IV ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is a supraventricular tachyarrhythmia defined by rapid, irregular atrial activation. This disordered atrial activation results in loss of coordinated atrial contraction; irregular electrical input to the atrioventricular (AV) node typically leads to sporadic ventricular contractions. On an electrocardiogram, AF is characterized by the absence of visible discrete P waves, the presence of irregular fibrillatory waves, or both, and an irregularly irregular ventricular response [*see Figure 1*].

AF may occur by itself or with other arrhythmias, notably, atrial flutter. Atrial flutter is more organized than AF, involving regular atrial activation that often produces a characteristic sawtooth pattern on ECG. Cardiac rhythm may alternate between AF and atrial flutter, AF may trigger atrial flutter, or atrial flutter may degenerate into AF.

Classification

Numerous classification schemes have been used to characterize AF patients, and the lack of a consistent classification scheme across studies has led to difficulties in comparison of analyses and an inability to extrapolate results to all patients. Consequently, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC), in collaboration with the North American Society of Pacing and Electrophysiology, have established guidelines for the classification of AF.[1] The ACC/AHA/ESC guidelines include the following categories:

- Recurrent—AF occurring in a patient who has experienced an episode of AF in the past.
- Lone—AF occurring in a patient younger than 60 years who has no clinical or echocardiographic evidence of cardiopulmonary disease.
- Valvular or nonvalvular—Valvular AF is AF that occurs in a patient who has evidence or history of rheumatic mitral valve disease or who has a prosthetic heart valve; all other forms of AF are classified as nonvalvular.
- Paroxysmal—AF that typically lasts 7 days or less and that converts spontaneously to sinus rhythm.
- Persistent—AF that typically lasts longer than 7 days or requires pharmacologic or direct current (DC) cardioversion.
- Permanent—AF that is refractory to cardioversion or that has persisted for longer than 1 year.

Paroxysmal, persistent, and permanent AF categories do not apply to episodes of AF lasting 30 seconds or less or to episodes precipitated by a reversible medical condition. Reversible conditions include acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, and acute pulmonary disease.

Epidemiology

AF is the most common sustained arrhythmia, currently affecting more than 2.2 million persons in the United States.[2] The incidence is approximately 0.1% per year for the entire population; however, the incidence of AF increases steadily with age. As a result, one out of 11 Americans older than 80 years has AF.[3-5]

AF is associated with significant morbidity and mortality. The annual incidence of ischemic stroke in patients with AF is 5%, which is two to seven times higher than the incidence in the general population. In addition, the mortality in patients with AF is approximately twice that of patients without AF.[3,6,7] AF frequently leads to reduced functional capacity, dyspnea, palpitations, fatigue, tachycardia-induced cardiomyopathy, heart failure, and angina, significantly impairing quality of life.[8]

Finally, AF results in tremendous health care expenditures. There are more than 370,000 hospital admissions for AF annually.[9] After the first diagnosis of AF, hospitalization costs are typically 35% higher for patients with AF than for age-matched control subjects.[10]

Pathophysiology

Central to the pathophysiology of AF are two factors: the electrical trigger that initiates the arrhythmia and the abnormal myocardial substrate that allows AF to be maintained. A spectrum of triggers is thought to initiate AF, ranging from premature atrial contractions to atrial tachycardias; ultimately, AF may be self triggering.[11-13] Ectopic atrial foci, frequently located in the pulmonary veins, have been shown to trigger AF.

For AF to persist, the atrial tissue must be primed to allow the propagation of multiple wavelets of electrical depolarization throughout the atria.[14] If a wavelet encounters refractory tissue, the wavelet can extinguish, divide into additional wavelets, or change direction. If the underlying atrial substrate leads to the extinction of the wavelets, then AF will not persist. In contrast, if the underlying atrial substrate promotes the generation of additional wavelets or the maintenance of the existing wavelets, then AF will continue. Fibrosis, hypertrophy, and fatty infiltration of atrial tissue likely allow for abnormal atrial electrical conduction and the maintenance of AF wavelets.

