart rate control within these limits. Hemodynamic and Clinical Consequences of Rapid Rate. Patients who are symptomatic hypo-tension, angina, or HF is present. A sustained, uncontrolled tachycardia may lead to deterioration of ventricular function (tachycardia-related cardiomyopathy)361 and that improves with adequate rate control. In the Ablate and Pace Trial (APT), 25% of patients with AF who had an ejection fraction below 45% displayed a greater than 15% increase in ejection fraction after ablation.363 Tachycardia-induced cardiomyopathy tends to
resolve within 6 mo of rate or rhythm control; when tachycardia recurs, LV ejection fraction declines and HF develops over a shorter period, and this is associated with a relatively poor prognosis.3648.1.3.1. Pharmacological Rate Control During Atrial FibrillationRECOMMENDATIONSCLASS IMeasurement of the heart rate at rest and control of the rate using pharmacological agents, in most cases) are recommended for patients with persistent or permanent AF. (Level of Evidence: B)In the absence of preexcitation intravenous administration of beta blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or HF. (Level of Evidence: B)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)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)Digoxin is effective following oral administration to control the heart rate at rest in patients with AF and is indicated for patients with AF, LV dysfunction, or for sedentary individuals. (Level of Evidence: C)CLASS IIaA 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)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)Intravenous amiodarone can be useful to control the heart rate in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative. (Level of Evidence: C)CLASS IIbWhen 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)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)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: B)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)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)Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular rate during AF are the intrinsic conduction characteristics and refractoriness of the AV node and sympathetic and parasympathetic tone. The functional refractory period of the AV node correlates inversely with ventricular rate during AF, and drugs that prolong the refractory period are generally effective for rate control. The efficacy of pharmacological interventions designed to achieve rate control in patients with AF has been about 80% in clinical trials.365 There is no evidence that pharmacological rate control has any adverse influence on LV function, but bradycardia and heart block may occur as an unwanted effect of beta blockers, amiodarone, digitalis glycosides, or nondihydropyridine calcium channel antagonists, particularly in patients with paroxysmal AF, especially the elderly When rapid control of the ventricular response to AF is required or oral administration of medication may be administered intravenously. Otherwise, in hemodynamically stable patients with a rapid ventricular response to AF, negative chronotropic medication may be administered intravenously. necessary to achieve rate control in both acute and chronic situations, but proper therapy requires careful dose titration. Some patients develop symptomatic bradycardia that requires permanent pacing. Nonpharmacological therapy should be considered when pharmacological therapy should be conside Pharmacological Agents for Heart Rate Control in Patients With Atrial FibrillationDrugClass/LOE RecommendationLoading DoseOnsetMaintenance DoseMajor Side EffectsACUTE SETTING Heart rate control in patients without accessory pathway Esmolol*†Class I, LOE C500 mcg/kg IV over 1 min5 min60 to 200 mcg/kg/min IV Propranolol†Class I, LOE C0.15 mg/kg IV5 minNA↓ BP, HB, ↓ HR, asthma, HF Metoprolol†Class I, LOE C2.5 to 5 mg IV bolus over 2 min; up to 3 doses5 minNA↓ BP, HB, ↓ HR, asthma, HF DiltiazemClass I, LOE B0.25 mg/kg IV over 2 min2 to 7 min5 to 15 mg/h IV↓ BP, HB, BP. HB. \downarrow HR. asthma. HF Heart rate control in patients with accessory pathway§ Amiodarone‡ Class IIa, LOE C150 mg over 10 minDays0.5 to 1 mg/min IV J BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal VerapamilClass I, LOE B0.075 to 0.15 mg/kg IV over 2 min3 to 5 minNA↓ BP, HB, HF DigoxinClass I, LOE B0.25 mg IV each 2 h, up to 1.5 mg60 min or more §0.125 to 0.375 mg daily IV or orallyDigitalis toxicity, HB, ↓ HR deposits, optic neuropathy, warfarin interaction, sinus bradycardia Heart rate control in patients with heart failure and without accessory pathway Amiodarone[‡]Class IIa, LOE C150 mg over 10 minDays0.5 to 1 mg/min IV BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardiaNON-ACUTE SETTING and CHRONIC MAINTENANCE THERAPY Heart rate control Metoprolol⁺Class I. LOE CSame as maintenance dose4 to 6 h25 to 100 mg twice a day, orally \downarrow BP, HB, \downarrow HR, asthma, HF Propranolol†Class I, LOE CSame as maintenance dose60 to 90 min80 to 240 mg daily in divided doses, orally J BP, HB, J HR, asthma, HF DiltiazemClass I, LOE BSame as maintenance dose2 to 4 h120 to 360 mg daily in divided doses VerapamilClass I, LOE BSame as maintenance dose1 to 2 h120 to 360 mg daily in divided doses; slow release available, orally 1 BP, HB, HF, digoxin interaction Heart rate control in patients with heart failure and without accessory pathway slow release available, orally↓ BP, HB, HF DigoxinClass I, LOE C0.5 mg by mouth daily2 days0.125 to 0.375 mg daily, orallyDigitalis toxicity, HB, \downarrow HR Amiodarone‡Class IIb, LOE C800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 1 to 3 wk200 mg daily, orally 1 BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia8.1.3.1.1. Beta Blockers.Intravenous beta blockade with propranolol, atenolol, metoprolol, or esmolol is effective for control of the rate of ventricular response to AF. These agents may be particularly useful in states of high adrenergic tone (eg, postoperative AF). After noncardiac surgery, intravenous esmolol produced more rapid conversion to sinus rhythm than diltiazem, but rates after 2 and 12 h were similar with both treatments.366In 7 of 12 comparisons, beta-adrenergic blockade proved safe and effective for control of heart rate in patients with AF and superior to placebo. Nadolol and atenolol were the most efficacious of the drugs tested. Patients taking beta blockers may experience slow rates at rest, or exercise tolerance may be compromised when the rate response is blunted excessively.367 Sotalol, a nonselective beta-blocking drug with type III antiarrhythmic activity used for rhythm control, also provides excellent rate control in the event of AF recurrence368 and may achieve lower heart rate than metoprolol during exercise. Atenolol, metoprolol, and sotalol provide better control of exercise-induced tachycardia than digoxin. 369,370 Carvedilol also lowers the ventricular rate at rest and during exercise. blockers were the most effective drug class for rate control, achieving the specified heart rate endpoints in 70% of patients with AF and HF who have reduced ejection fraction.3728.1.3.1.2. Nondihydropyridine Calcium Channel Antagonists. The nondihydropyridine calcium channel antagonist agents verapamil and diltiazem are commonly used for treatment of AF and are the only agents that have been associated with an improvement in guality of life and exercise tolerance. Intravenous bolus injection of either drug is effective to control the ventricular rate, 367, 373 although their short duration of action usually requires continuous infravenous infusion to maintain rate control. These agents should be used cautiously or avoided in patients with HF due to systolic dysfunction because of their negative inotropic effects. Eight randomized studies comparing calcium channel blockers to placebo370 found significant decrease infusion to maintain rate control. heart rate with diltiazem. Verapamil decreased heart rate both at rest (by 8 to 23 beats per minute) and during exercise (by 20 to 34 beats per minute). Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness, 374 with preserved or improved exercise tolerance in most patients. 374 These agents may be preferred for long-term use over beta blockers in patients, and the peak effect
does not develop for up to 6 h. Digoxin is a delay of at least 60 min before onset of a therapeutic effect in most patients, and the peak effect does not develop for up to 6 h. Digoxin is no more effective than placebo in converting AF to sinus rhythm and may perpetuate AF.375,376 Its efficacy is reduced in states of high sympathetic tone, a possible precipitant of paroxysmal AF. In a review of 139 episodes of paroxysmal AF detected by Holter monitoring, there was no difference in the ventricular rates of patients taking digoxin and those not taking this agent.376 Other investigators, however, have reported that digoxin reduces the frequency and severity of AF recurrences,30 and the combination of digoxin are control.377 Given the availability of more effective agents, digoxin is no longer considered first-line therapy for rapid management of AF, except in patients with HF or LV dysfunction, or perhaps in patients who are so sedentary as to obviate the need for rate control during activity. Digoxin exerts only a transient rate-slowing effect in patients with recent-onset AF,378 perhaps as a result of a vagotonic effect on the AV node. In contrast to its limited negative chronotropic effect in patients with paroxysmal AF, digoxin is moderately effective in those with persistent AF, particularly when HF is present.362,370 According to a systematic review, digoxin administered alone slows the heart rate more than placebo by an average of 4 to 21 beats per minute at rest, but it does not slow heart rate during exercise in patients with AF.367,370 The most frequent adverse effects of digoxin are ventricular arrhythmias, atrioventricular block, and sinus pauses, all of which are dose dependent. Because of drug interactions, the serum digoxin concentration may rise and toxic effects may be potentiated when verapamil or antiarrhythmic agents such as propafenone or amiodarone are administered concurrently.8.1.3.1.4. Antiarrhythmic Agents. Amiodarone has both sympatholytic and calcium antagonistic properties, depresses AV conduction, and is effective for controlling the ventricular rate in patients with AF. Intravenous amiodarone is generally well tolerated in critically ill patients who develop rapid atrial tachyarrhythmias refractory to conventional treatment, but efficacy has not been sufficiently evaluated in this indication.379 When conventional measures are ineffective, amiodarone may be considered as an alternative agent for heart rate control in patients with AF,379 but this represents an off-label use in the United States and in some other countries and the potential toxicity of this drug. Patients given amiodarone who did not convert from AF to sinus rhythm experienced substantially lower ventricular rates than those treated with placebo, 370 but important adverse effects make this agent a second-line therapy for rate control. In one study, oral amiodarone decreased the ventricular rate without affecting exercise capacity, quality of life, or AF symptoms. 380 High-dose oral amiodarone loading can worsen hemodynamics in patients with recent decompensation of HF or hypotension.381 Amiodarone may cause potentially fatal toxicity, including pulmonary fibrosis, hepatic injury, and proarrhythmia.Dofetilide are effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF but are not effective for conversion of atrial flutter and AF conduction across the AV node, but this is seldom sufficient to control the rate in patients with AF, and AV conduction may accelerate when the atrial rhythm becomes slower and more regular, so other agents in addition to propafenone are generally required to maintain control of the heart rate when AF recurs.8.1.3.1.5. Combination Therapy.Combinations of drugs may be required to achieve adequate rate control in some patients with AF, but care should be taken to avoid brady-cardia.370 The addition of digoxin and atenolol produces a synergistic effect on the AV node,377 and the combination of digoxin and pindolol provided better control during exercise than digoxin alone or in combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and pindolol provided better control during exercise than digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and pindolol provided better control during exercise than digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin and a beta blocker appears more effective than the combination of digoxin appears more effective than the com Parkinson-White (WPW) Syndrome.Intravenous beta blockers, digitalis, adenosine, lidocaine, and nondihydropyridine calcium channel antagonists, all of which slow conduction across the AV node, are contraindicated in patients with the WPW syndrome and tachycardia associated with ventricular preexcitation, because they can facilitate antegrade conduction along the accessory pathway during AF,3 resulting in acceleration, type I antiarrhythmia is associated with hemodynamic compromise, however, early direct-current cardioversion, or ventricular fibrillation.181 When the arrhythmia is associated with preexcitation, type I antiarrhythmia is associated with preexcitation, type I antiarrhythmia is associated with hemodynamic compromise, however, early direct-current cardioversion is indicated. agents or amiodarone may be administered intravenously. Beta blockers and calcium channel blockers are reasonable for oral chronic use.3838.1.3.2. Pharmacological Therapy to Control Heart Rate in Patients With Both Atrial Fibrillation and Atrial 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. 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 and may reduce the number of short ventricular cycles and may reduce the number of short ventricular cycles and may reduce the number of short ventricular cycles related to rapid AV conduction during AF. Pacing ventricular rhythm during AF.384 This may be useful for patients with marked variability in ventricular rates or for those who develop resting bradycardia during RV pacing. At least 2 multicenter studies examined a ventricular rate regularization algorithm. In one study, patients with paroxysmal AF indicated a preference for the paced regularization strategy, while patients with permanent AF showed no preference for the paced regularization strategy, while patients with permanent of irregularization strategy. patients with paroxysmal or permanent AF.3868.1.3.4. AV Nodal AblationAV nodal ablation in conjunction with permanent pacemaker implantation provides highly effective control of the heart rate and improves symptoms in selected patients with AF.363,387-389 In general, patients most likely to benefit from this strategy are those with symptoms or tachycardia-mediated cardiomyopathy related to rapid ventricular rate during AF that cannot be controlled adequately with antiar-rhythmic or negative chronotropic medications. Meta-analysis of 21 studies published between 1989 and 1998 that included a total of 1181 patients concluded that AV nodal ablation and permanent pacemaker implantation significantly improved cardiac symptoms, quality of life, and healthcare utilization for patients with refractory AF displayed improvements in quality of life, exercise capacity, and ventricular function over 1 y.363 In a study of 56 patients with impaired LV function (ejection fraction less than 40%), the mean ejection fraction improved from 26% plus or minus 13% after AV nodal ablation and became normal in 16 patients (29%).390 Patients with persistent LV dysfunction after ablation and persistent LV dysfunction after ablation and became normal in 16 patients (29%).390 Patients with persistent LV dysfunction after ablation and persistent LV dysfunction after ablation and became normal in 16 patients (29%).390 Patients with persistent LV dysfunction after ablation and persistent LV dysfunction after ablation after ablation after ablation after ablation after ablation and persistent LV dysfunction after ablation a less than 60% survival at 5 y. In small randomized trials
involving patients with paroxysmal388 and persistent.387 AF, significantly greater proportions experienced improvement in symptoms and guality of life after AV nodal ablation than with antiar-rhythmic medication therapy. Of 2027 patients randomized to make control in the AFFIRM study, AV nodal ablation was performed in 5%360 after failure to achieve adequate rate control with a mean of 2.4 plus or minus 0.7 medications. Another 147 patients required pacemaker implantation because of symptomatic bradycardia. without pacemaker implantation.391,392 This technique has several limitations, however, including inadvertent complete AV block and a tendency of ventricular rate to rise over the 6 mo following ablation. Two small, randomized trials comparing this type of AV nodal modification with complete AV block and a tendency of ventricular rate to rise over the 6 mo following ablation. implantation demonstrated better symptom relief with the complete interruption procedure. Thus, AV nodal modification without pacemaker implantation is only rarely used. Ablation of the AV inputs in the atrium may improve the reliability of the junctional escape mechanism. 393 This involves selective ablation of fast and slow AV nodal pathways followed, if necessary, by ablation between these inputs to achieve complete AV block. Complications of AV nodal ablation include those associated with interruption of anticoagulation, the rare occur-rence of LV dysfunction, and progression from paroxysmal to persistent AF. The 1-y mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3% (95% confidence interval [CI] 5.5% to 7.2%), including a 2.0% risk of sudden death (95% CI 1.5% to 2.6%). Although a causal relationship between the procedure and sudden death remains controversial, it has been suggested that programming the pacemaker to a relatively high nominal rate (90 beats per minute) for the first month after ablation may reduce the risk.394,395Although the symptomatic benefits of AV nodal ablation are clear, limitations include the persistent need for anticoagulation, loss of AV synchrony, and lifelong pacemaker dependency. There is also a finite risk of sudden death due to torsades de pointes or ventricular fibrillation.396 Patients with abnormalities of diastolic ventricular compliance who depend on AV synchrony to maintain cardiac output, such as those with hypertrophic cardiomyopathy or hypertensive heart disease, may experience persistent symptoms after AV nodal ablation and pacemaker implantation. Hence, patients should be counseled regarding each of these considerations before proceeding with this irreversible measure. The adverse hemodynamic effects of RV apical pacing following AV nodal ablation have been a source of concern. Compared with RV apical pacing, LV pacing significantly improves indices of both LV systolic function (pressure-volume loop, stroke work, ejection fraction, and dP/dt) and diastolic filling.397 Acutely, LV pacing was associated with a 6% increase in mitral regurgitation.398 The Post AV Node Ablation Evaluation (PAVE) randomized 184 patients undergoing AV nodal ablation because of permanent AF to standard RV apical pacing or biventricular pacing. 399 After 6 mo, the biventricular pacing group walked 25.6 meters farther in 6 min (P=0.03), had greater peak oxygen consumption, and had higher scores in 9 of 10 quality-of-life domains than the RV pacing group. While there was no difference in LV ejection fraction between the groups at baseline, the LV ejection fraction remained stable in the biventricular pacing group (46% vs. 41%, respectively; P=0.03). There was no significant difference in mortality. A subgroup analysis suggested that functional improvements were confined to patients with LV ejection fraction below 35% before ablation. Patients with normal LV function or reversible LV dys-function undergoing AV nodal ablation are most likely to benefit from standard AV nodal ablation and pacemaker with or without defibrillator capability should be considered. Upgrading to a biventricular device should be considered for patients with HF and an RV pacing system who have undergone AV node ablation.4008.1.4. Preventing Thromboetic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications. (Level of Evidence: A)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. heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis. (Level of Evidence: A)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)Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. A)INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. (Level of Evidence: A)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)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. 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: C)CLASS IIaFor 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)For patients with nonvalvular AF who have 1 or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 y, female gender, or CAD. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences. (Level of Evidence: B)It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (ie, paroxysmal, persistent, or permanent) of AF. (Level of Evidence: B)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)CLASS IIbIn patients 75 y of age and older at increased risk of bleeding but without frank contraindications to oral 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)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)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)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)In patients with AF younger than 60 y 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)In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity of anticoagulation to a maximum target INR of 3.0 to 3.5. (Level of Evidence: C)CLASS IIILong-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease
(lone AF) or any risk factors for thromboembolism. (Level of Evidence: C)8.1.4.1. Risk Stratification8.1.4.1.1. Epidemiological Data.In a small, retrospective, population-based study in Olmsted County, Minnesota, over 3 decades, the 15-y cumulative stroke rate in people with lone AF (defined as those younger than 60 y with no clinical history or echocardiographic signs of cardiopulmonary disease) was 1.3%.11 Conversely, in the Framingham Study, 28 the age-adjusted stroke rate over a mean follow-up period of 11 y was 28.2% in those with lone AF, more liberally defined to include patients with a history of hyper-tension or cardiomegaly on chest roentgenography, compared with 6.8% in normal controls.28 In the SPAF study, the annualized rate of ischemic stroke during aspirin treatment was similar in those with paroxysmal (3.2%) and permanent (3.3%) AF.401 Those with prior stroke or TIA have a rate of subsequent stroke of 10% to 12% per year when treated with aspirin, and these patients benefit substantially from adjusted-dose oral anticoagulation.402,403 In addition to prior thromboembolism, HF, hypertension, increasing age, and diabetes mellitus have consistently emerged as independent risk factors for ischemic stroke associated with nonvalvular AF.47,261,264,382,405 Other factors, such as female gender, systolic blood pressure over 160 mm Hg, and LV dysfunction, have been variably linked to stroke.261,266,406 The relative risk for ischemic stroke associated with specific clinical features, derived from a collaborative analysis of participants given no antithrombotic therapy in the control groups of 5 randomized trials, is displayed in Table 11. Table 11. Risk Factors for Ischemic Stroke and Systemic Embolism in Patients With Nonvalvular Atrial FibrillationRisk FactorsRelative RiskPrevious stroke or TIA2.5Diabetes mellitus1.7History of hypertension1.6Heart failure1.4Advanced age (continuous, per decade)1.4In 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 relatively low stroke risks by virtue of the absence of other risk factors did not identify any reliable predictors.261,407-409 The pathogenic constructs of stroke in AF are incomplete, but available data indicate that all patients with prior stroke or TIA are at high risk of recurrent thromboembolism and require anticoagulation unless there are firm contraindications. in a given patient. Efforts to enhance risk stratification should remove such patients from consideration and focus instead on the predictor of stroke (Fig. 8). In 7 studies in which the variable was assessed, hazard ratios averaged 1.5 per decade. Nearly half of AF-associated strokes occur in patients over 75 y, and AF is the most frequent cause of disabling stroke in elderly women.21,405,406 Older people are also at increased risk for anticoagulant-related bleeding410 and are less likely to be treated with oral anticoagulation, even in situations for which it has been

proved efficacious, in part because of concern about the risk of bleeding.411 Special consideration of these older patients is therefore a critical aspect of effective stroke prophylaxis.405 Figure 8. Stroke rates in relation to age among patients is therefore a critical aspect of effective stroke prophylaxis.405 Figure 8. Stroke rates in relation to age among patients in untreated control groups of randomized trials of antithrombotic therapy. Data are from the Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57.47Female gender has emerged as an independent predictor of stroke in 3 cohort studies of patients with AF but not in several others.47,268,404 The relative increase was 1.6 in the largest study of the ATRIA cohort.262 In the SPAF analyses of aspirin-treated patients, gender interaction was not apparent in the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) cohort.262,412Similarly, hypertension is a consistent, powerful predictor of stroke, with a history of hypertension independently predictive in 5 studies (median relative risk approximately 2.0). A history of hypertension and systolic blood pressure significant in 2 others (mean relative risk approximately 2.0). predictive of stroke in the SPAF aspirin-treated cohorts. Diabetes was a significant independent predictor may be greater in lower-risk patients with AF, prompting speculation that it may be associated with noncardioembolic strokes. Diabetes is a less powerful independent predictor than prior stroke/TIA, hypertension, or age, but analysis of the type, duration, or control of diabetes was below average in 2 studies.413,414In 2 studies, CAD was a univariate predictor of stroke in otherwise low-risk patients;47,415 it has not been conclusively shown to have independent predictive value for stroke in any study of AF patients. In the SPAF I and II studies,412 recent (within 3 mo) HF or impaired LV systolic function (defined as M-mode echocardiographic fractional shortening less than 25%) was a significant independent predictor, as was LV systolic dys-function by 2-dimensional echocardiography in placebo-treated patients in some studies 266 but not in others. 261,268 Clinical diagnosis of HF may be difficult in elderly patients with AF, and misclassification could blunt the power of association. In short, while it seems logical based on pathophysiological concepts and echocardiographic correlates that HF should be an independent predictor of stroke in patients with nonvalvular AF, available data do not provide strong support.8.1.4.1.2. Echocardiography and Risk Stratification. Echocardiography is valuable to define the origin of AF (eg, detecting rheumatic mitral valve disease or HCM) and may add information useful in stratifying thromboembolic risk. Among high-risk AF patients, impaired LV systolic function on transthoracic echocardiography, thrombus, dense SEC or reduced velocity of blood flow in the LAA, and complex atheromatous plaque in the thoracic aorta on TEE have been associated with thromboembolism, and oral anticoagulation effectively lowers the risk of stroke in AF patients with these features. LA diameter and fibrocalcific endocardial abnormalities have been less consistently associated with thromboembolism. Whether the absence of these echocardiographic abnormalities identifies a low-risk group of patients who could safely avoid anticoagulation has not been established, limiting the value of echocardiography as a prime determinant of the need for chronic anticoagulation in patients with AF. Transthoracic Echocardiography. Correlations in placebo-assigned participants in randomized trials of antithrombotic therapy provide information about the independent predictive value of transthoracic echocardiography for thromboembolic events in patients with nonvalvular AF.265,416 Meta-analysis of 3 trials found moderate to severe LV dysfunction to be the only independent echocardiographic predictor of stroke in patients with AF after adjustment for clinical features; the diameter of the LA was less useful.266 Secondary analyses of aspirin-assigned patients in multicenter trials yield variable results regarding the role of transthoracic echocardiography for predicting thromboembolic risk.54,203 In the SPAF I and II studies, LV fractional shortening less than 25% (estimated by M-mode echocardiography) was the only independent echocardio-graphic predictor of stroke. Among 2012 aspirin-assigned to a relatively ineffective fixed-dose combination of aspirin plus warfarin), no transthoracic echocardio graphic parameter independently predicted thromboembolism when clinical risk factors were considered. Similarly, no independent predictors of thromboembolism in the Embolism were identified by transthoracic echocardiography and TEE at entry in the Embolism in the Embolism were identified by transthoracic echocardiography and TEE at entry in the Embolism were identified by transthoracic echocardiography and TEE at entry in the Embolism in the Embolism were identified by transthoracic echocardiography and TEE at entry in the Embolism in t daily.268Transesophageal Echocardiography. TEE is a sensitive and specific technique for detection of LA and LAA thrombus, far surpassing transthoracic echocardiography. 203 This modality also permits superior evaluation for other causes of cardiogenic embolism, 320 as well as a means of measuring LAA function. 319 Several TEE features have been associated with thromboembolism, including thrombus, reduced flow velocity, and SEC in the LA or LAA and atheromatous disease of the aorta.252,417Detection of AF. Unfortunately, the absence of a detectable thrombus does not preclude stroke after cardioversion in the absence of anticoagulation therapy.324,418 A TEE-guided strategy for elective cardioversion of AF yielded comparable outcomes for thromboembolism and death compared with conventional anticoagulation for 3 wk before and 4 wk after cardioversion.3208.1.4.1.3. Therapeutic Implications. The efficacy and safety of oral anticoagulation and platelet inhibitor therapy with aspirin for prevention of stroke in patients with AF have been well characterized.420 The selection 8.1.6, Pharmacological Agents to Maintain Sinus Rhythm, and Section 8.1.7, Outof-Hospital Initiation of Antiarrhythmic Drugs in Patients With Atrial Fibrillation). Patients with AF who have low rates of stroke when treated with aspirin may not gain sufficient benefit from anticoagulation to outweigh the attendant risks and the need for close medical monitoring.421,422 Estimating the risk of stroke for individual AF patients is crucial for the decision to provide anticoagulation therapy to individual patients with AF,54 but the threshold risk that warrants anticoagulation, which would require treating 100 or more patients for 1 y to prevent a single stroke.420 For high-risk AF patients with stroke rates of 6% per year or greater, the comparable number needed-to-treat is 25 or fewer, strongly favoring anticoagulation. Opinion remains divided about routine anticoagulation for patients with AF, several clinical schemes have been proposed based on analyses of prospectively monitored cohorts of participants in clinical trials in which antithrombotic therapy was controlled.391,421,423 One set of criteria (Atrial Fibrillation Investigators [AFI]) is based on multivariate pooled analysis of 1593 participants assigned to the control or placebo groups of 5 randomized primary prevention trials in which 106 ischemic strokes occurred over a mean follow-up of 1.4 y.47 Patients were divided into 2 strata, distinguishing low-risk patients from those at intermediate or high risk. Although echocardiographic features were not considered initially, a subsequent analysis of 3 of the trials identified abnormal LV systolic function as an independent predictor of stroke.421 The SPAF study criteria were based on multivariate analysis of 854 patients assigned to aspirin and followed for a mean of 2.3 y, during which 68 ischemic strokes were observed. These criteria were subsequently used to select a low-risk cohort for treatment with aspirin in the SPAF III study. Over a mean followup of 2 y, the rate of ischemic stroke was 2.0% per year (95% CI 1.5% to 2.8%) and the rate of disabling ischemic stroke was 0.8% per year (95% CI 0.5% to 1.3%). Patients with a history of hypertension had a higher rate of thromboembolism (3.6% per year) than those without hyper-tension (1.1% per year; P less than 0.001). Other criteria have been developed by expert consensus423,424 based on consideration of the foregoing schemes to classify patients into low-, intermediate-, and high-risk groups. Still others have been promulgated based on multivariate analysis of clinical and/or echocardiographic predictors. Three were derived from overlapping patient cohorts, 2 involved participants in randomized trials, 2 were based on clinical case series, one was a population based epidemiological study, and the other was a hospital-based case-control study 262 was limited to analysis from the Framingham Heart Study examined risk factors for stroke among 705 patients with recently detected AF, excluding those who had sustained ischemic stroke, TIA, or death within 30 d of diagnosis.425 The only significant predictors of ischemic stroke were age (RR=1.9), and diabetes mellitus (RR=1.8), consistent with earlier studies. included in a time-dependent Cox proportional hazards model. With a scoring system based on age, gender, systolic hypertension, diabetes, and prior stroke or TIA, the proportion of patients classified as low risk varied from 14.3% to 30.6% depending upon whether stroke rate thresholds were less than 1.5% per year or less than 2% per year. Observed stroke rates were 1.1% to 1.5% per year based on 88 validated events. In the
future, it may be possible to consider other characteristics that may contribute to stroke risk, including genetic abnormalities of hemostatic factors and endothelial dysfunction, but none have yet been identified that have sufficient predictive value for clinical use in risk stratification.230,413Another stroke risk classification scheme, known as CHADS2 (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) integrates elements from several of the foregoing schemes. The CHADS2 risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age over 75 y, a history of hypertension, diabetes, or recent HF (Table 12).415,426 The predictive value of this scoring system was evaluated in 1733 Medicare beneficiaries with nonvalvular AF between the ages of 65 and 95 y who were not given warfarin at hospital discharge. stroke rate in this elderly cohort, few patients had a score of 5 or more or a score of 0. In the same cohort, the modified AFI scheme had high-risk (prior stroke or TIA, hypertension, or diabetes) and moderate-risk (age greater than 65 y without other high-risk features) categories, corresponding to stroke at 05% CI 4.2% to 6.5% per year) for high-risk and 2.2% per year (95% CI 1.1% to 3.5% per year) for moderate-risk patients. Patients with high-risk features according to the SPAF criteria (prior stroke or TIA, women older than 75 y, or recent HF) had a stroke rate of 5.7% per year (95% CI 4.4% to 7.0% per year); moderate-risk patients (history of hyper-tension with no other high-risk features) had a rate of 3.3% per year (95% CI 1.7% to 5.2% per year); and low-risk patients (without risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.7% to 5.2% per year); and low-risk factors) had a stroke rate of 1.5% per year (95% CI 1.5 stroke or TIA2Age >75 y1Hypertension1Diabetes mellitus1Heart failure1Patients (N=1733)Adjusted Stroke Rate (%/y)* (95% CI)CHADS2 Score1201.9 (1.2 to 3.0)04632.8 (2.0 to 3.8)15234.0 (3.1 to 5.1)23375.9 (4.6 to 7.3)32208.5 (6.3 to 11.1)46512.5 (8.2 to 17.5)5518.2 (10.5 to 27.4)6Although the schemes for stratification of stroke risk identify patients who benefit most and least from anticoagulation for those at intermediate risk (stroke rate 3% to 5% per year). Some advocate the routine use of anticoagulation for those with stroke rate 3% to 5% per year). selective anticoagulation of patients at intermediate risk, with weight given to individual bleeding risks and patient preferences.54,428 The threshold of benefit at which AF patients choose anticoagulation, whereas others do not.429 Our recommendations for antithrombotic therapy in patients with AF are summarized in Table 13. Table 13. Antithrombotic Therapy for Patients With Atrial FibrillationRisk CategoryRecommended TherapyNo risk factorAspirin, 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 factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factor or more than 1 moderate-risk factorWarfarin (INR 2.0 to 3.0, target 2.5)Any high-risk factorWarfarin (INR 2.0, target 2.5)Any high-risk factorWarfarin (INR 2.0, target 2.5)Any high-risk factorWarfarin (INR 2.0, target 2.5)Any high-risk factorWarfarin (I to 3.0, target 2.5)*Less Validated or Weaker Risk FactorsModerate-Risk FactorsFemale genderAge greater than or equal to 75 yPrevious stroke, TIA or embolismAge 65 to 74 yHypertensionMitral stenosisCoronary artery diseaseHeart failureProsthetic heart valve*ThyrotoxicosisLV ejection fraction 35% or lessDiabetes mellitusAtrial flutter is uncommon as a chronic arrhythmia, and the risk of thromboembolism is not as well established as it is for AF but is generally estimated as higher than that for those with persistent or permanent AF. On the basis of multivariate analysis, Wood et al430 reported hypertension as the only significant correlate of previous thromboembolism for patients, including 17 413 with atrial flutter and 337 428 with AF, 3 of 4 patients with atrial flutter atrial flutte was 1.406, and for those with AF, it was 1.642 compared with the control group. Coexisting HF, rheumatic heart disease, and hypertension predicted an episode of AF in patients with atrial flutter. Risk ratios for patients with these comorbid conditions were 1.243, 1.464, and 1.333, respectively.431Although the overall thromboembolic risk associated with atrial flutter may be somewhat lower than with AF, it seems prudent to estimate risk by the use of similar stratification criteria for both arrhythmias until more robust data become available (Tables 13 and 14). Table 14. Risk-Based Approach to Antithrombotic Therapy in Patients With Atrial FibrillationPatient FeaturesAntithrombotic TherapyClass of RecommendationAge less than 60 y, no heart disease (lone AF)Aspirin (81 to 325 mg per day)IAge 65 to 74 y, no risk factors*Aspirin (81 to 325 mg per day)IAge 65 to 74 y, no risk factors*Aspirin (81 to 325 mg per day)IAge 65 to 74 y. 3.0)IAge 75 y or older, womenOral anticoagulation (INR 2.0 to 3.0)IAge 75 y or older, men, no other risk factorsOral anticoagulation (INR 2.0 to 3.0)ILV ejection fraction less than 35% or fractional shortening less than 25%, and hypertensionOral anticoagulation (INR 2.0 to 3.0)IRheumatic heart disease (mitral stenosis)Oral anticoagulation (INR 2.0 to 3.0)IProsthetic heart valvesOral anticoagulation (INR 2.0 to 3.0) or higher)IParistent atrial thrombus on TEEOral anticoagulation (INR 2.0 to 3.0 or higher)IIa8.1.4.2. Antithrombotic Strategies for Prevention of Ischemic Stroke and Systemic