Diagnosis

clinical manifestations

AF can result in a wide variety of signs and symptoms. Some patients are asymptomatic, although they may have an irregularly irregular pulse. Other patients experience strokes, palpitations, fatigue, dyspnea, reduced exercise capacity, heart failure, angina, presyncope, or syncope. Additional complications include

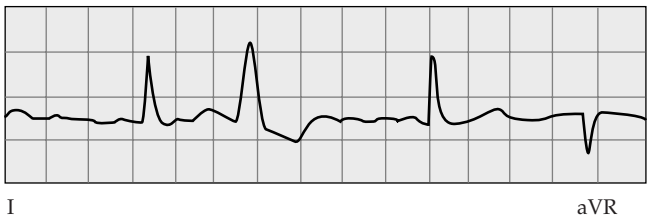

Figure 1 **An electrocardiographic tracing shows characteristic features of atrial fibrillation, with absent P waves, irregular fibrillatory waves, and an irregularly irregular ventricular response.**

Table 1 Initial Clinical Evaluation of Atrial Fibrillation[10]

Evaluation	*Features to Assess*
History and physical examination	Presence, frequency, onset, duration, termination, exacerbating and alleviating factors of AF; date of AF onset; AF classification; associated symptoms; reversible and irreversible contributing conditions; thromboembolic and hemorrhagic risk factors; response to pharmacologic or mechanical interventions
Laboratory studies	Thyroid function,* serum electrolytes, hemoglobin or hematocrit
Chest radiography	Lung parenchyma for intrinsic lung disease; abnormal pulmonary vasculature for pulmonary hypertension; cardiac size and shape for heart failure and pericardial disease
ECG	AF verification; P wave morphology for atrial flutter; preexcitation; atrial arrhythmias besides AF, as possible AF triggers; LVH, for hypertension and hypertrophic cardiomyopathy; bundle branch block and previous MI as markers for CAD, left ventricular dysfunction, and conduction system disease; RR, QRS, and QT intervals to guide antiarrhythmic drug therapy
Transthoracic echocardiography	Left and right atrial size and function; left ventricular size, function, and hypertrophy; valvular heart disease, including rheumatic heart disease; right ventricular systolic pressure for pulmonary hypertension; left atrial thrombus; spontaneous echocardiographic contrast (low sensitivity); pericardial disease; aortic plaque (low sensitivity)

*Reassessment of thyroid function should be considered if ventricular rate becomes difficult to control or atrial fibrillation recurs unexpectedly after conversion to sinus rhythm.
AF—atrial fibrillation CAD—coronary artery disease ECG—electrocardiogram LVH—left ventricular hypertrophy MI—myocardial infarction

thromboembolism and tachycardia-induced cardiomyopathy.[15] The effect of AF on the patient's quality of life is often a critical component that guides decisions regarding AF management.

CLINICAL EVALUATION

The initial evaluation of a patient with AF focuses on the following tasks: (1) confirming the diagnosis of AF, (2) classifying the type of AF, (3) identifying factors (both reversible and irreversible) that contribute to or cause AF, (4) establishing the risk of thromboembolism and additional adverse outcomes, and (5) defining the most effective treatment strategy. In taking the history, the clinician should try to determine whether this is the first episode of AF. If more than one episode of AF has occurred, the AF is defined as recurrent. If no reversible condition is detected in recurrent AF, the clinician may be able to classify the AF as paroxysmal, persistent, or permanent [*see* Classification, *above*].

LABORATORY STUDIES

The standard blood tests that are recommended by the ACC/AHA/ESC are thyroid function tests and measurement of serum electrolytes and hemoglobin or hematocrit. Other recommended laboratory studies include chest radiography, ECG, and transthoracic echocardiography [*see Table 1*]. Additional tests that may be indicated in specific situations are event and Holter monitoring, exercise testing, transesophageal echocardiography (TEE), and electrophysiologic study (EPS).

Event and Holter Monitors

Event monitors are of particular use for documenting infrequent symptomatic episodes in patients in whom AF has not been confirmed previously. In addition to their diagnostic utility for documenting AF, Holter monitors may be used for therapeutic follow-up to evaluate rate control.[16]

Exercise Testing

Exercise testing can confirm the presence of ischemic heart disease and may unmask exercise-mediated AF. In addition, exercise testing can be used to explore the safety of using specific antiarrhythmic medications and to assess rate control.

Transesophageal Echocardiography

TEE is of greatest use in establishing the risk for embolic stroke, most notably in association with cardioversion to sinus rhythm. Risk factors for cardiogenic embolism that are best identified with TEE include the following: left atrial and left atrial appendage thrombus, left atrial and left atrial appendage spontaneous echo contrast (smoke), left atrial appendage flow velocity, and aortic plaque.[17]

Electrophysiologic Study

EPS can define specific forms of AF that are amenable to catheter-based intervention (i.e., radiofrequency ablation). In addition, EPS allows for assessment of the underlying conduction system to determine the etiology of wide-complex tachycardias, whether supraventricular or ventricular in origin.