Embolism in patients with AF was limited mainly to those with rheumatic heart disease or prosthetic heart valves. 21 Anticoagulation was also accepted therapy for patients who had sustained ischemic stroke to prevent recurrence but was often delayed to avoid hemorrhagic transformation. Some advocated anticoagulation of patients with thyrotoxicosis or other conditions associated with cardiomyopathy. Since then, 24 randomized trials involving patients with thyrotoxicosis or other conditions associated with cardiomyopathy. with an average follow-up of 1.6 y, a total exposure of about 32 800 patient-y (Table 15). In these studies, patient age averaged 71 y; 36% were women. Most trials, 8349 participants) or North America (7 trials, 8349 participants). Most studied oral vitamin K inhibitors or aspirin in varying dosages/ intensities, but other anticoagulants (low-molecular-weight heparin, ximelagatran) and other antiplatelet 57,403,432-435 or anticoagulation436-438 comparisons. Table 15. Randomized Trials of Antithrombotic Therapy in Patients With Nonvalvular AFTrialsReferenceYear PublishedNo. of PatientsInterventionsLarge published trials Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I)43219891007VK A, ASA, placebo Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II)4391998677VKA, ASA, LDA + ASA, LDA Stroke Prevention in Atria Fibrillation I (SPAF I)5719911330VKA, ASA, placebo Stroke Prevention in Atrial Fibrillation II (SPAF II)44019941100VKA, ASA Stroke Prevention in Atrial Fibrillation III (SPAF III)40219961044VKA, LDA + ASA Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)4281990420VKA, control Canadian Atria Fibrillation Anticoagulation (CAFA)4361991378VKA, placebo Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)4371992571VKA, placebo European Atrial Fibrillation Trial (EAFT)40319931007VKA, ASA, placebo Studio Italiano Fibrillazione Atriale (SIFA)4411997916VKA, indobufen Minidose Warfarin in Nonrheumatic Atrial Fibrillation4421998303VKA, LDA* Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF)4431999729VKA, LDA,* ASA Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients with Atrial Fibrillation (SPORTIF-III)47720033407DTI, VKA Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients With Atrial Fibrillation (SPORTIF-V)43820053922DTI, VKA National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF)44520041209VKA, triflusal, VKA + triflusalSmall or pilot trials Harenberg et al.446199375LMW heparin, control Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF)4471996285ASA, placeboSubgroups with AF in other trials European Stroke Prevention Study II (ESPS II)4041997429ASA, dipyridamole, placebo8.1.4.2.1. Anticoagulation With Vitamin K Antagonist Agents. Five large randomized trials published between 1989 and 1992 evaluated oral anticoagulation mainly for primary prevention of thromboembolism in patients with nonvalvular AF57,428,432,436,437 (Fig. 9, Table 15). A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or TIA.403 Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 62% (95% CI 48% to 72%) versus placebo420 (Fig. 9). This reduction was similar for both disabling and nondisabling strokes. By on-treatment analysis (excluding patients not undergoing oral anticoagulation at the time of stroke), the preventive efficacy of oral anticoagulation exceeded 80%. Four of these trials were placebo controlled; of the 2 that were double blinded with regard to anticoagulation,437 one was stopped early because of external evidence that oral anticoagulation was superior to placebo, and the other included no female subjects. In 3 of the trials, oral anticoagulant dosing was regulated according to the prothrombin time ratio; 2 used INR target ranges of 2.5 to 4.0 and 2.0 to 3.0. These trials are summarized in Table 15. The duration of follow-up was generally between 1 and 2 y; the longest was 2.2 y, whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods. Figure 9. Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation. Adjusted-dose warfarin compared with placebo (six random trials. Adapted with permission from Hart RG, Benavente O, McBride R, et al. Anti-thrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.420 AFASAK indicates Copenhagen Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; CI, confidence interval; EAFT, European Atrial Fibrillation; Trial; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. All reported trials excluded patients considered at high risk of bleeding. 449-454 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.19,431,455The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications (Fig. 10). 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 3.0,456 whereas an INR range of 1.6 to 2.5 is associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher-intensity anticoagulation.432,449 Two randomized trials with a target INR of 1.4 to 2.8 (estimated mean achieved INR 2.0 to 2.1) found the largest relative risk reductions for ischemic stroke. A trial in which AF patients with prior stroke or TIA were randomly assigned to target INR ranges of 2.2 to 3.5 versus 1.5 to 2.1 found a greater rate of major hemorrhage with the higher intensity.450 For patients with nonvalvular AF, an INR of 1.6 to 3.0 is efficacious and relatively safe. For primary prevention in most AF patients with nonvalvular AF, an INR of 2.5 (target range 2.0 to 3.0) is recommended. A target INR of 2.0 (target range 1.6 to 2.5) seems reasonable for primary prevention in patients older than 75 y who are considered at high risk of bleeding. In clinical trials, INRs achieved during follow-up were more often below than above the target range 1.6 to 2.5) seems reasonable for primary prevention in patients older than 75 y who are considered at high risk of bleeding. In clinical trials, INRs achieved during follow-up were more often below than above the target range. below the target range, during which stroke protection is sharply reduced. The major bleeding rate for 5 randomized clinical trials was 1.2% per year202 (Fig. 11). Figure 10. Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from Hylek EM, Singer DE. Risk factors for schemic stroke and intracranial bleeding in relation to intensity of anticoagulation. intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897-902.451 Data from Odén A, Fahlén M and Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. Thromb Res 2006;117:493-9.452 Figure 11. Annual rates of major hemorrhage during anticoagulation in primary prevention trials involving patients with nonvalvular atrial fibrillation. The mean age of participants was 69 years. Major hemorrhage was variously defined but typically involved a critical anatomical site, or was permanently disabling or fatal. Data adapted from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation; Apprin, Anticoagulation; BAATAF, Boston Area Anticoagulation; Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; Apprind Apprint, Anticoagulation; BAATAF, Boston Area Anticoagulation; CAFA, Canadian Atrial Fibrillation; Apprind Apprint, Anticoagulation; BAATAF, Boston Area Anticoagulation; CAFA, Canadian Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; BAATAF, Boston Area Anticoagulation; CAFA, Canadian Atrial Fibrillation; CAFA, Canadian Atria Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation, and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation, and spice are considerably lower than in the past, typically between 0.1% and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension.438,457 In 2 time-dependent INR analyses of anticoagulation in elderly AF cohorts, intracranial bleeding increased with INR values over 3.5 to 4.0, and there was no increment with values between 2.0 and 3.0 compared with lower INR levels.454,456 Pooled results of randomized trials and a large cohort comparison, however, suggest a doubling of intracranial hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values
between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhages with mean INR values between 2.0 and 2.5.458 Other than dose intensity, advanced age, advanced age, advanced age, advanced age, advanced age, advanced age, advanced cerebrovascular disease and possibly concomitant antiplatelet therapy, tobacco or alcohol consumption, ethnicity, genotype, and certain vascular abnormalities detected by brain imaging, such as amyloid angiopathy, leukoaraiosis, or microbleeds.457 No stratification scheme for prediction of intracerebral hemorrhage during anticoagulant therapy has been prospectively evaluated.8.1.4.2.2. Aspirin for Antithrombotic Therapy in Patients With Atrial Fibrillation. Aspirin offers only modest protection against stroke for patients with AF46,57,403,432,439,440,443,447,448 (Fig. 12). Meta-analysis of 5 randomized trials showed a stroke reduction of 19% (95% CI 2% to 34%).420 The effect of aspirin (in which the stroke rate with placebo averaged 14% per year).420 Aspirin may be more efficacious for AF patients.200 Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes.250 Aspirin appears to prevent nondisabling strokes more than disabling strokes. 420 Thus, the greater the risk of disabling cardioembolic stroke in a population of patients with AF, the less protection is afforded by aspirin. 250 Figure 12. Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation: warfarin compared with aspirin and aspirin compared with placebo. Modified with permission from Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation; a meta-analysis. Ann Intern Med 1999;131:492-501.420 AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation; Trial; ESPS, European Stroke Prevention of Arterial Fibrillation; SPAF, Stroke, Atrial Fibrillation; SPAF, Stroke, Atrial Fibrillation; SPAF, Stroke, Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. Additional information about event rates on aspirin or no antithrombotic therapy can be extracted from contemporary databases such as the ATRIA cohort of 13 428 ambulatory patients with AF enrolled in the Kaiser Permanente Medical Care Program in North Carolina during the period 1996 through 1999.262,456,458,461 In the 11 526 patients without apparent contraindications to anticoagulation,458 6320 patients not treated with warfarin. Among the 5089 patients not treated with warfarin, the absolute rate of thromboembolism was 2.0% per year.461 There was a history of stroke or TIA in only 4% of the patients not treated with anticoagulation, making this mainly a primary prevention cohort.458 During a mean follow-up of 2.2 y (median 2.35 y), 249 thromboembolic events outside the central nervous system) occurred among the patients who were not anticoagulated (2.0% per year [95% CI 1.8% to 2.3%]). From a nested case-control study of 294 patients, it was estimated that about 45% were using aspirin. When those from the larger cohort with contraindications to warfarin (who were older and more often had prior stroke or TIA) were included, the rate of thromboembolism was 2.5% per year. While the use of administrative and claims-based data from a managed care organization may have been prone to underdetection of stroke events, these rates were not very different from those in other reported populations. By comparison, among 1853 patients without prior thromboembolic events assigned to aspirin in the SPAF I, II, and III trials, the rate of ischemic stroke was 2.7% per year.261 In the AFI cohort of 2732 patients from 6 randomized trials (about half from the SPAF trials), without prior stroke or TIA, the rate of ischemic stroke was 2.1% per year with aspirin therapy. Among 210 patients in the population-based Cardiovascular Health Study (mean age 74 y) followed without anticoagulation, the stroke rate was 2.6% per year.462 When stratified according to the CHADS2 stroke risk scheme, 426 patients in the ATRIA cohort with a single stroke risk factor (32% of the cohort) who were not anticoagulated had a rate of stroke and systemic embolism of 1.5% per year (95% CI 1.2% to 1.9%).458 Of 670 patients treated with aspirin in 6 clinical trials, the stroke rate was 2.2% per year for those with a CHADS2 score of 1 (95% CI 1.6% to 3.1% per year).463In summary, adjusted-dose oral anticoagulation is more efficacious than aspirin for prevention of stroke in patients with AF, as suggested by indirect comparisons and by a 33% risk reduction (95% CI 13% to 49%) in a meta-analysis of 5 trials.420 Randomized trials involving high-risk AF patients (stroke rates greater than 6% per year) show larger relative risk reductions by adjusted-dose oral anticoagulation may be most beneficial for AF patients with lower stroke rates. Accordingly, oral anticoagulation relative to aspirin (Fig. 12), whereas the relative risk reductions by adjusted-dose oral anticoagulation relative risk reductions are consistently smaller in trials of AF patients at higher intrinsical for AF patients at higher thromboembolic risk, offering only modest reductions over aspirin in both the relative risk and absolute rates of stroke for patients with AF.8.1.4.2.3. Other Antiplatelet Agents for Antithrombotic Therapy in Patients With Atrial Fibrillation.Anticoagulation with oral vitamin K antagonists has been compared with platelet cyclooxygenase inhibitors other than aspirin in 2 trials involving 1395 participants. In the Italian Studio Italiano Fibrillazione Atriale (SIFA) study, 441 indobufen, 100 to 200 mg twice daily, was compared with warfarin (INR 2.0 to 3.5) in 916 patients with recent cerebral ischemic events. Incidences of the combined endpoint of nonfatal stroke, intracerebral bleeding, pulmonary or systemic embolism, MI, and vascular death were not significantly different between treatment groups, but more ischemic strokes occurred in the indobufen group18 than in the warfarin group.10 In the primary prevention cohort of the Spanish National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial,445 the rate of the composite of thromboembolism plus cardiovascular death was lower with acenocoumarol than with triflusal. There was no significant difference in rates of ischemic stroke and systemic embolism. Neither indobufen nor trifusal is widely available; these agents have not been compared with a spirin for efficacy and safety, nor do they offer advantages over anticoagulation with a vitamin K antagonist in patients with AF at high risk of thromboembolism. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W), which was stopped on the recommendation of the Data Safety and Monitoring Board before planned follow-up was completed, the combination of the thienopyridine antiplatelet agent clopidogrel (75 mg daily) proved inferior to warfarin (target INR 2.0 to 3.0) in patients with an average of 2 stroke risk factors in addition to AF.464 Additional studies are ongoing to assess the impact of this therapy for patients unable or unwilling to take warfarin.8.1.4.2.4. Combining Anticoagulant and Platelet-Inhibitor Therapy (UPDATED). For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated. Combinations of oral anticoagulants plus antiplatelet agents to reduce the risk of hemorrhage by allowing lower intensities of anticoagulation or to augment efficacy for selected patients at particularly high risk of thromboembolism, such as those with prior stroke, have been evaluated in several trials. Such a strategy has been successful in reducing the risk of thromboembolism in patients with mechanical heart valves. 465 Still another objective of combination therapy is to enhance protection against ischemic cardiac events in patients with AF who have established coronary atherosclerosis or diabetes. In 2 trials, SPAF III and Copenhagen Atrial FIbrillation, Aspirin, and Anticoagulation (AFASAK) 2, the combination of low-dose oral anticoagulation (INR less than 1.5) with aspirin added little protection against stroke compared with aspirin added little pro Combination in High Risk Patients With AF (FFAACS) study compared the oral anticoagulant fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6)
plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione (target INR 2.0 to 2.6) plu hemorrhage in the group receiving the combination therapy.433In the larger Spanish National Study for Primary Prevention of Embolism in Nonrheumatic Atrial Fibrillation (NASPEAF) study, patients were stratified into a high-risk group (n=495) with AF and rheumatic mitral stenosis or AF and a history of stroke, TIA, or systemic embolism, and a lower-risk group (n=714) with AF and age greater than 60 y, hypertension, or HF.445 The higher-risk patients were randomized to anticoagulation with the platelet cyclooxygenase inhibitor triflusal (600 mg daily). The lower-risk patients were randomized to triflusal alone, acenocoumarol alone (INR 2.0 to 3.0), or the combination of triflusal plus acenocoumarol (INR 1.25 to 2.0). The achieved anticoagulation intensities in the anticoagulation and combination of triflusal plus acenocoumarol (INR 1.25 to 2.0). for the combination arms in the lower- and higher-risk groups during median follow-up of 2.6 and 2.9 y, respectively). The primary outcome was a composite of thromboembolism, stroke, bleeding, or HF but not MI). Patients in both risk categories had a lower risk of primary events with the combination therapy might be effective and relatively protective if targeted INR levels are closer to the standard range, but the superiority of combination therapy with a vitamin K antagonist for prevention of ischemic stroke and MI has not been convincingly established. Combining aspirin with an oral anticoagulant at higher intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients. 466 In a retrospective analysis of 10 093 patients with AF after hospital discharge (mean age 77 y), platelet inhibitor medication was associated with a higher rate of intracerebral hemorrhage (relative risk 3.0, 95% CI 1.6% to 5.5%),467 but 2 case-control studies yielded conflicting results.454,468The superior efficacy of anticoagulation over aspirin for prevention of recurrent stroke in patients with AF was demonstrated in the European Atrial Fibrillation Trial.403 Therefore, unless a clear contraindication exists, AF patients with a recent stroke or TIA should be treated with long-term anticoagulation with an antiplatelet agent reduces the risk of stroke compared with anticoagulation rather than antiplatelet therapy. for AF patients who sustain cardioembolic events while receiving low-intensity anticoagulation intensity should be increased to a maximum target INR of 3.0 to 3.5 rather than routinely adding antiplatelet agents. Several studies have evaluated anticoagulation in combination with aspirin for prevention of ischemic cardiac events in patients with CAD. From these it may be possible to draw inferences regarding management of antithrombotic therapy published between 1960 and 1999 involving patients with CAD treated for at least 3 mo and stratified by the intensities of anticoagulation and aspirin therapy came to the following conclusions.469 High-intensity (INR 2.8 to 4.8) and moderate-intensity (INR 2.0 to 3.0) oral anticoagulation regimens reduced rates of MI and stroke but increased the risk of bleeding 6.0- to 7.7-fold. Combining aspirin with low-intensity anticoagulation (INR less than 2.0) was not superior to aspirin alone. While the combination of moderate- to high-intensity oral anticoagulation plus aspirin appeared promising compared with aspirin alone, the combination was associated with acute myocardial ischemia470-473 and the Combined Hemotherapy and Mortality Prevention Study (CHAMP),474 it appears that high-intensity oral anticoagulation (INR 3.0 to 4.0) is more effective than aspirin alone but is associated with a greater risk of bleeding. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is as effective as high-intensity warfarin and associated with a similar risk of bleeding. The contemporary trials, however, have not addressed the effectiveness of moderate-intensity warfarin (INR 2.0 to 3.0) alone. In the absence of direct evidence, it cannot be assumed that moderate-intensity warfarin is superior to aspirin alone, aspirin al are more effective than aspirin alone but are associated with more bleeding and inconvenience. Further, without close INR control, the combination regimen may be associated with a greater risk of bleeding. For most patients with AF who have stable CAD, warfarin anticoagulation alone (target INR 2.0 to 3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events. The importance of platelet-inhibitor drugs for prevention, 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. then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0) for 9 to 12 mo, following which warfarin may be continued as mono-therapy in the absence of a subsequent coronary event.8.1.4.2.5. Emerging and Investigational Antithrombotic Agents (UPDATED). For new or updated text, view the 2011 Focused Update and 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated. While clearly efficacious against stroke in patients with AF, warfarin carries a substantial risk of hemorrhage, a narrow therapeutic margin necessitating frequent monitoring of the INR level, and interactions with numerous drugs and foods that may cause a need for dose adjustments. These limitations result in undertreatment of a considerable proportion of the AF population at risk, particularly the elderly, for whom numerous concomitant medications are typically prescribed, 455, 475 engendering a quest for safer, more convenient alternatives. Because of its central role in thrombogenesis, thrombin (factor IIa) represents an attractive target for specific inhibition. Direct thrombin inhibitors bind to the active and coagulation of platelets and coagulation factors V, VIII, XI, and XIII. Ximelagatran is administered orally and converted after absorption to the active direct thrombin inhibitor melagatran. The compound appears to have stable pharmacokinetics independent of the hepatic P450 enzyme system and a low potential for food or drug interactions.476 Two long-term phase III studies compared ximelagatran with Warfarin in patients with AF, SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation) -III and -V, with a combined population of more than 7000.444 In these trials, ximelagatran was administered without dose titration or coagulation of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without
dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered without dose titration of more than 7000.444 In these trials, ximelagatran was administered hemorrhagic) and systemic embolism.SPORTIF-III involved an open-label design444 and careful regulation of dosing among patients assigned to warfarin, with INR values within the therapeutic range for 66% of the duration of exposure. The relative risk reduction of 29% and absolute risk reduction of 0.7% per year according to intention-to-treate confirmed the noninferiority of ximelagatran to warfarin. By on-treatment analysis, the relative risk reduction with ximelagatran was 41% (P=0.018. There was no significant difference between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding, but when minor hemorrhages are considered as well, ximelagatran caused significantly less bleeding (25.5% vs. 29.5% per year, P=0.007). The results of the SPORTIF-V trial, in which treatment was administered in a double-blind manner, were similar to those of SPORTIF-III.438 The primary event rates were 1.6% per year with ximelagatran and 1.2% per year with warfarin (absolute difference 0.45% per year, 95% CI 0.13% to 1.03% per year, P less than 0.001 for the noninferiority hypothesis), and there was no difference between treatment groups in rates of major plus minor) was lower with ximelagatran. In both the SPORTIF-III and V trials, serum alanine aminotransferase levels rose to greater than 3 times the upper limit of normal in about 6% of patients treated with ximelagatran. Hence, despite evidence of efficacy comparable to carefully adjusted warfarin and some advantage in terms of bleeding risk, ximelagatran. Hence, despite evidence of efficacy comparable to carefully adjusted warfarin and some advantage in terms of bleeding risk, ximelagatran will not be marketed for clinical use as an anticoagulant, mainly because of concerns about hepatic toxicity.478 Trials of a variety of investigational oral anticoagulation for Diagnostic or Therapeutic Procedures. From time to time, it may be necessary to interrupt oral anticoagulant therapy in preparation for elective surgical procedures. In patients with mechanical prosthetic heart valves, it is generally appropriate to substitute unfractionated or low-molecular-weight heparin to prevent thrombosis.479,480 In patients with AF who do not have mechanical valves, based on extrapolation from the annual rate of thromboembolism in patients with nonvalvular AF, it is the consensus of the Writing Committee 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 instead of unfractionated heparin in patients with AF is based largely. on extrapolation from venous thromboembolic disease states and from limited observational studies.481 In general, low-molecular-weight heparins have several pharmacological advantages over unfractionated heparin. These include a longer half-life, more predictable bioavailability (greater than 90% after subcutaneous injection), predictable bioava clearance (enabling once- or twice-daily subcutaneous administration), and a predictable antithrombotic response based on body weight, which permits fixed-dose treatment without laboratory monitoring except under special circumstances such as obesity, renal insufficiency, or pregnancy.482 Treatment with low-molecular-weight heparin is associated with a lower risk of heparin-induced thrombocytopenia than unfractionated heparin.483 The favorable properties of low-molecular-weight heparins out 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.4848.1.4.3. Nonpharmacological Approaches to Prevention of Thromboembolism (UPDATED). For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated. An emergine option for patients with AF who cannot safely undergo anticoagulation, which is not yet sufficiently investigated to allow general clinical application, is obliteration of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation or truncation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the LAA to remove a principal nidus of thrombus formation.485,486 In addition to direct surgical amputation of the law of t achieve this with intravascular catheters or transpericardial approaches.487 The efficacy of these techniques is presumably related to the completeness and permanence of elimination of blood flow into and out of the LAA. This has been demonstrated by TEE at the time of intervention, but the durability of the effect has not been confirmed by subsequent examinations over several years. Whether mechanical measures intended to prevent embolism from thrombotic material in the LAA will prove to be comparably effective and safer than anticoagulation for this type of intervention have not been convincingly established.8.1.5. Cardioversion of Atrial FibrillationRECOMMENDATIONSRecommendations for Pharmacological Cardioversion of Atrial FibrillationRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSRECOMMENDATIONSR IIaAdministration of amiodarone is a reasonable option for pharmacological cardioversion of AF. (Level of Evidence: A)A single oral bolus dose of propafenone or flecainide ("pill-inthe-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)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 IIbAdministration 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 IIIDigoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. (Level of Evidence: B)8.1.5.1. Basis for Cardioversion of Atrial FibrillationCardioversion may be performed electively to restore sinus rhythm in patients with persistent AF. The need for cardio-version 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, cardio-version carries a risk of thromboembolism unless anticoagulation prophylaxis is initiated before the procedure, and this risk is greatest when the arrhythmia has been present for longer than 48 h.8.1.5.2. Methods of CardioversionCardioversion 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, but the disadvantages include the risk of drug-induced torsades de pointes or other serious arrhythmias. used. The disadvantage of electrical cardioversion is that it requires conscious sedation or anesthesia, which pharmacological and electrical methods of cardioversion. The recommendations for anticoagulation are therefore the same for both methods, as outlined in Section 8.1.4 (Preventing Thromboembolism. Cardioversion in patients with AF following recent heart surgery or MI is addressed later (see Section 8.4, Special Considerations).8.1.5.3. Pharmacological cardioversion is patients with AF following recent heart surgery or MI is addressed later (see Section 8.4, Special Considerations).8.1.5.3. 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. approaches appear simpler but are less efficacious. The major risk is related to the toxicity of
antiarrhythmic 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 antiar-rhythmic drug have, however, been considered as well.Pharmacological cardioversion seems most effective when initiated within 7 d after the onset of AF at the time of treatment. (See Section 3, Classification.) A large proportion of patients with recent-onset AF experience spontaneous cardioversion 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 within 24 to 48 h.493-495 Spontaneous cardioversion 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. may accelerate restoration of sinus rhythm in patients with recent-onset AF, but the advantage over placebo is modest after 24 to 48 h, and drug therapy is much less effective in patients with persistent AF. Some drugs have a delayed onset of action, and conversion may not occur for several days after initiation of treatment.496 Drug treatment abbreviated the interval to cardioversion compared with placebo in some studies without affecting the proportion of patients who remained in sinus rhythmic 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 antiar-rhythmic 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 management of AF are given in Figures 13, 14, 15, and 16. Throughout this document, reference is made to the Vaughan Williams classification of antiarrhythmic drugs, 497 modified to include drugs that became available after the original classification was developed (Table 19). Considerations specific to individual agents are summarized below. Within each category, drugs are listed alphabetically. The antiarrhythmic drugs listed have been approved by federal regulatory agencies in the United States and/or Europe for clinical use, but their use for the treatment of AF has not been approved in all countries. The recommendations given in this document are based on published data and do not necessarily adhere to the regulations and labeling requirements of government agencies. Table 16. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation of Up to 7-d DurationDrug*Route of AdministrationClass of RecommendationLevel of EvidenceReferencesAgents with proven efficacy DofetilideOralIA498-503 FlecainideOral or intravenousIA489-491, 493, PropafenoneOral or intravenousIA491, 494, 495, 505, 509, 516-526, 557 AmiodaroneOral or intravenousIIaA496, 504, 516, 527-534Less effective or incompletely studied agents 504-509 IbutilideIntravenousIA510-515 DisopyramideIntravenousIIbB544 ProcainamideIntravenousIIbB510, 512, 536 QuinidineOralIIbB489, 494, 524, 529, 537-539, 698Should not be administered SotalolOral or intravenousIIIA513, 538-540, 543Table 17. Recommendations for Pharmacological Cardioversion of Atrial Fibrillation Present for More Than 7 dDrug*Route of DigoxinOral or intravenousIIIA375, 494, 505, 526, 530, 542 IbutilideIntravenousIIaA510-515Less effective or incompletely studied agents DofetilideOralIA498-503 AmiodaroneOral or intravenousIIaA496, 504, 516, 527-534 AdministrationRecommendation ClassLevel of EvidenceReferencesAgents with proven efficacy DisopyramideIntravenousIIbB544 PropafenoneOral or intravenousIIbB494, 495, 505, 509, 516-526 OuinidineOralIIbB489, 494, 524, 529, 537-539, 698Should not be administered ProcainamideIntravenousIIbC510, 512, 536, 557 DigoxinOral or intravenousIIIB375, 494, 505, 526, 530, 542 FlecainideOralIIbB489-491, 493, 504-509 SotalolOral or intravenousIIIB513, 538-540, 543Table 18. Recommended Doses of Drugs Proven EffectsReferencesAmiodaroneOralInpatient: 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 maintenanceHypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)496, 504, 516, 527-534, 537, 545Intravenous/oral5 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 maintenanceDofetilideOralCreatinine Clearance (mL/min)Dose (mcg BID)More than 60500QT prolongation, torsades de pointes; adjust dose for renal function, body size and age498-50340 to 6025020 to 40125Less than 20ContraindicatedFlecainideOral200 to 300 mg‡Hypotension, atrial flutter with high ventricular rate489-491, 493, 504, 505, 507-509Intravenous1.5 to 3.0 mg/kg over 10 to 20 min‡IbutilideIntravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 494, 495, 505, 506, 506, 506, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 494, 495, 505, 506, 506, 506, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 494, 495, 505, 506, 506, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 494, 495, 505, 506, 506, 506, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 494, 495, 505, 506, 506, 506, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 495, 505, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mgHypotension, atrial flutter with high ventricular rate491, 495, 505, 507-509Intravenous1 mg over 10 min; repeat 1 mg when necessaryQT prolongation, torsades de pointes510-515PropafenoneOral600 mg Hypotension, atrial flutter with high ventricular rate491, 495, 505, 507-509Intravenous1 509, 516-526, 557Intravenous1.5 to 2.0 mg/kg over 10 to 20 min‡Quinidine§Oral0.75 to 1.5 g in divided doses over 6 to 12 h, usually with a rate-slowing drugQT prolongation, torsades de pointes, GI upset, hypotension489, 494, 524, 529, 537-539Figure 13. Pharmacological management of patients with newly discovered atrial fibrillation (AF). *See Figure 15. HF indicates heart failure.Figure 14. Pharmacological management of patients with recurrent paroxysmal atrial fibrillation (AF). *See Figure 15. (UPDATED) For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated. 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 for details. LVH indicates left ventricular hypertrophy. Figure 16. Pharmacological management of patients with recurrent persistent or permanent atrial fibrillation (AF). Procainamide of early recurrence of AF. *See Figure 15. AAD indicates antiarrhythmic drug. Table 19. Vaughan Williams Classification of Antiarrhythmic DrugsType IA Disopyramide QuinidineType IB Lidocaine MexiletineType IC Flecainide PropafenoneType II Beta blockers (eq. Nondihydropyridine calcium channel antagonists (verapamil and diltiazem)8.1.5.4. Agents With Proven Efficacy for Cardioversion of Atrial Fibrillation8.1.5.4.1. Amiodarone. Data on amiodarone are confusing because the drug may Dofetilide Bretylium Ibutilide SotalolType IV propranolol)Type III Amiodarone be given intravenously or orally and the effects vary with the route of administration. Five meta-analyses of trials compared amiodarone to placebo or other drugs for conversion of recent-onset AF.546-549 One concluded that intravenous amiodarone to placebo or other drugs for conversion of recent-onset AF.546-549 One concluded that intravenous amiodarone was no more effective than placebo 550 while another found amiodarone effective but associated with adverse reactions.546 Another meta-analysis found amiodarone more effective than placebo after 6 to 8 h and at 24 h, indicating delayed conversion with amiodarone. In another meta-analysis of 21 trials involving heterogeneous populations, the relative likelihood of achieving sinus rhythm over a 4-wk period with oral/intravenous amiodarone was 4.33 in patients with AF of less than 48-h duration.548 In a meta-analysis of 18 trials, the efficacy of amiodarone ranged from 34% to 69% with bolus (3 to 7 mg/kg body weight) regimens and 55% to 95% when the bolus was followed by a continuous infusion (900 to 3000 mg daily).550 Predictors of successful conversion were shorter duration of AF, smaller LA size, and higher amiodarone was not superior to other
antiarrhythmic drugs for conversion of recent-onset AF but was relatively safe in patients with structural heart disease, including those with LV dysfunction for whom administration of class IC drugs is contraindicated. In addition, limited information suggests that amiodarone is equally effective for conversion of AF or atrial flutter. Because safety data are limited, randomized trials are needed to determine the benefit of amiodarone for conversion of recent-onset AF in specific patient populations. In the SAFE-T trial involving 665 patients with persistent AF, conversion occurred in 27% of patients after 28 d of treatment with amiodarone, compared with 24% with sotalol and 0.8% with placebo. 292 Although the speed of response may differ during sustained oral therapy, amiodarone, compared with 24% with sotalol and 0.8% with placebo. 292 Although the speed of response may differ during sustained oral therapy, amiodarone, compared with 24% with sotalol and 0.8% with placebo. 292 Although the speed of response may differ during sustained oral therapy, amiodarone, compared with 24% with sotalol and 0.8% with placebo. 292 Although the speed of response may differ during sustained oral therapy. propafenone, and sotalol seemed equally effective in conversion early after onset of AF (within 24 h), antiarrhythmic drug agents may also be given over a longer period of time in an effort to achieve cardioversion after a longer period of AF. Under these circumstances, administration of oral amiodarone is associated with a conversion rate between 15% and 40% over 28 d.292,529,533, 551 In a comparative study, amiodarone and propafenone were associated with similar rates (40%) of converting persistent AF averaging 5 mo in duration.551 Remarkably, all cases in which conversion followed administration of amiodarone occurred after 7 d, with responses continuing to 28 d, whereas conversion occurred more rapidly with propafenone (between 1 and 14 d). Adverse effects of amiodarone include bradycardia, hypotension, visual disturbances, thyroid abnormalities, nausea, and constipation after oral administration and phlebitis after peripheral intravenous administration. Serious toxicity has been reported, including death due to bradycardia ending in cardiac arrest.496,504,516,527-534,537,5518.1.5.4.2. Dofetilide. Oral dofetilide is more effective than placebo for cardioversion of AF that has persisted longer than 1 wk, but available studies have not further stratified patients on the basis of the duration of the arrhythmia. Dofetilide appears more effective for cardioversion of atrial flutter than of AF. A response may take days or weeks when the drug is given orally or intravenous form is investigational.498-5028.1.5.4.3. Flecainide.Flecainide administered orally or intravenous form is investigational.498-5028.1.5.4.3. trials. In 7 studies, the success of a single oral loading dose (300 mg) for cardioversion of recent-onset AF ranged from 57% to 68% at 2 to 4 h and 75% to 91% at 8 h after oral loading and intravenous loading regimens of flecainide were equally efficacious, but a response usually occurs within 3 h after oral administration and 1 h after intravenous administration. Arrhythmias, including atrial flutter with rapid ventricular rates and bradycardia after conversion, are relatively frequent with flecainide than with propafenone, and these drugs should be avoided in patients with underlying organic heart disease involving abnormal ventricular function.489-491,493,504,505,507-5098.1.5.4.4. Ibutilide. In placebo-controlled trials, intravenous ibutilide has proved effective for cardioversion within a few weeks after onset of AF. Available data are insufficient to establish its efficacy for conversion of persistent AF of longer duration. Ibutilide may be used in patients who fail to convert following treatment with propafenone or flecainide.554 The risk of torsades de pointes was about 1% in these studies, lower than the approximate 4% incidence observed during ibutilide is more effect of sodium channel blockade with type IC drugs.554 Ibutilide is more effect of sodium channel blockade with in 1 h after administration. In clinical practice, there is a 4% risk of torsades de pointes ventricular tachycardia and appropriate resuscitation equipment must therefore be immediately available. Women are more susceptible than men to this complication (5.6% vs. 3% in a meta-analysis).555 Ibutilide should be avoided in patients with very low ejection fractions or HF because of the higher risk of ventricular proarrhythmia.556 Serum concentrations of potassium and magnesium should be measured before administration of ibutilide, and patients should be monitored for at least 4 h afterward. Hypotension is an infrequent adverse response.510–5158.1.5.4.5. Propafenone.Placebo-controlled trials have verified that propafenone, given orally or intravenously, is effective for pharmacological cardioversion of recent-onset AF. The effect occurs between 2 and 6 h after oral administration and earlier after intravenous injection, so that when compared with the intravenous regimen, oral propafenone (600 mg) for cardioversion of recent-onset AF ranged from 56% to 83%.557 Oral propafenone was as efficacious as flecainide but superior to oral amiodarone and quinidine plus digoxin.494,558 Limited data suggest reduced efficacy in patients with persistent AF, in conversion of atrial flutter, and in patients with structural heart disease. Adverse effects are uncommon but include rapid atrial flutter, ventricular tachycardia, intraventricular conduction disturbances, hypotension, and bradycardia at conversion. Available data on the use of various regimens of propafenone loading in patients with organic heart disease are scant. This agent should be used cautiously or not at all for conversion of AF in such cases and should be avoided in patients with HF or severe obstructive lung disease.491,495,505,506,509,516-526,5578.1.5.5. Less Effective or Incompletely Studied Agents for Cardioversion of Atrial Fibrillation8.1.5.5.1. Quinidine.Quinidine is used less frequently than other pharmacological agents, due to the perception that it is less efficacious and has more frequent side effects, although direct comparative studies are lacking. Quinidine is usually administered after digoxin or verapamil has been given to control the ventricular response rate. Potential adverse effects include QT-interval prolongation that may precede torsades de pointes, nausea, diarrhea, fever, hepatic dysfunction, thrombocytopenia, and hemolytic anemia. During the initiation of quinidine therapy, hypotension and acceleration of the ventricular response may be expected 2 to 6 h after administration.489,491,494,524,529,537-539,5458.1.5.5.2. Procainamide.Intravenous procainamide has been used extensively for conversion within 24 h of onset of AF, and several studies suggest that it may be superior to placebo.510,512,536 Procainamide appears less useful than some other drugs and has not been tested adequately in patients with persistent AF. Hypotension is the major adverse effect after intravenous administration.8.1.5.5.3. Beta Blockers. When given intravenously, the short-acting beta blocker esmolol may have modest efficacy for pharmacological cardioversion is probably mediated through slowing of the ventricular rate. It is not useful in patients with persistent AF, and there are no data comparing its relative efficacy for atrial flutter and AF. A response may be expected within 1 h after initiation of intravenous infusion. Hypotension and bronchospasm are the major adverse effects of esmolol and other beta blockers.492,5598.1.5.5.4. Nondihydropyridine Calcium Channel Antagonists (Verapamil and Diltiazem). The nondihydropyridine calcium channel antagonists verapamil and diltiazem have not been found effective for pharmacological cardioversion of recent-onset or persistent AF, but they act rapidly to control the rate of ventricular response.373,491,492,532 The negative instropic effects of nondihydropine calcium channel blockers might result in hypotension; caution should be used in patients with HF.8.1.5.5.5. Digoxin.Digitalis glycosides are generally not more effective than placebo for conversion of recent-onset AF to sinus rhythm. Digoxin may prolong the duration of episodes of paroxysmal AF in some patients. 375 and it has not been evaluated adequately in patients with persistent AF except to achieve rate control. Digoxin has few adverse effects after acute administration in therapeutic doses, aside from AV block and increased ventricular ectopy, but all manifestations of digitalis toxicity are dose related.375,378, 494,505,526,530,540,5428.1.5.5.6. Disopyramide has not been tested adequately for conversion of AF but may be effective when administered intravenously. Adverse effects include dryness of mucous membranes, especially in the mouth, constipation, urinary retention, and depression of LV contractility. The last reaction makes it a relatively unattractive option for pharmacological conversion of AF.8.1.5.5.7. Sotalol.In contrast to its relative efficacy for maintenance of sinus rhythm, sotalol has no proved efficacy for pharmacological cardioversion of recent-onset or persistent AF when given either orally or intravenously. It does, however, control the heart rate.513,538-540,543 In patients who tolerate AF relatively well, a wait-and-see approach using oral sotalol is an appropriate option. Side effects consist mainly of QT prolongation associated with torsades de pointes.8.1.6. Pharmacological Agents to Maintain Sinus Rhythm8.1.6.1. Agents With Proven Efficacy to Maintain Sinus Rhythm8.1.6.1. Agents to Maintain Sinus Rhythm8.1.6.1.

controlled trials of drug prophylaxis involving patients with paroxysmal AF, and 22 trials of drug prophylaxis for maintenance of sinus rhythm in patients with persistent AF were identified. Comparative data are not sufficient to permit subclassification by drug or etiology. Individual drugs, listed alphabetically, are described below, and doses for maintenance of sinus rhythm are given in Table 20. It should be noted that any membrane-active agent may cause proarrhythmia. Table 20. Typical Doses of Drugs Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation*Drug†Daily DosagePotential Adverse EffectsAmiodarone‡100 to 400 mgPhotosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complicationsDisopyramide400 to 750 mgTorsades de pointes, HF, glaucoma, urinary retention, dry mouthDofetilide§500 to 1000 mcgTorsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complicationsDisopyramide400 to 750 mgTorsades de pointes (rare) and the second de point rapid conduction through the AV nodePropafenone450 to 900 mgVentricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV nodeSotalol§160 to 320 mgTorsades de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease8.1.6.1.1. Amiodarone. Available evidence suggests that amiodarone is more effective than either class I drugs, sotalol, or placebo in the long-term maintenance of sinus rhythm in patients with paroxysmal or persistent AF refractory to other drugs.560-574 However, amiodarone is associated with a relatively high incidence of potentially severe extracardiac toxic effects, making it a second-line or last-resort agent in many cases. The use of low-dose amiodarone (200 mg daily or less) may be effective and associated with fewer side effects 37,561,565,566 than higher-dose regimens. In patients with LVH, HF, CAD, and/or previous MI, amiodarone is associated with a low risk of proarrhythmia, making it an appropriate initial choice to prevent recurrent AF in these situations. Use of amiodarone for AF is associated with the added benefit of effective rate control, frequently eliminating the need for other drugs to control the ventricular rate. A majority of the 403 patients in the CTAF study561 had first-time paroxysmal (46%) or persistent (54%) AF of less than 6-mo duration. AF was considered persistent when more than half the previous episodes had required cardioversion, implying that many of the cases designated as persistent AF actually had spontaneously terminating paroxysmal AF. Amiodarone maintained sinus rhythm more successfully than propafenone or sotalol (69% vs. 39%) over a 16-mo follow-up period. The reduced recurrence of AF was associated with improved quality of life, fewer AF-related procedures, and lower cost. 347 Nevertheless, 18% of patients assigned to sotalol or propafenone. Of 222 patients randomized to either amiodarone or class I agents in the AFFIRM study, 62% treated with amiodarone remained in sinus rhythm at 1 y compared with 23% on class I agents. In 256 patients randomized between amiodarone was more effective than propafenone575 and sotalol, 562 but this advantage was offset by a higher incidence of side effects.562 In patients who develop recurrent AF during long-term therapy with oral amiodarone, intravenous amiodarone exerted an additional therapeutic effect to terminate recurrences.576Amiodarone increases the success rate of electric cardio-version and prevents relapses by suppressing atrial ectopy in patients with persistent AF.577-579Experimentally, amiodarone, but not dofetilide or flecainide, reverses pacing-induced atrial remodeling and inhibits the inducibility and stability of AF.580 To date, only a few randomized studies have been performed with amiodarone after cardioversion in patients with persistent AF. Amiodarone was tested as a first-line agent in a study of patients postcardioversion537 stratified according to age, duration of AF, mitral valve disease, and cardiac surgery. After 6 mo, amiodarone was associated with fewer side effects than quinidine (43%). Amiodarone was more effective (83% of patients remaining in sinus rhythm) than quinidine over 6 mo, but side effects often occur after more prolonged treatment with amiodarone. In a crossover study of 32 patients who had persistent AF for more than 3 wk randomized to amiodarone or quinidine537 when pharmacological conversion did not occur with quinidine (direct-current cardioversion was not used), amiodarone was better tolerated and far more effective in achieving restoration and long-term maintenance of sinus rhythm. After 9 mo, 18 of 27 (67%) amiodarone-treated patients were in sinus rhythm versus 2 of 17 (12%) taking quinidine. The double-blind, placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received sotalol, and 137 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received sotalol, and 137 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom 267 received amiodarone, 261 received placebo-controlled SAFE-T trial292 involved 665 patients with persistent AF, of whom After a run-in period of 28 d allowing for a full antiarrhythmic effect, spontaneous conversion occurred in 27% of those given amiodarone, 24% on sotalol, and 0.8% on placebo. Among patients who did not experience conversion pharmacologically, direct-current shocks subsequently failed in 28%, 26.5%, and 32% of patients in the 3 treatment groups respectively. This indicates that sotalol and amiodarone, when given on a chronic basis, are equally effective in converting persistent AF to sinus rhythm (see Section 8.1.5.4, Agents With Proven Efficacy for Cardioversion of Atrial Fibrillation). The median times to recurrence of AF were significantly longer with amiodarone (487 d) than with sotalol (74 d) or placebo (6 d). In patients with ischemic heart disease, the median time to AF recurrence did not differ between amiodarone (569 d) and sotalol (428 d). There were no significant differences in major adverse events, but the duration of amiodarone is more effective than sotalol, sotalol was equally effective in patients with CAD, for whom it is preferred because of lower toxicity. One uncontrolled study involved 89 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study 563 of 110 patients with refractory AF (57) were in sinus rhythm after 3 y of amiodarone therapy. 566 In another study with paroxysmal AF) or atrial flutter in whom a median of 2 class I agents had failed, amiodarone (268 plus or minus 100 mg daily) was associated with persistent AF and 40% of those with paroxysmal AF over 5 y. Several other uncontrolled studies also
support the use of amiodarone as an agent of last resort.564,568,581,582 In one, a dose of 200 mg daily appeared effective in patients for whom cardioversion had failed; 52% underwent repeated cardioversion had failed; 52% underwent repeated cardioversion had failed; 52% underwent repeated cardioversion with success for 12 mo.5318.1.6.1.2. Beta Blockers are generally not considered primary therapy for maintenance of sinus rhythm in patients with AF and structural heart disease. Various beta blockers have shown moderate but consistent efficacy to prevent AF recurrence or reduce the frequency of paroxysmal AF, comparable to conventional antiarrhythmic drugs.583-586 One placebo-controlled study583 of 394 patients with persistent AF found a lower risk of early recurrence after cardioversion and slower ventricular response with sustained-release metoprolol than placebo.583 Two studies found atenolol587 and bisoprolol584 as effective as sotalol and better than placebo in reducing the probability of relapse after cardioversion, but proarrhythmic events occurred more often during treatment with sotalol. In patients with persistent AF, carvedilol and bisoprolol initiated after cardioversion produced similar reductions in relapse over the course of 1 y.585 These results confirm a previous observational study in which beta blockers reduced the risk of developing AF during an average follow-up of 3.2 y.25 Beta blockers have the advantage of controlling the ventricular rate when AF recurs and reduce or abolish associated symptoms, but unawareness of recurrent AF may have disadvantages. These agents may be effective in postoperative patients but potentially aggravate vagally mediated AF.8.1.6.1.3. Dofetilide. Two large-scale, double-blind, randomized studies support theorem. efficacy of dofetilide for prevention of AF or atrial flutter.503 Results from the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study found d in maintaining sinus rhythm 1 y after cardioversion compared with only 25% in the placebo group. In the Distensibility Improvement And Remodeling in Diastolic Heart Failure (DIAMOND)588 study of patients with compromised LV function, sinus rhythm was maintained in 79% of the dofetilide group compared with 42% of the placebo group. The incidence of torsades de pointes was 0.8%. Four of 5 such events occurred in the first 3 d. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital at a dose titrated to renal function and the QT interval.8.1.6.1.4. Disopyramide. Several small, randomized studies support the efficacy of disopyramide to prevent recurrent AF after direct-current cardioversion. One study comparing propafenone and disopyramide for more than 3 mo after cardioversion was associated with an excellent long-term outcome in an uncontrolled study: 98 of 106 patients were free of recurrent AF, and 67% remained in sinus rhythm after a mean of 6.7 y. Although the duration of AF was more than 12 mo in most patients, few had significant underlying cardiac disease other than previously treated thyrotoxicosis. It is not clear, therefore, whether disopyramide was the critical factor in suppressing AF.544 Disopyramide has negative inotropic and negative dromotropic effects that may cause HF or AV block.544,589-592 Disopyramide may be considered first-line therapy in vagally induced AF, and its negative inotropic effects may be desirable in patients with HCM associated with dynamic outflow tract obstruction.5938.1.6.1.5. Flecainide.Two placebo-controlled studies594,595 found flecainide effective in postponing the first recurrence of AF and the overall time spent in AF; and in other randomized studies598-600 found that flecainide delayed recurrence. Severe ventricular proarrhythmia or sudden death was not observed at a mean dose of 199 mg daily among patients with little or no structural heart disease. Side effects in 5 patients (9%) were predominantly related to negative dromotropism, with or without syncope. Flecainide (200 mg daily) in preventing recurrent AF after cardioversion and associated with fewer side effects, but one patient died a month after entry, presumably due to proarrhythmia.6008.1.6.1.6. Propafenone. The United Kingdom Paroxysmal Supraventricular Tachycardia (UK PSVT) study was a large, randomized, placebo-controlled trial of propafenone in which transtelephonic monitoring was used to detect relapses to AF.601 The primary endpoint was time to first recurrence or adverse event. A dose of 300 mg twice daily was effective, but the higher dose was associated with more frequent side effects. In a small, placebo-controlled study,602 propafenone, compared with placebo, reduced days in AF from 51% to 27%. Propafenone was more effective than quinidine in another randomized comparison.603 In an open-label randomized study involving 100 patients with AF (with balanced proportions of paroxysmal and persistent AF), propafenone and sotalol were equally effective in maintaining sinus rhythm at 12 mo, respectively).604 The pattern of AF (paroxysmal or persistent), LA size, and previous response to drug therapy did not predict efficacy, but statistical power for this secondary analysis was limited. Other uncontrolled studies, usually involving selected patients refractory to other antiarrhythmic drugs, also support the efficacy of propafenone.605-609In a randomized study. propafenone and disopyramide appeared equally effective in preventing postcardioversion AF, but propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found propafenone was better tolerated.589 A few observational studies involving mixed cohorts of patients with paroxysmal and persistent AF found complaints.608In 2 placebo-controlled studies on patients with symptomatic recurrence and reduced the ventricular rate at the time of relapse. Like other highly effective class IC drugs, propafenone should not be used in patients with ischemic heart disease or LV dysfunction due to the high risk for proarrhythmic effects. Close follow-up is necessary to avoid adverse effects due to the development of ischemia or HF.8.1.6.1.7. Sotalol.Sotalol is not effective for conversion of AF to sinus rhythm, but it may be used to prevent AF. Two placebo-controlled studies612,613 involving patients in sinus rhythm and at least one documented prior episode of AF found sotalol safe and effective at doses ranging from 80 to 160 mg twice daily. Patients considered at risk of proarrhythmia, HF, or AV conduction disturbances were excluded; whether any of the participants had undergone previous direct-current cardioversion was not reported.561,612 The effects of the reverse use dependence of sotalol and proparent in sinus rhythm in patients with AF. In the CTAF study, sotalol and propafenone (given separately) were less effective than amiodarone as assessed by the number of patients without documented recurrence of AF. The difference between outcomes with these drugs was less marked when the number of patients without side effects was considered. In an uncontrolled study of a stepped-care approach beginning with propafenone and, after failure, then sotalol, paroxysmal AF occurred in nearly 50% of patients, but only 27% of those with persistent AF in a multicenter study.614 Moreover, sotalol was more effective in suppressing symptoms in patients who relapsed into AF, probably because it induced a slower ventricular rate. In patients with recurrent AF, propafenone was as effective as sotalol in maintaining sinus rhythm 1 y after cardioversion. Recurrences occurred later and were less symptomatic with either drug thar with placebo.615 Several studies found sotalol and the combination of quini-dine and verapamil equally effective after cardioversion of AF, although ventricular arrhythmias (including torsades de pointes) were more frequent with quinidine.538,615 Sotalol should be avoided in patients with asthma, HF, renal insufficiency, or QT interval prolongation.8.1.6.2. Drugs With Unproven Efficacy or No Longer Recommended8.1.6.2.1. Digoxin. Available evidence does not support a role for digitalis in suppressing recurrent AF in most patients. The lack of an AV blocking effect during sympathetic stimulation results in poor rate control with digoxin, and hence it does not usually reduce symptoms associated with recurrent paroxysmal AF.308.1.6.2.2. Procainamide. No adequate studies of procain-amide are available. Long-term treatment is frequently associated with arthralgia or agranulocytosis.8.1.6.2.3. Quinidine. Quinidine has not been evaluated extensively in patients with paroxysmal AF but appears approximately as effective as class IC drugs.596,597,616 In one study,603 quinidine was less effective than propafenone). Side effects
are more prominent than with other antiarrhythmic drugs, and proarrhythmia is a particular concern. A meta-analysis of 6 trials found quini-dine superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) than among those not given quinidine (3 of 387 patients; 2.9%) than among those not given quinidine (3 of 387 patients; 2.9%) than among those not given quinidine (3 of 387 patients; 2.9%) than among the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) than among those not given quinidine (3 of 387 patients; 2.9%) than among the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) than among the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) than among the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no treatment to maintain sinus rhythm after cardioversion of AF (50% vs. 25% of patients; 2.9%) the superior to no t 0.8%).609 In a registry analysis,616 6 of 570 patients less than 65 y old died shortly after restoration of sinus rhythm while taking quinidine. Up to 30% of patients less than 65 y old died shortly after restoration of sinus rhythm after direct-current cardioversion of AF. Sotalol, but not guinidine, reduced heart rate in patients with recurrent AF, and there were fewer symptoms with sotalol.535,592,614,617-624In 2 European multicenter studies, the combination of guinidine plus verapamil was as effective as or superior to sotalol in preventing recurrences of paroxysmal and persistent AF. In the Suppression Of Paroxysmal AF either received high-dose quinidine (480 mg per day) plus verapamil (240 mg per day) plus verapamil (160 mg per day; 255 patients), sotalol (320 mg per day; 264 patients), or placebo (251 patients). Each of the active treatments was statistically superior to placebo and not different from one another with respect to time to first recurrence or drug discontinuation. The symptomatic AF burden also improved (3.4%, 4.5%, 2.9%, and 6.1% of days for each treatment group, respectively). Four deaths, 13 episodes of syncope, and 1 episode of ventricular tachycardia were documented, with 1 death and occurrence of VT related to quinidine plus verapamil. Sotalol and the quinidine-verapamil. Sotalol and the quinidine-verapamil. (PAFAC) trial287 compared the efficacy and safety of the combination of quinidine plus verapamil (377 patients), and placebo (88 patients) in patients), and placebo (88 patients), and placebo (67%), and AF recurrence became persistent in 348 (41%). Over 1 y, recurrence rates were 83% with placebo, 67% with sotalol, and 65% with the quinidineverapamil combination superior to placebo and to sotalol. About 70% of AF recurrences were asymptomatic. Adverse events were comparable on sotalol group. Therefore, the combination of quinidine/verapamil appeared useful to prevent recurrent AF after cardioversion of persistent AF.8.1.6.2.4. Verapamil and Diltiazem. There is no evidence to support the antiarrhythmic efficacy of calcium channel antagonist drugs in patients with paroxysmal AF, but they reduce the number of AF episodes occurring in a 3-mo period by approximately 50%.6268.1.7. Out-of-Hospital Initiation of Artiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients With Atrial Fibrillation of AF is whether to initiate antiarrhythmic Drugs in Patients Wi adverse effects, including torsades de pointes (Table 21). With the exception of those involving low-dose oral amiodarone,533 virtually all studies of pharmacological cardioversion have involved hospitalized patients. However, one study627 provided a clinically useful approach with out-of-hospital patient-controlled conversion using class IC drugs (see Tables 6, 7, and 8). Table 21. Types of Proarrhythmia During Treatment With Various Antiarrhythmic Drugs for AF or Atrial Flutter According to the Vaughan Williams ClassificationVentricular proarrhythmia Torsades de pointes (VW types IA and III drugs*) Sustained monomorphic ventricular tachycardia (usually VW type IC Increase of defibrillation threshold (a potential problem with VW type IC Provocation of recurrence (probably VW types IA, IC, and III drugs) Conversion of AF to flutter (usually VW type IC drugs) Sustained polymorphic ventricular tachycardia/VF without long QT (VW types IA, IC, and III drugs)Atrial proarrhythmia drugs) drugs)Abnormalities of conduction or impulse formation Acceleration of ventricular rate during AF (VW types IA and IC drugs) Accelerated conduction over accessory pathway (digoxin, intravenous verapamil, or diltiazem[†]) Sinus node dysfunction, atrioventricular block (almost all 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.628 Recommendations for out-of-hospital initiation or intermittent use of antiar-rhythmic drugs differ for 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, or to enhance the success of direct-current cardioversion by lowering the defibrillation threshold and prevent early recurrence of AF. In patients with lone AF without structural heart disease, class IC drugs may be initiated on an outpatient basis. For other selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease, "pill-in-the-pocket" administration of propafenone and flecainide outside the hospital becomes an option once treatment has proved safe in hospital given the relative safety (lack of organ toxicity and low estimated incidence of proarrhythmia).181,557,629-631 Before these agents are initiated, however, a beta blocker or nondihydropyridine calcium channel antagonist is generally recommended to prevent rapid AV conduction in the event of atrial flutter.632-636 Unless AV node con- duction is impaired, a short-acting beta blocker or nondihydropyridine calcium channel antagonist should be given at least 30 min before administration of a type IC antiarrhythmic agent to terminate an acute episode of AF, or the AV nodel blocking agents should be prescribed as continuous background therapy. Sudden death related to idiopathic ventricular fibrillation may occur in patients with structurally normal hearts.637,638 Because termination of paroxysmal AF may be associated with bradycardia due to sinus node or AV node dysfunction, an initial conversion trial should be undertaken in hospital before a patient is declared fit for outpatient "pill-in-the-pocket" use of flecainide or propafenone for conversion of subsequent recurrences of AF. Table 22 lists other factors associated with proarrhythmic toxicity, including proarrhythmic effects, which vary according to the electrophysiological properties of the various drugs. For class IC