Management

Treatment of AF includes either restoration and maintenance of sinus rhythm or control of ventricular rate if AF is persistent or if future paroxysmal events are likely to occur. In ad-

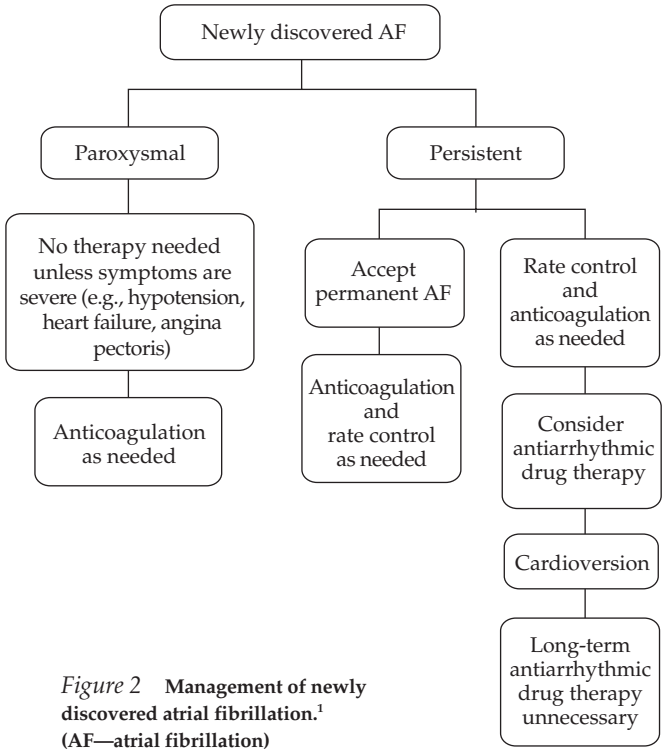

Figure 2 **Management of newly discovered atrial fibrillation.[1] (AF—atrial fibrillation)**