agents, risk factors for proarrhythmia include female gender. Table 22. Factors Predisposing to Drug-Induced Ventricular Proarrhythmia W Types IA and III AgentsVW Type IC AgentsLong QT interval (QTc greater than or equal to 460 ms)Wide QRS duration (more than 120 ms)Long QT interval syndromeConcomitant VTStructural heart disease, substantial LVHStructural heart diseaseDepressed LV function*Hypokalemia/hypomagnesemia*Female genderRenal dysfunction*Bradycardia*Rapid ventricular response rate* 1. (Drug-induced) sinus node disease or AV block1. During exercise induced) conversion of AF to sinus rhythm2. During rapid AV conduction 3. Ectopy producing short-long R-R sequencesRapid dose increaseRapid dose increaseHigh dose (sotalol, dofetilide), drug accumulation*High dose, drug accumulation*Addition of drugs*Addition of drugs* 1. Diuretics1. Negative inotropic drugs 2. Other OT 3. Nonantiarrhythmic drugs listed in proarrhythmiaAfter initiation of drug Excessive QT lengtheningExcessive (more than 150%) QRS wideningFew prospective data are available on the relative safety of initiating antiarrhythmic drug therapy in the outpatient versus inpatient setting, and the decision to prolonging antiarrhythmic drugs initiate therapy out of hospital should be carefully individualized. The efficacy and safety of self-administered oral loading of flecainide and propafenone in terminating recent-onset AF.627 Fifty-eight patients (22%) were excluded because of treatment failure or side effects. Using resolution of palpitations within 6 h after drug ingestion as the criterion of efficacy, treatment was successful in 534 episodes (94%), during 15-mo follow-up, with conversion occurring over a mean of 2 h. Compared with conversion occurring over a mean of 2 h. hospitalizations were significantly reduced. Among patients with recurrences, treatment was effects (mostly nausea), or anxiety. Thus, the "pill-in-the-pocket" approach appears feasible and safe for selected patients with AF, but the safety of this approach without previous inpatient evaluation remains uncertain. As long as the baseline uncorrected QT interval is less than 450 ms, serum electrolytes are normal, and risk factors associated with class III drug-related proarrhythmia are considered (Table 23), sotalol may be initiated in outpatients with little or no heart disease. It is safest to start sotalol when the patient is in sinus rhythm. Amiodarone can also usually be given safely on an outpatient basis, even in patients with persistent AF, because it causes minimal depression of myocardial function and has low proarrhythmic potential,566 but in-hospital loading may be necessary for earlier restoration of sinus rhythm in patients with HF or other forms of hemodynamic compromise related to AF. Loading regimens typically call for a dministration of 600 mg daily for 1 wk,531 followed by lower maintenance doses. Amiodarone, class IA or IC agents, or sotalol can be associated with bradycardia 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) 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 by checking the pulse rate, using an event recorder, or reading ECG tracings obtained at the office. The dose of other medication for rate control should be reduced when the rate slows after initiation of amiodarone and stopped if the rate slows after initiation of amiodarone and sl 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 23. Pharmacological Treatment Before Cardioversion in Patients With Persistent AF: Effects of Various Antiarrhythmic Drugs on Immediate Recurrence, Outcome of Transthoracic Direct-Current Shock, or BothEfficacyEnhance Conversion by DC Shock and Prevent IRAF*Recommendation ClassLevel of EvidenceSuppress SRAF and Maintenance Therapy ClassKnownAmiodaroneIIaBAll drugs in recommendation class I (except ibutilide) plus beta blockersFlecainideIbutilidePropafenoneQuinidineSotalolUncertain/unknownBeta blockersIIbCDiltiazemDofetilideProcainamideVerapamil8.1.8. Drugs Under DevelopmentTo overcome the limited efficacy and considerable drugs for maintaining sinus rhythm, selective blockers of atrial ion channels and nonselective ion channel blockers are under development. Use of nonantiarrhythmic drugs, such as inhibitors of the renin-angiotensin system, n-3 polyunsaturated fatty acids, and statins, which might modify the underlying atrial remodeling, have not been extensively investigated for this purpose.640-6458.1.8.1. Atrioselective AgentsThe finding that the ultra-rapid delayed rectifier (IKur) exists in atrial but not ventricular tissue opened the possibility that atrioselective drugs without ventricular proarrhythmic toxicity could be developed for treatment of patients with AF.643,646IKur blockers (NIP-142, RSD1235, AVE0118) prolong atrial refractoriness (left more than right with no effect on ventricular repolarization and show strong atrial antiarrhythmic efficacy.642,644,645,647 AVE0118 is an IKur and Itoblocker that, unlike dofetilide, increases refractoriness in electrically remodeled atria, prolongs atrial wavelength, and converts persistent AF to sinus rhythm without disturbing intra-atrial conduction velocity or prolonging the QT interval.6488.1.8.2. Nonselective Ion Channel-Blocking DrugsAzimilide and dronedarone block multiple potassium, sodium, and calcium currents and prolong the cardiac action potential without reverse use-dependence.641-643,645Azimilide has a long elimination half-life (114 h), allowing for once-daily administration. In patients with paroxysmal SVT enrolled in 4 clinical trials, azimilide at doses of 100 and 125 mg daily prolonged time to recurrence of AF and atrial flutter647,649 and reduced symptoms associated with recurrence.650 Patients with ischemic heart disease and HF displayed greater efficacy than those without structural heart disease. In a placebo-controlled trial involving 3717 survivors of MI with LV systolic dysfunction,651 azimilide, 100 mg daily, was associated with a 1-y mortality rate similar to placebo, 651 and more patients in the azimilide group developed AF or new or worsening HF than those given placebo. adverse effects of azimilide were severe neutropenia (less than 500 cells per microliter) in 0.9% and torsades de pointes in 0.5% of treated patients.651Dronedarone is a noniodinated amiodarone derivative.653,654 In a randomized, placebo-controlled study involving 204 patients undergoing cardioversion of persistent AF,655 dronedarone (800 mg daily) delayed first recurrence from 5.3 to 60 d. Higher doses (1200 and 1600 mg daily) were no more effective and associated with gastrointestinal side effects (diarrhea, nausea, and vomiting. To date, neither organ toxicity nor proarrhythmia has been reported. In 2 placebo-controlled trials, European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for Maintenance of Sinus Rhythm (EURIDIS)656 and American-Australian Trial with Dronedarone prolonged the time to first documented AF/atrial flutter recurrence and helped control the ventricular rate. Tedisamil, an antianginal agent, blocks several potassium channels and causes a reverse rate-dependent QT-interval prolongation. Tedisamil (0.4 and 0.6 mg/kg) was superior to placebo for rapid conversion (within 35 min) of recent-onset AF or atrial flutter.658 The main side effects were pain at the injection site and ventricular tachycardia.8.1.8.3. Recommendations for Dronedarone for the Prevention of Recurrent Atrial Fibrillation (NEW SECTION)For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated text, view the 2011 Focused Update. response does not respond promptly to pharmacological measures for patients with AF with ongoing
myocardial ischemia, symptomatic hypotension, angina, or HF, immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs. (Level of Evidence: B)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: B)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 IIIFrequent 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)Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia. (Level of Evidence: C)8.2.1. TerminologyDirect-current cardioversion involves delivery of an electrical stimulation does not occur during the vulnerable phase of the cardiac cycle.659 Direct-current cardioversion is used to normalize all abnormal cardiac rhythms except ventricular fibrillation. The term defibrillation implies an asynchronous discharge, which is appropriate for correction of ventricular fibrillation. AspectsSuccessful cardioversion of AF depends on the underlying heart disease and the current density delivered to the atrial myocardium. Current may be delivered to the atrial myocardium. and in patients with obstructive lung disease, it has not been widely applied. The frequency of recurrent AF does not differ between the 2 methods.355,660-664The current density delivered to the heart by transthoracic electrodes depends on the defibrillator capacitor voltage, output waveform, size and position of the electrode paddles, and thoracic impedance. For a given paddle surface area, current density decreases with increasing impedance, related to the thickness and composition of the paddles, body size, respiratory phase, number of shocks, and interval between shocks.665Use of electrolyte-impregnated pads can minimize the electrical resistance between paddles and the heart inhibits conduction, so shocks delivered during expiration or chest compression deliver higher energy to the heart. Large paddles lower impedance but may make current density in cardiac tissue insufficient; conversely, undersized paddles may cause injury due to excess current density. Animal experiments have shown that the optimum diameter of 8 to 12 cm665 is generally recommended. Because the combination of high impedance and low energy reduces the success of cardioversion, measurement of impedance has been proposed to shorten the procedure and improve outcomes.666,667 Kerber et al668 reported better efficacy by automatically increasing energy delivery during direct-current cardioversion. In a randomized trial, 77 patients treated with sinusoidal monophasic shocks, and the latter required less energy. In addition to rectilinear biphasic shocks, independent correlates of successful conversion were thoracic impedance and the duration of AF.669 For cardioversion of AF, a biphasic shock waveform, and represents the present standard for cardioversion of AF.670In their original description of cardioversion, Lown et al659,671 recommended an anterior-posterior electrode configuration over anterior-posterior positioning, but others disagree.665,672,673 Anterior-posterior positioning allows current to reach a sufficient mass of atrial myocardium to achieve cardioversion of AF when the pathology involves both atria (as in patients with atrial septal defects or cardiomyopathy). A drawback of this configuration is the amount of pulmonary tissue separation the heart, particularly in patients with emphysema. Placing the anterior paddle and the heart, particularly in patients with emphysema. breast tissue. Other paddle positions result in less current flow through crucial parts of the heart.665 In a randomized study involving 301 subjects undergoing elective external cardioversion, the energy shocks) was greater with the anterior posterior configuration (87%) than with the anterior-lateral alignment (76%).674 Animal experiments show a wide margin of safety between the energy required for cardioversion of AF and that associated with myocardial depression.675,676 Even without apparent myocardial depressio cardioversion677,678 and blood levels of creatine kinase may rise. Serum troponin-T and troponin related to energy delivered. Microscopic myocardial damage related to direct-current cardioversion has not been confirmed and is probably clinically insignificant.8.2.3. Procedural AspectsCardioversion should be performed with the patient under adequate general anesthesia in a fasting state. conscious sedation are preferred to enable rapid recovery after the procedure; overnight hospitalization is seldom required.680 The electric shock should be synchronized with the QRS complex, triggered by monitoring the R wave with an appropriately selected ECG lead that also clearly displays atrial activation to facilitate assessment of outcome The initial energy may be low for cardioversion of atrial flutter, but higher energy is required for AF. The energy output has traditionally been increased successively in increments of 100 J to a maximum of 400 J, but some physicians begin with higher energy energy is required for AF. damage, some have sug- gested that the interval between consecutive shocks should be at least 1 min.681 In 64 patients randomly assigned to initial energy was significantly more effective than low levels (immediate success rates 14% with 100 J, 39% with 360 J, high initial energy was significantly more effective than low levels (immediate success rates 14% with 100 J, 39% with 360 J, and 95% with 360 J, and 95\% with 360 J, respectively), resulting in fewer shocks and less cumulative energy when 360 J was delivered initially.682 These data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence, an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence, an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence, an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence, an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indicate that an initial shock of 100 J with monophasic waveform is often too low for direct-current cardioversion of AF; hence data indic to biphasic waveforms, particularly when cardioversion of AF with a rectilinear biphasic sinusoidal waveform (92.4% of 2818 procedures in 1361 patients) was more effective than a monophasic sinusoidal waveform (92.4% of 2818 procedures in 2025 patients; P less than 0.001), but comparable for patients with atrial flutter (99.2% and 99.8%, respectively). The median successful energy level was 100 J with the biphasic waveform.6848.2.4. Direct-Current Cardioversion in Patients With Implanted Pacemakers and DefibrillatorsWhen 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. temporary or permanent increase in stimulation threshold, resulting in loss of ventricular capture. To ensure appropriate function, the implanted anteriorly, so the paddles used for external cardioversion should be positioned as distantly as possible, preferably in the anterior-posterior configuration. The risk of exit block is greatest when one paddle is positioned near the impulse generator and the other over the cardiocersion does not solve and lower with the anterior-posterior electrode systems. 685,686 Low-energy internal cardioversion does not solve and lower with the anterior-posterior electrode systems. interfere with pacemaker function in patients with electrodes positioned in the RA, coronary sinus, or left pulmonary artery.6878.2.5. Risks and Complications of Atrial FibrillationThe risks of direct-current cardioversion are mainly related to thromboembolism and arrhythmias. reported in 1% to 7% of patients not given prophylactic anticoagulation before cardioversion.) Various benign arrhythmias, especially
ventricular and supraventricular premature beats, bradycardia, and short periods of sinus arrest, may arise after cardioversion and commonly subside spontaneously.690 More dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may arise in the face of hypokalemia, digitalis intoxication, or improper synchronization.691,692 Serum potassium levels should be in the normal range for safe, effective cardioversion. Magnesium supplementation does not enhance cardio-version.693 Cardioversion is contraindicated in cases of digitalis toxicity because resulting ventricular tachyarrhythmia may be difficult to terminate. A serum digitalis level in the therapeutic range does not exclude clinical toxicity but is not generally associated with malignant ventricular arrhythmias during cardioversion, 694 so it is not routinely necessary to interrupt digoxin before elective cardioversion until a toxic state has been corrected, which usually requires withdrawal of digoxin for longer than 24 h.In patients with long-standing AF, cardioversion commonly unmasks underlying sinus node dysfunction. A slow ventricular response to AF in the absence of drugs that slow conduction across the AV node may indicate an intrinsic conduction defect. The patient should be evaluated before cardioversion with this in mind so a transvenous or transcutaneous pacemaker can be used prophylactically.6958.2.6. Pharmacological Enhancement of Direct-Current CardioversionRECOMMENDATIONSCLASS IIaPretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent atrial fibrillation. (Level of Evidence: B)In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure following prophylactic administration of beta blockers, disopyramide, diltiazem, dofetilide, procainamide, or vera-pamil may be considered, although the efficacy of these agents to enhance the success of cardioversion or to prevent early recurrence of AF is uncertain. (Level of Evidence: C)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)Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients. (Level of Evidence: C)Although most recurrences of AF occur within the first month after direct-current cardioversion, research with internal atrial cardioversion696 and postconversion696 and postconversion studies using transthoracic shocks697 have established several patterns of AF recurrent countershock fails to elicit even a single isolated sinus or ectopic atrial beat, tantamount to a high atrial defibrillation threshold. In others, AF recurs within a few minutes after a period of sinus rhythm,698,699 and recurrence occur in approximately 25% of patients undergoing direct-current cardioversion of AF, and subacute recurrences occur within 2 wk in almost an equal proportion.698 Figure 17. Hypothetical illustration of cardioversion failure. Three types of recurrences after electrical cardioversion for wan Gelder IC, by othetical illustration of cardioversion for wan Gelder IC and suppression of recurrences. Tuinenburg AE, Schoonderwoerd BS, et al. Pharmacologic versus direct-current electrical cardioversion; IRAF, immediate recurrence of AF after cardioversion; and fibrillation. Am J Cardiol 1999;84:147R-51R, with permission from Excerpta Medica Inc.704 ECV indicates external cardioversion; and SR, sinus rhythm.Restoration and maintenance of sinus rhythm are less likely when AF has been present for longer than 1 y than in patients with AF of shorter duration. The variation in immediate success rates for direct-current cardioversion from 70% to 99% in the literature617,682,684,700,701 is partly explained by differences in patient characteristics and the waveform used but also depends upon the definition of success, because the interval at which the result is evaluated ranges from moments to several days. Over time, the proportion of AF caused by rheumatic heart disease has declined, the average age of the AF population has increased, 700-702 and the incidences of lone AF have remained constant, making it difficult to compare the outcome of cardioversion across various studies. In a large consecutive series of patients undergoing cardioversion of AF published in 1991, 24% were classified as having ischemic heart disease, 24% with rheumatic valvular disease, 15% with lone AF, 11% with hypertension, 10% with cardiomyopathy, 8% with nonrheumatic valvular disease, 6% with congenital heart disease, and 2% with hyperthyroidism.700 Seventy percent were in sinus rhythm 24 h after cardioversion. Multivariate analysis found a short duration of AF, atrial flutter, and younger age to be independent predictors of success, whereas LA enlargement, underlying organic heart disease, and cardiomegaly were associated with HF. A decade later, a study of 166 consecutive patients followed after first direct-current cardioversion found that short duration of AF, smaller LA size, and treatment with beta blockers, verapamil, or diltiazem were clinical predictors of both initial success and maintenance of sinus rhythm.703 In another series of 100 patients, the primary success rate assessed 3 d after cardioversion was 86%,701 increasing to 94% when the procedure was repeated during treatment with quinidine or disopyramide. Only 23% of patients remained in sinus rhythm after 1 y, however, and 16% remained after 2 y. In those who relapsed to AF, repeated cardioversion after administration of antiarrhythmic medication resulted in sinus rhythm in 40% and 33% after 1 and 2 y, respectively. For patients who relapsed again, a third cardioversion resulted in sinus rhythm in 54% after 1 y and 41% after 2 y. Thus, sinus rhythm can be restored in a substantial proportion of patients by direct-current cardioversion, but the rate of relapse is high without concomitant antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current cardioversion, the primary aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrhythmic drug therapy704 (Fig. 17). When given in conjunction with direct-current aims of antiarrh efficacy may involve multiple mechanisms, such as decreasing the energy required to achieve cardioversion, prolonging atrial ectopy that may cause early recurrence of AF.580,705 Antiarrhythmic medications may be initiated out of hospital immediately prior to direct-current cardioversion. (See Section 8.1.7, Out-of-Hospital Initiation of Anti-arrhythmic Drugs in Patients With Atrial Fibrillation.) The risks of pharmacological treatment include the possibility of paradoxically increasing the defibrillation.) The risks of pharmacological treatment include the possibility of paradoxically increasing the defibrillation threshold, as described with flecainide,600 accelerating the ventricular rate when class IA or IC drugs are given without an AV nodal blocking agent,632-636,706 and inducing ventricular arrhythmias (see Table 21). Prophylactic drug therapy to prevent early recurrence of AF should be considered individually for each patient. Patients with lone AF of relatively short duration, 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-currence and those undergoing initial cardioversion of persistent AF, pretreatment is optional. Antiarrhythmic drug therapy is recommended in conjunction with a second cardioversion, beyond a second attempt, is of limited value and should be reserved for carefully selected patients. Infrequently repeated cardioversions may be acceptable in patients who are highly symptomatic upon relapse to AF. Specific Pharmacological Agents for Prevention of Recurrent AF in Patients with amiodarone for 6 wk before and after cardioversion 8.2.6.1. AmiodaroneIn patients with persistent AF, treatment with amiodaroneIn patients who are highly symptomatic upon relapse to AF. Specific Pharmacological Agents for Prevention of
Recurrent AF in Patients With amiodaroneIn patients with persistent AF, treatment with amiodaroneIn patients who are highly symptomatic upon relapse to AF. Specific Pharmacological Agents for Prevention of Recurrent AF in Patients With amiodaroneIn patients with persistent AF. likelihood of maintaining sinus rhythm and reduced supraventricular ectopic activity that may trigger recurrent AF.579 Prophylactic treatment with amiodarone was also effective when an initial attempt at direct-current cardioversion had failed.531,569 In patients with persistent AF randomly assigned to treatment with carvedilol, amiodarone, or placebo for 4 wk before direct-current cardioversion, the 2 drugs yielded similar cardioversion rates, but amiodarone proved superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrence of AF, and a superior at maintaining sinus rhythm after conversion.7078.2.6.2. Beta-Adrenergic AntagonistsAlthough beta blockers are unlikely to enhance the superior at maintaining sinus rhythma. they may reduce subacute recurrences.5838.2.6.3. Nondihydropyridine Calcium Channel Antagonists Therapy with calcium-channel antagonists prior to electrical cardioversion of AF. On the other hand, verapamil and diltiazem may increase AF duration, shorten refractoriness, and increase the spatial dispersion of refractoriness leading to more sustained AF.710,711 In patients with persistent AF, the addition of verapamil to class II drugs can prevent immediate recurrence after cardioversion,712 and prophylaxis against subacute recurrence was enhanced when this combination was given for 3 d before and after cardio-version.713,714 Verapamil also reduced AF recurrence when a second cardioversion was performed after early recurrence, whereas at 1 mo the recurrence rate was lower with amiodarone (28%) than with diltiazem (56%) or digoxin (78%). In patients with persistent AF, treatment with verapamil 1 mo before and after direct-current cardioversion.7168.2.6.4. QuinidineA loading dose of quinidine (1200 mg orally 24 h before direct-current cardioversion) significantly reduced the number of shocks and the energy required in patients with persistent AF. Quinidine prevented immediate recurrence in 25 cases, whereas recurrence in defibrillation shold between patients randomized to continue or withdraw the drug.6178.2.6.5. Type Ic Antiarrhythmic AgentsIn-hospital treatment with oral propafenone started 2 d before direct-current cardioversion decreases early recurrence of AF after shock, thus allowing more patients to be discharged from the hospital with sinus rhythm. Compared with placebo, propafenone did not influence either the mean defibrillation threshold or the rate of conversion (shock efficacy 84% vs. 82%, respectively) but suppressed immediate recurrences (within 10 min), and 74% versus 53% of patients were in sinus rhythm after 2 d.522 In patients with persistent AF, pretreatment with intravenous flecainide had no significant effect on the success of direct-current cardioversion.7178.2.6.6. Type III Antiarrhythmic AgentsControlled studies are needed to determine the most effective treatment of immediate and subacute recurrences of AF. 23). Available data suggest that starting pharmacological therapy and establishing therapeutic plasma drug concentrations before direct-current cardioversion to sinus rhythm, patients receiving drugs that prolong the QT interval should be monitored in the hospital for 24 to 48 h to evaluate the effects of heart rate slowing and allow for prompt intervention in the event torsades de pointes develops. In randomized studies of direct-current cardioversion, patients pretreated with ibutilide were more often converted to sinus rhythm than untreated controls, and those in whom cardioversion initially failed could more often be converted when the procedure was repeated after treatment with ibutilide.556,718 Ibutilide was more effective than verapamil in prevention of Thromboembolism in 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)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)For patients with AF of less than 48-h duration associated with hemodynamic instability (angina pectoris, MI, shock, or pulmonary edema), cardioversion should be performed immediately without delay for prior initiation of anticoagulation. (Level of Evidence: C)CLASS IIaDuring the first 48 h after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism. (Level of Evidence: C)CLASS IIaDuring the first 48 h after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism. to cardioversion of AF, it is reasonable to perform TEE in search of thrombus in the LA or LAA. (Level of Evidence: B)2a. For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (eg, initiate by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value until oral anticoagulation has been established with a vitamin K antagonist (eg, warfarin), as evidenced by an INR equal to or greater than 2.0.). (Level of Evidence: B)Thereafter, oral anticoagulation (INR 2.0 to 3.0) is reasonable for a total anticoagulation period of at least 4 wk, as for patients undergoing elective cardioversion. (Level of Evidence: 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)For patients with atrial flutter undergoing cardioversion, anticoagulation can be beneficial according to the recommendations as for patients with AF. (Level of Evidence: C)Randomized studies of antithrombotic therapy are lacking for patients with a for patients with a for patients with a for patient studies of antithrombotic therapy are lacking for patients with a for patient studies of antithrombotic therapy are lacking for patients with a for patient studies of antithrombotic therapy are lacking for patients with a for patient studies of antithrombotic therapy are lacking for patient studies of antithrombotic therapy are anticoagulation (INR 2.0 to 3.0) was given for 3 to 4 wk before and after conversion.54,181,695 It is now common practice to administer anticoagulant drugs when preparing patients without LAA thrombus who do not require anticoagulation, but a subsequent investigation 324 and meta-analysis found this approach to be unreliable. 720If most AF-associated strokes result from the LAA, then restoration and maintenance of atrial contraction should logically reduce thromboembolic risk. LV function can also improve after cardioversion, 721 potentially lowering embolic risk and improving cerebral hemodynamics. 722 There is no evidence, however, that cardioversion of AF to sinus rhythm results in transient mechanical dysfunction of the LA and LAA417 known as "stunning," which can occur after spontaneous, pharmacological,723,724 or electrical724-726 conversion of AF before advised with SEC.417 Recovery of mechanical function may be delayed for several weeks, depending in part on the duration of AF before conversion.191.727.728 This could explain why some patients without demonstrable LA thrombus on TEE before cardioversion subsequently experience thrombos
forms during the clustering of thrombos bolic events. during the first 10 d after cardioversion. 212Patients with AF or atrial flutter in whom LAA thrombus is identified by TEE are at high risk of thromboembolism and should be anticoagulated for at least 3 wk prior to and 4 wk after pharmacological or direct-current cardioversion. In a multicenter study, 1222 patients with either AF persisting longer than 2 d or atrial flutter and previous AF729 were randomized to a TEE-guided or conventional strategy. In the group undergoing TEE, cardioversion was identified, and warfarin 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 approach and 0.50% with the conventional approach) after 8 wk, there were no differences in the proportion of patients achieving successful cardioversion, and the risk of major bleeding did not differ significantly. The clinical benefit of the TEE-guided approach was limited to saving time before cardioversion. Anticoagulation is recommended for 3 wk prior to and 4 wk after cardioversion for patients with AF of unknown duration or with AF for more than 48 h. Although LA thrombus and systemic embolism have been documented in patients with AF of shorter duration, the need for anticoagulation is less clear. When acute AF produces hemodynamic instability in the form of angina pectoris, MI, shock, or pulmonary edema, immediate cardioversion should not be delayed to deliver therapeutic anticoagulation, but intravenous unfractionated heparin or subcutaneous injection of a low-molecular-weight heparin should be initiated before cardioversion by direct-current countershock or intravenous antiarrhythmic medication. Protection against late embolism may require continuation of a nore extended period after the procedure, and the duration of anticoagulation after cardio-version depends both on the likelihood that AF will recur in an individual patient with or without symptoms and on the intrinsic risk of thromboembolism. Late events are probably due to both the development of thrombus as a consequence of atrial stunning and the delayed recovery of atrial contraction after cardioversion. Pooled data from 32 studies of cardio-version of AF or atrial flutter suggest that 98% of clinical thromboembolic events occur within 10 d.212 These data, not yet verified by prospective studies, support administration of an anticoagulant for at least 4 wk after cardioversion, and continuation of anticoagulation for a considerably longer period may be warranted even after apparently successful cardioversion. Stroke or systemic embolism has been reported in patients with atrial flutter undergoing cardioversion of atrial flutter has been performed with a low rate of systemic embolism, particularly when patients are stratified for other risk factors on the basis of clinical and/or TEE features.600,7338.3. Maintenance of Sinus Rhythm (UPDATED)For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated.RECOMMENDATIONSCLASS IBefore initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)CLASS IIaPharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (Level of Evidence: C)CLASS IIaPharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. C)Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (Level of Evidence: C)Outpatient initiation of antiarrhythmic drug therapy. structural heart disease, initiation of propafenone or flecainide 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)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)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)Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement. C)CLASS IIIAntiarrhythmic 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)Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (Level of Evidence: C)8.3.1. Pharmacological Therapy (UPDATED)For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated.8.3.1.1. Goals Of TreatmentWhether paroxysmal or persistent, AF is a chronic disorder, and recurrence at some point is likely in most patients 704,734,735 (see Fig. 13). Many patients eventually need prophylactic antiarrhythmic drug therapy to maintain sinus rhythm, suppress symptoms, improve exercise capacity and hemodynamic function, and prevent tachycardia-induced car- diomyopathy due to AF. Because factors that predispose to recurrent AF (advanced age, HF, hypertension, LA enlargement, and LV dysfunction) are risk factors for thromboembolism, the risk of stroke may not be reduced by correction of the rhythm disturbance. It is not known whether maintenance of sinus rhythm prevents thromboembolism, HF, or death in patients with a history of AF.736,737 Trials in which rate-versus rhythm-control strategies were compared in patients with persistent and paroxysmal AF293,294,296,343,344 found no reduction in death, disabling stroke, hospitalizations, new arrhythmias, or thromboembolic complications in the rhythm-control group.296 Pharmacological maintenance of sinus rhythm may reduce morbidity in patients with HF.501.738 but one observational study demonstrated that serial cardioversion in those with persistent AF did not avoid complications.739 Pharmacological therapy to maintain sinus rhythm is indicated in patients who have troublesome symptoms related to paroxysmal AF or recurrent AF after cardioversion who can tolerate antiarrhythmic drugs and have a good chance of remaining in sinus rhythm over an extended period (eg, young patients without organic heart disease or hypertension, a short duration of AF, and normal LA size).293,740 When antiarrhythmic medication does not result in symptomatic improvement or causes adverse effects, however, it should be abandoned.8.3.1.2. Endpoints in Antiarrhythmic Drug Studies Various antiarrhythmic drugs have been investigated for maintenance of sinus rhythm in patients with AF. The number and quality of studies with each drug are limited; endpoints vary, and few studies meet current standards of good clinical practice. The arrhythmia burden and quality of life have not been assessed consistently. In studies of patients with paroxysmal AF, the time to first recurrence, number of recurrence during follow-up, and combinations of these data have been reported. The proportion of patients in sinus rhythm during follow-up is a less useful endpoint in studies of paroxysmal rather than persistent AF. Most studies of persistent AF. Most studies of recurrences in the first few weeks after cardioversion, 697,713 the median time to first recurrence detected by transtelephonic monitoring may not differ between 2 treatment strategies. Furthermore, because recurrent AF tends to persist, neither the interval between recurrences nor the number of episodes in a given period represents a suitable endpoint unless a serial cardioversion strategy is employed. Given these factors, the appropriate endpoints for evaluation of treatment efficacy in patients with paroxysmal and persistent AF have little in common. This hampers comparative evaluation of treatments aimed at maintenance of sinus rhythm in cohorts therefore do not contribute heavily to these guidelines. The duration of follow-up varied considerably among studies and was generally insufficient to permit meaningful extrapolation to years of treatment failure. In several studies, 594, 598 patients with recurrent AF often chose to continue antiarrhythmic treatment, perhaps because episodes of AF became less frequent, briefer, or less symptomatic. A reduction in arrhythmia burden may therefore constitute therapeutic success for some patients, while to others any recurrence of AF may seem intolerable. Assessment based upon time to recurrence in patients with paroxysmal AF or upon the number of patients with persistent AF who sustain sinus rhythm after cardioversion may overlook potentially valuable treatment strategies. Available studies are heterogeneous in other respects as well. The efficacy of treatment for atrial flutter and AF is usually not reported separately. Underlying heart disease or extracardiac disease is present in 80% of patients with persistent AF, but this is not always described in detail. It is often not clear when patients first experienced AF or whether AF was persistent, and the frequencies of previous AF episodes and cardioversions are not uniformly described. Most controlled trials of antiarrhythmic drugs included few patients at risk of drug-induced HF, proarrhythmia, or conduction disturbances, and this should be kept in mind in applying the recommendations below. The AFFIRM substudy investigators found that with AF recurrence,
if one is willing to cardiovert the rhythm and treat the patient on the same antiarrhythmic drug, about 80% of all patients will be in sinus rhythm by the end of 1 y.5708.3.1.3. Predictors of Recurrent AfMost patients with AF, except those with postoperative or self-limited AF secondary to transient or acute illness, eventually experience recurrence. Risk factors for frequent recurrence of paroxysmal AF (more than 1 episode per month) include female gender and

underlying heart disease.741 In one study of patients with persistent AF, the 4-y arrhythmia-free survival rate was less than 10% after single-shock direct-current cardioversion without prophylactic drug therapy.735 Predictors of recurrences within that interval included hypertension, age over 55 y, and AF duration longer than 3 mo. Serial cardioversions and prophylactic drug therapy resulted in freedom from recurrent AF in approximately 30% of patients,735 and with this approach predictors of recurrent AF include LA enlargement and rheumatic heart disease.8.3.1.4. Future Directions in Catheter-Based Ablation Therapy for Atrial Fibrillation (NEW SECTION)For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated.8.3.2. General Approach to Antiarrhythmic Drug TherapyBefore administering any antiarrhythmic Drug TherapyBefore administering identified and corrected. Most are related to coronary or valvular heart disease, hypertension, or HF. Patients who develop HF in association with alcohol intake should abstain from alcohol consumption. Indefinite antiarrhythmic treatment is seldom prescribed after a first episode, although a period of several weeks may help stabilize sinus rhythmic after cardioversion. Similarly, patients experiencing breakthrough arrhythmics 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, but antiarrhythmic therapy. Selection of an appropriate agent is based first, but antiarrhythmic therapy. flecainide, propafenone, and sotalol are particularly effective. Amiodarone and dofetilide are recommended as alternative therapies. Quinidine, procainamide, and 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 AF. In patients with adrenergically mediated AF, beta blockers represent first-line treatment, followed by sotalol and amiodarone. In patients with adrenergically mediated lone AF, amiodarone represents a less appealing selection. Vagally induced AF can occur by itself, but more typically it is part of the overall patient profile. In patients with nocturnal AF, the possibility of sleep apnea should be considered (see Fig. 15).When treatment with a single antiarrhythmic drug fails, combinations may be tried. Useful combinations include a beta blocker, such as diltiazem, with a class IC agent, such as flecainide or propafenone, is advantageous in some patients. A drug that is initially safe may become proarrhythmic if coronary disease or HF develops or if the patient begins other medication that exerts a proarrhythmic interaction. Thus, the patient should be alerted to the potential significance of such symptoms as syncope, angina, or dyspnea and warned about the use of noncardiac drugs that might prolong the QT interval. A useful source of information on this topic is the Internet site optimum method for monitoring antiarrhythmic drug treatment varies with the agent involved as well as with patient factors. Prospectively acquired data on upper limits of drug-induced prolongation of QRS duration or QT interval are not available. Given recommendations represent the consensus of the writing committee. With class IC drugs, prolongation of the QRS interval should not exceed 50%. Exercise testing may help detect QRS widening that occurs only at rapid heart rates (use-dependent conduction slowing). For class II drugs, with the possible exception of amiodarone, the corrected QT interval in sinus rhythm should be kept below 520 ms. During follow-up, plasma potassium and magnesium levels and renal function should be checked periodically because renal insufficiency leads to drug accumulation and predisposes to proarrhythmia. In individual patients, serial noninvasive assessment of LV function is indicated, especially when clinical HF develops during treatment of AF.8.3.3. Selection of Antiarrhythmic Agents in Patients With Cardiac DiseasesPharmacological management algorithms to maintain sinus rhythm in patients with AF (see Figs. 13, 14, 15, and 16) and applications in specific cardiac disease states are based on available evidence and extrapolated from experience with these agents in other situations.8.3.3.1. Heart FailurePatients with HF are particularly prone to the ventricular proarrhythmic effects of antiarrhythmic effects of antiarrhythmic drugs because of myocardial vulnerability and electrolyte imbalance. Randomized trials have demonstrated the safety of amiodarone and dofetilide (given separately) in patients with HF,501,743 and these are the recommended drugs for maintenance of sinus rhythm in patients with AF in the presence of HF.In a subgroup analysis of data from the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHFSTAT) study,738 amiodarone reduced the incidence of AF over 4 y in patients with HF to 4% compared with 8% with placebo. Conversion to sinus rhythm occurred in 31% of patients on amiodarone versus 8% with placebo and was associated with significantly better survival. The Danish Investigations of Arrhythmias and Mortality on Dofetilide in Heart Failure (DIAMOND-CHF) trial randomized 1518 patients with symptomatic HF. In a substudy of 506 patients with HF and AF or atrial flutter, 501, 588 dofetilide (0.5 mg twice daily initiated in hospital) increased the probability of sinus rhythm after 1 y to 79% compared with 42% with placebo. In the dofetilide group, 44% of patients with AF converted to sinus rhythm after 1 y to 79% compared with 39% in the placebo. In the dofetilide group, 44% of patients with AF converted to sinus rhythm after 1 y to 79% compared with 39% in the placebo. endpoint of all-cause mortality and HF hospitalization was lower in the treated group than with placebo.501,588 Torsades de pointes developed in 25 patients treated with beta blockers and ACE inhibitors and/or angiotensin II receptor antagonists, because these agents help control the heart rate, improve ventricular function, and prolong survival.744-747 In patients with HF or LV dysfunction post-MI, ACE inhibitor therapy reduced the incidence of AF.36,748,749 In a retrospective analysis of patients with LV dysfunction in the SOLVD trials,38 enalapril reduced the incidence of AF by 78% relative to placebo. In the CHARM and Val-HeFT studies, angiotensin II receptor antagonists given in combination with ACE inhibitors alone for prevention of AF. A post hoc analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS II), however, found no impact of bisoprolol on survival or hospitalization for HF in patients with AF.750 In the Carvedilol Post-Infarct Survival Con- trol in Left Ventricular Dysfunction (CAPRICORN)751 and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials,752 AF and atrial flutter were more common in the placebo groups than in patients treated with carvedilol. Retrospective analysis of patients in the U.S. Carvedilol Heart Failure Trial program with AF complicating HF753 suggested that carvedilol and digoxin reduced symptoms, improved ventricular function, and improved ventricular rate control compared with either agent alone.8.3.3.2. Coronary Artery DiseaseIn stable patients with CAD, beta blockers may be considered first, although their use is supported by only 2 studies583,587 and data on efficacy for maintenance of sinus rhythm in patients with persistent AF after cardioversion are not convincing.583 When antiarrhythmic therapy beyond beta blockers is needed for control of AF in survivors of acute MI, several randomized trials have demonstrated that sotalol,755 amiodarone,756,757 dofetilide,758 and azimilide651 have neutral effects on survival. Sotalol has substantial beta-blocking activity and may be the preferred initial anti-arrhythmic agent in patients with AF who have ischemic heart disease, because it is associated with less long-term toxicity than amiodarone. Amiodarone increases the risk of bradyarrhythmia requiring permanent pacemaker implantation in elderly patients with AF who have previously sustained MI759 but may be preferred over sotalol in patients with HF.755-757 Neither flecainide nor propafenone is recommended in these situations, but quinidine, procain-amide, and disopyramide may be considered as third-line choices in patients with coronary disease. The Danish Investigations of Arrhythmias and Mortality on Dofetilide in Myocardial Infarction (DIAMOND-MI) trial758 involved selected post-MI patients in whom the antiarrhythmic benefit of dofetilide balanced the risk of proarrhythmic toxicity, making this a second-line antiarrhythmic toxicity, making this a second-line antiarrhythmic toxicity and more experience is needed before this drug can be recommended even as a second-line agent in such patients.8.3.3.3. Hypertensive Heart DiseaseHypertension is the most prevalent and potentially modifiable independent risk factor for the development of AF. Patients with LVH may face an increased risk of torsades de pointes related to early ventricular after-depolarizations.742,762,763 Thus, class IC agents as first-line therapy. In the absence of ischemia or LVH, propafenone or flecainide is a reasonable choice. Proarrhythmic agents as first-line therapy. predict this response to another, and patients with LVH who develop torsades de pointes during treatment with a class II agent may tolerate a class II agent may tolerate a class II agent. Amiodarone prolongs the QT interval but carries a very low risk of ventricular proarrhythmia. Its extracardiac toxicity relegates it to second-line therapy in these individuals, but it becomes a first-line agent in the face of substantial LVH. When amiodarone and sotalol either fail or are inappropriate, disopyramide, quinidine, or procainamide represents a reasonable alternative. Beta blockers may be the first line of treatment to maintain sinus rhythm in patients with MI, HF, and hypertension. Compared with patients with lone AF, those with hypertension are more likely to maintain sinus rhythm after cardio-version of persistent AF when treated with a lower incidence of AF compared with a lower incidence of AF compared with a lower incidence of AF compared with a beta blocker.764 Drugs modulating the renin-angiotensin system reduce structural cardiac changes,765 and ACE inhibition was associated with a lower incidence of AF compared with a lower during 4.5 y of follow-up in a retrospective, longitudinal cohort study from a database of 8 million patients in a managed care setting.42 In patients at increased risk of cardiovascular events, therapy with either the ACE inhibitor ramipril766-768 or angiotensin receptor antagonist losartan769,770 lowered the risk of stroke. A similar benefit has been reported with perindopril in a subset of patients with AF treated for prevention of recurrent stroke.771 New-onset AF and stroke were significantly reduced by losartan compared with atenolol in hypertensive patients with AF than those with sinus rhythm for the primary composite endpoint (cardiovascular mortality, stroke, and MI) and for cardiovascular mortality alone.772 Presumably, the beneficial effects of beta blockers and drugs modulating the renin-angiotensin system are at least partly related to lower blood pressure.8.3.4. Nonpharmacological Therapy for Atrial FibrillationThe inconsistent efficacy and potential toxicity of antiarrhythmic drug therapies have stimulated exploration of a wide spectrum of alternative nonpharmacological therapies for the prevention and control of AF.8.3.4.1. Surgical AblationOver the past 25 y, surgery has contributed to understanding of both the anatomy and electrophysiology of commonly encountered arrhythmias, including the WPW syndrome, AV nodal reentry, ventricular tachycardia. A decade of research in the 1980s demonstrated the critical elements necessary to cure AF surgically, including techniques that entirely eliminate macroreentrant circuits in the atria while preserving sinus node and atrial transport functions. The surgical approach was based on the hypothesis that reentry is the predominant mechanism responsible for the development and maintenance of AF,773 leading to the concept that atrial incisions at critical locations would create barriers to conduction and prevent sustained AF. The procedure development that atrial incisions at critical locations would create barriers to conduction and prevent sustained AF. 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.774Since 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.775 Success rates of around 95% over 15 y of follow-up have been reported in patients undergoing mitral valve surgery.776 Other studies suggest success rates around 70%.777 Atrial transport function is maintained and, when combined with amputation or obliteration of the LAA, postoperative thromboembolic events are substantially reduced. Risks include death (less than 1% when performed as an isolated procedure), the need for permanent pacing (with right-sided lesions), recurrent bleeding requiring reoperation, impaired atrial transport function, delayed atrial arrhythmias (especially atrial flutter), and atrioesophageal fistula. Variations of the maze procedure have been investigated at several centers to determine the lesion sets necessary for success. Studies in patients with persistent AF have demonstrated the importance of complete lesions that extend to the mitral valve annulus; electrical isolation of the PV alone is associated with a lower success rate. Bipolar radiofrequency,778 cryoablation, and microwave energy have been used as alternatives to the "cut-and-sew" technique. In one study, maintenance of sinus rhythm following the maze procedure in patients with AF was associated with improvement in some aspects of quality of life.348Despite its high success rate, the maze operation has not been widely adopted other than for patients undergoing cardiac surgery because of the need for cardiopulmonary bypass. A wide variety of less invasive modifications are under investigation, including thoracoscopic and catheter-based epicardial techniques.777 If the efficacy of these adaptations approaches that of the endocardial maze procedure and they can be performed safely, they may become acceptable alternatives for a larger proportion of patients with AF.8.3.4.2. Catheter AblationEarly radiofrequency catheter ablation techniques emulated the surgical maze procedure by introducing linear scars in the atrial endocardium.779 While the success rate was approximately 40% to 50%, a relatively high complication rate diminished enthusiasm for this approach.105 The observation that potentials arising in or near the ostia of the PV often provoked AF, and demonstration that potentials arising in or near the ostia of the PV often provoked AF. based ablation.105 Initially, areas of automaticity within the PV were targeted, and in a series of 45 patients with paroxysmal AF, 62% became free of symptomatic AF over a 6-mo follow-up.780 Subsequent research has demonstrated that potentials may arise in multiple regions of the RA and LA, including the LA posterior wall, superior vena cava, vein of Marshall, crista terminalis, interatrial septum, and coronary sinus, 109 and modification of the procedures has incorporated linear LA ablation, mitral isthmus ablation, or both for selected patients. 781The technique of ablation has continued to evolve from early attempts to target individual ectopic foci within the PV to circumferential electrical isolation without antiarrhythmic medications during a mean follow-up of 4 mo, but 29 patients required a second procedure to reach this goal. However, postablation AF may occur transiently in the first 2 mo.782 Advances involving isolation of the PV at the antrum using a circular mapping catheter, guided by intracardiac echocardiography, have reportedly yielded approximately 80% freedom of recurrent AF or atrial flutter after the first 2 mo in patients with paroxysmal AF,783 but success rates were lower in patients with cardiac dysfunction.784 Still another approach785,786 uses a nonfluoroscopic guidance system and radiofrequency energy delivered circumferentially outside the ostia of the PV. In a series of 26 patients, 85% were free of recurrent AF during a mean follow-up of 9 mo, including 62% taking no antiarrhythmic medications. The accumulated experience involves nearly 4000 patients, 786 with approximately 90% success in cases of paroxysmal AF and 80% in cases of paroxysmal AF, 784, 787, 788 Another anatomic approach to radiofrequency catheter ablation targets complex fractionated electrograms, 789 with 91% efficacy reported at 1 y Restoration of sinus rhythm after catheter ablation.790 While that study lacked a control group of patients with HF, in another study catheter ablation of AF was associated with reduced mortality and morbidity due to HF and thromboembolism.791In selected patients, radiofrequency catheter ablation of the AV node and pacemaker insertion decreased symptoms of AF and improved quality-of-life scores compared with medication therapy.363,387,388,792-794 Baseline quality-of-life scores are generally lower for patients with AF or atrial flutter than for those undergoing ablation for other arrhythmias.795 A meta-analysis of 10 studies involved selected patients who remained in AF, the consistent improvement suggests that quality of life was impaired before intervention. Two studies have described improvement in symptoms and quality of life after radiofrequency catheter ablation of atrial flutter.796,797 New studies comparing strict versus lenient rate control are under way to investigate this issue further. Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrate 1 y or more free from recurrent AF in most (albeit carefully selected) patients. 798–800 It is important to bear in mind, however, that AF can recur without symptoms and be unrecognized by the patient or the physician. Therefore, it remains uncertain whether apparent cures represent elimination of AF or transformation into an asymptomatic form of paroxysmal AF. The distinction has important implications for the duration into an asymptomatic form of paroxysmal AF. available about the late success of ablation in patients with HF and other advanced structural heart disease, who may be less likely to enjoy freedom from AF recurrence.8.3.4.2.1. Complications of Catheter-Based Ablation.Complications of Catheter-Based Ablation.Complications of Catheter ablation include the adverse events associated with any cardiac catheterization procedure in addition to those specific to ablation of AF. Major complications have been reported in about 6% of procedures and include PV stenosis, thromboembolism, atrioesophageal fistula, and LA flutter.788 The initial ablation approach targeting PV ectopy was associated with an unacceptably high rate of PV stenosis, 780,801 but the incidence has dramatically decreased as a result of changes in technique. Current approaches avoid delivering radiofrequency energy within the PV and instead target areas outside the veins to isolate the ostia from the remainder of the LA conducting tissue. Use of intracardiac echocardiographically detected microbubble formation to titrate radiofrequency energy has also been reported to reduce the incidence of PV stenosis.783Embolic stroke is among the most serious complication reduces the risk of thrombus formation during ablation.802 A comparison of 2 heparin dosing regimens found LA thrombus in 11.2% of patients when the activated clotting time (ACT) was 250 to 300 s compared with 2.8% when the ACT was kept greater than 300 s. Based on these observations, it seems likely that more aggressive anticoagulation may reduce the incidence of thromboembolism associated with catheter-based ablation of AF.Atrioesophageal fistula has been reported with both the circumferential Pappone approach803,804 and the Haissaguerre PV ablation techniques804 but is relatively rare. This complication may be more likely to occur when extensive ablative lesions are applied to the posterior LA wall, increasing the risk of atrial perforation. The typical manifestations include sudden neurological symptoms or endocarditis, and the outcome in most cases is, unfortunately, fatal.Depending on the ablation approach, LA flutter may develop during treatment of AF,805 and this is typically related to scars created during catheter ablation. An incomplete line of ablation is an important predictor of postprocedural LA flutter, and extending the ablation line to the mitral annulus may reduce the frequency of this complication. In most cases, LA flutter is amenable to further ablation.8068.3.4.2.2. Future Directions in Catheter-Based Ablation Therapy for Atrial Fibrillation.Catheter-Based 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 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, 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 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 of patients with AF and provide a valuable for management of patients with AF and provide a valuable foundation for future practice guidelines.8.3.4.3. Suppression of Atrial Fibrillation Through PacingSeveral studies have examined the role of atrial pacing, either in the RA alone or in more than one atria location, to prevent recurrent paroxysmal AF. In patients with symptomatic bradycardia, the risk of AF is lower with atrial than with ventricular pacing.807 In patients with sinus node dysfunction, data from several randomized trials support atrial or dual-chamber rather than ventricular pacing for prevention of AF.808-811 The mechanisms by which atrial pacing prevents AF in patients with sinus node dysfunction include prevention of bradycardia-induced dispersion of repolarization and suppression of atrial premature beats. Atrial or dual-chamber pacing also maintains AV synchrony, preventing retrograde ventriculoatrial conduction that can cause valvular regurgitation and stretch-induced changes in atrial electrophysiology. When ventricular pacing with dual-chamber devices is unavoidable because of the AV conduction system, the evidence is less clear that atrial-based pacing is superior. While atrial pacing is effective in preventing development of AF in patients with symptomatic bradycardia, its utility as a treatment for paroxysmal AF in patients without conventional indications for pacing has not been proved.812 In the Atrial Pacing Peri-Ablation for the Prevention of AF (PA3) study, patients under consideration for AV junction ablation received dual-chamber pacemakers and were randomized to atrial pacing versus no pacing. There was no difference in time to first occurrence of AF or total AF burden.812 In a continuation of this study comparing atrial pacing with AV synchronous pacing, patients were randomized to DDDR versus VDD node pacing after ablation of the AV junction. Once again, there was no difference in time to first recurrence of AF or AF burden, and 42% of the patients lapsed into permanent AF by the end of 1 y.813It has been suggested that the incidence of AF may be lower with atrial septal sites results in preferential conduction to the LA via Bachmann's bundle. Pacing from this site shortens P-wave duration and interatrial conduction time. Clinical trials of pacing in the interatrial septum to prevent episodes of paroxysmal AF and the incidence of persistent AF at 1 y compared with RA appendage pacing,815,816 a larger trial showed no effect on AF burden despite reduction in symptomatic AF.817Both bi-atrial (RA appendage and coronary sinus) and dual-site (usually RA appendage and coronary sinus) and dual-site (usually RA appendage and coronary sinus) and dual-site (usually RA appendage and either the proximal or distal coronary sinus) and dual-site (usually RA appendage and coronary biatrial pacing to prevent recurrent AF found no benefit compared with conventional RA pacing, 818 and a larger trial revealed no benefit from dual-site compared with single-site pacing, except in certain subgroups. 819 The greater complexity and more extensive appearatus required have limited the appeal of dual-site pacing. been developed to increase the percentage of atrial pacing time to suppress atrial premature beats, prevent atrial pauses, and decrease atrial cycle length variation in the hope of preventing AF. Prospective studies of devices that incorporate these algorithms have yielded mixed results. In one large trial, these pacemaker algorithms decreased symptomatic AF burden, but the absolute difference was small, and there was no gain in terms of quality of life, mean number of AF episodes, hospitalizations, or mean duration of AF detected by the pacemaker's automatic mode-switching algorithm.820 Other trials have failed to show any benefit of atrial pacing in preventing AF.817,821In addition to pacing algorithms to prevent AF, some devices are also capable of pacing for termination of AF. While efficacy has been little demonstrated effect on total AF burden.821,822In summary, atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, but the value of pacing as a primary therapy for prevention of AF,354 delivery of synchronous shocks between the high RA and coronary sinus effectively terminated episodes of AF. A clinical trial of a low-energy transvenous atrial cardioversion, but the energy required in patients with persistent AF was relatively high (mean 3.5 J).355 Intense basic and clinical research to find more tolerable shock waveforms led to evaluation of an implantable device capable of both atrial sensing and ventricular sensing and pacing in 290 patients with mean LV ejection fraction greater than 50% who had not responded satisfactorily to therapy with 4 antiarrhythmic drugs.355 In total, 614 episodes of AF were treated with 1497 shocks (mean 2.4 shocks per episode), and the rate of conversion to sinus rhythm was 93%. As spontaneous episodes were treated quickly, the interval between episodes of AF lengthened. Several available devices combining both atrial cardioversion and ventricular defibrillation capabilities with dual-chamber sensing and pacing have been designed to treat both atrial and ventricular arrhythmias by pacing before delivering low- or high-energy shocks. A number of other techniques to terminate AF by pacing are also under investigation, but indications may be limited to atrial flutter. Because these units accurately record the occurrence of AF, however, they provide valuable representation of AF control. An important limitation of atrial defibrillators, unrelated to efficacy, is that most patients find discharge energies over 1 J uncomfortable without sedation requiring a medical setting, and the mean cardioversion threshold is approximately 3 J, making such devices in their current form unacceptable for wide clinical use. Optimal devices would use atrial pacing to maintain sinus rhythm after cardioversion, and some patients require additional therapy to avoid frequent paroxysms of AF. Candidates for atrial cardioversion, and some patients require additional therapy to avoid frequent paroxysms of AF. limited utility, except for patients with LV dysfunction who are candidates for implantable ventricular defibrillators.8.4.1. Postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral beta blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment with an oral blocker to prevent postoperative AFRECOMMENDATIONSCLASS IUnless contraindicated, treatment of Evidence: A)Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF. (Level of Evidence: B)CLASS IIaPreoperative administration of amiodarone reduces the incidence of AF in patients at high risk for postoperative AF. (Level of Evidence: A)It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide or direct-current cardioversion in patients. (Level of Evidence: B)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)It is reasonable to administer antithrombotic medication in patients who develop AF. administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. (Level of Evidence: B)Although AF may occur after noncardiac surgery, the incidence of atrial arrhythmias including AF after open-heart surgery is between 20% and 50%,823-825 depending on definitions and methods of detection. The incidence of postoperative AF is increasing, perhaps more because of the age of surgical patients than because of technical factors, and this is associated with increased morbidity and costs.8.4.1.1. Clinical and Pathophysiological CorrelatesPostoperative AF usually occurs within 5 d of open-heart surgery, with a peak incidence on the second day. A number of studies have examined the predictors of AF, cost impact, length of hospital stay, and the effects of various prophylactic interventions aimed at reducing the incidence of AF,824,826-830 but many of these reflect earlier models of patient management. In an observational study of 4657 patients undergoing coronary artery bypass graft (CABG) surgery at 70 centers between 1996 and 2000, predictors of AF included age, a history of AF, COPD, valvular heart disease, atrial enlargement, perioperative HF, and withdrawal of either beta blocker or ACE inhibitor medications before or after surgery831 (Table 24). Many patients have none of these factors, however, and it is likely that the greater collagen content of the atria in older patients or other factors related to the biology of aging are responsible825 for the greater propensity of elderly patients to develop AF after cardiac surgery832 (Table 24). Other contributing factors are pericarditis826 and increased sympathetic tone. In a review of 8051 consecutive patients without previously documented AF (mean 64 y, 67% males) undergoing cardiac surgery (84% involving CABG only) between 1994 and 2004, there was a strong, independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there was a strong independent association between 1994 and 2004, there w of those over age 85 y, compared with 6.2% of patients younger than 40 y. Among the extremely obese, the relative risk of postoperative AF was 2.39. "Off-pump" CABG was associated with 39% lower likelihood of developing AF than conventional on-pump surgery, and the risk of AF correlated with the duration of cardiopulmonary bypass.833 The arrhythmia is usually self-correcting, and sinus rhythm resumes in more than 90% of patients by 6 to 8 wk after surgery,832 a rate of spontaneous resolution higher than for other forms of AF. Patients with postoperative AF have a higher inpatient mortality than patients without this arrhythmia (4.7% vs. 2.1%) and longer hospital stay (median difference 2 d).831 In another study, postoperative AF was an independent predictor of long-term mortality (adjusted odds ratio [OR] 1.5, P less than 0.001 in retrospective cohort, and OR 3.4, P=0.0018 in a case-control analysis) over 4 to 5 y.834Table 24. Multivariate Predictors of Postoperative Atrial Arrhythmias in Patients Undergoing Myocardial Revascularization SurgeryAdvanced ageMale genderDigoxinPeripheral arterial diseaseChronic lung diseaseChronic lung diseaseLeft atrial enlargementPrevious cardiac surgeryDiscontinuation of Postoperative AfA meta-analysis of 13 randomized trials of prophylactic antiarrhythmic therapy involving 1783 patients undergoing cardiac surgery in which effects on hospital length of stay were less concordant and amounted to a 1.0 plus or minus 0.2 d overall decrease in length of hospital stay (P less than 0.001).835 A systematic Cochrane database review found 58 studies with a total of 8565 participants in which interventions included amiodarone, beta blockers, solatol, and pacing. By meta-analysis, the effect size for prevention of stroke by prophylactic treatment for AF was not statistically significant, nor was the effect on length or cost of hospital stay. Beta blockers had the greatest magnitude of effect across 28 trials (4074 patients).836 In a meta-analysis of 24 trials825 limited to patients with ejection fraction greater than 30% undergoing CABG, prophylactic administration of beta-blocker medication protected against supraventricular tachycardia (OR 0.28, 95% CI 0.21 to 0.36). In a meta-analysis of 27 trials including 3840 patients, sotalol (80 or 120 mg twice daily) was more effective in reducing postoperative AF than either other beta-blocker medication or placebo, 829 but the results were not confirmed in another study, 491 in which the difference between sotalol and beta-blocker treatment was small. When the prophylactic value of amiodarone, 600 mg per day, initiated at least 7 d preoperatively, was evaluated in 124 patients undergoing cardiac surgery, the incidence of AF was 25% in the treated group compared with 53% in patients randomized to placebo (P=0.003).837 This approach is impractical unless patients are identified and treatment started at least 1 wk before surgery. The Amiodarone Reduction in Coronary Heart (ARCH) trial involving 300 patients found that postoperative intravenous administration of amiodarone (1 q daily for 2 d) reduced the incidence of postoperative AF from 47% to 35% compared with placebo (P=0.01). The higher overall incidence of postoperative AF and less pronounced prophylactic effect than in other studies may have been partly related to less-frequent use of beta blockers.838 More convincing evidence of the efficacy of amiodarone for the Prevention of Arrhythmias that Begin Early after Revascularization, Valve Replacement, or Repair (PAPABEAR) trial, in which a 13-d perioperative course of oral amiodarone (10 mg/kg daily beginning 6 d before and continuing for 6 d after surgery) halved the incidence of postoperative atrial tachyarrhythmias, including AF patients undergoing CABG, valve replacement, or valve repair surgery with or without CABG surgery.839 Although efficacy was evident whether or not beta-blocker therapy withdrawal of beta blockers from more patients in the placebo group may have exaggerated the apparent effect of amiodarone.840Pretreatment with either digoxin or verapamil does not reliably prevent postoperative AF.825,841,842 Results with procainamide have been inconsistent, and this drug is not widely used for prevention of postoperative AF.843 One report suggested that n-3 polyunsaturated fatty acids may be effective for prevention of AF in patients undergoing CABG surgery.844There is limited evidence that single-chamber and biatrial overdrive pacing prevents postoperative biatrial pacing significantly reduced the incidence of AF in the biatrial pacing group by 12.5% compared with the other 3 groups (36% LA pacing, 33% RA pacing, and 42% without pacing; P

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