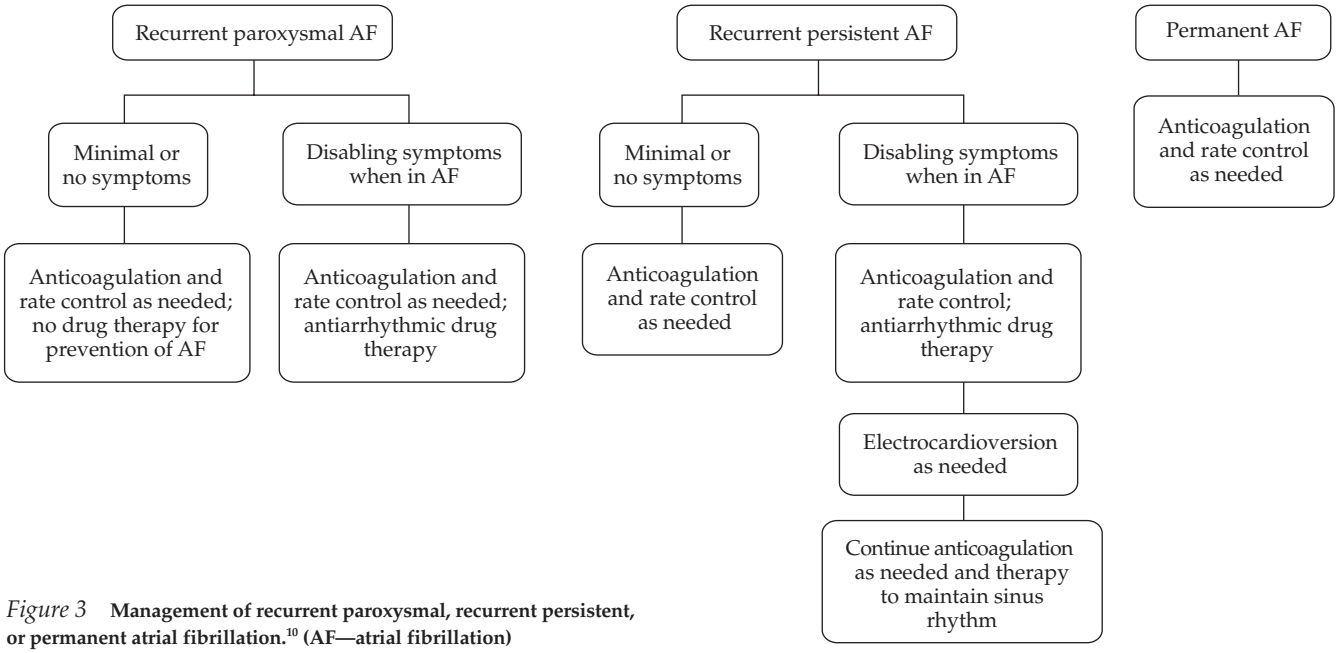

Figure 3 **Management of recurrent paroxysmal, recurrent persistent, or permanent atrial fibrillation.[10] (AF—atrial fibrillation)**

dition, antithrombotics are used to reduce embolic risk [*see Figures 2 through 4*].[10] Treatment decisions involve a synthesis of research results with the characteristics of the individual patient.

Several trials have compared restoration of sinus rhythm with control of ventricular rate in patients with AF. Outcomes evaluated have included overall mortality, stroke, symptoms, and quality of life. Contrary to the expectations of many experts, maintenance of sinus rhythm provided no survival advantage and possibly a higher mortality when compared with ventricular rate control.[18,19] Maintenance of sinus rhythm frequently requires the use of antiarrhythmic medications that may precipitate ventricular arrhythmias, bradycardia, and depression of left ventricular function. It was theorized that maintenance of sinus rhythm would reduce rates of thromboembolism and the need for anticoagulation; however, trial results demonstrated no significant reduction in thromboembolic risk. Peak exercise capacity may improve with maintenance of sinus rhythm, but both treatment strategies result in a similar degree of perceived symptomatic impairment.[8,20,21]

Nevertheless, ventricular rate control frequently is not feasible because of the complications that patients experience while in AF. Clinical scenarios in which AF often is not tolerated include unstable angina, acute myocardial infarction, heart failure, and pulmonary edema. In addition, patients in whom atrial contraction provides a significant proportion of ventricular filling because of impaired ventricular relaxation often need to be maintained in sinus rhythm.

RESTORATION AND MAINTENANCE OF SINUS RHYTHM

Sinus rhythm can be restored with medication, electrical shocks, or a combination of both. Electrical shocks typically are more effective than medication for cardioversion and pose a lower risk of life-threatening ventricular arrhythmias. However, shocks require conscious sedation. In a proportion of patients refractory to medication or electrical shocks, the combination of both therapies results in return of sinus rhythm.

Pharmacologic Cardioversion

Antiarrhythmic medications typically alter the conduction properties of both diseased and normal atrial tissue, suppressing AF triggers or inhibiting the propagation of AF electrical wavelets. Although pharmacologic cardioversion might seem simpler than electrical cardioversion, it has a lower success rate and it poses a risk of life-threatening arrhythmias; the latter risk often precludes use of this strategy. The efficacy of medications for cardioversion of AF typically declines as the duration of AF increases.[22]

A number of medications can be used for cardioversion or for maintenance of sinus rhythm [*see Tables 2 and 3*]. Some medications can be used for both purposes, but others should be used for cardioversion only or for maintenance of sinus rhythm only.

Medication selection for pharmacologic cardioversion must be based on individual patient characteristics. Amiodarone, dofetilide, and ibutilide (agents with potassium channel blocking effects) can be given safely to patients with heart failure or reduced left ventricular systolic function. In contrast, flecainide and propafenone may exacerbate heart failure and should be avoided in such patients. Dofetilide and ibutilide have higher success rates for conversion of atrial flutter than of AF, whereas flecainide and propafenone have higher success rates with conversion of AF than of atrial flutter. Flecainide, propafenone, disopyramide, procainamide, and quinidine also may increase ventricular rate response, especially if patients convert from AF to atrial flutter. Before receiving one of these medications, the patient should be pretreated with an AV nodal blocking agent (typically, diltiazem or verapamil, or possibly digoxin).

Disopyramide, procainamide, and quinidine have either limited efficacy for cardioversion of AF or are associated with significant adverse effects that preclude their use except in rare circumstances. Sotalol effectively maintains sinus rhythm and controls ventricular rate in patients who have undergone cardioconversion from AF, but it has not been shown to effectively convert AF to sinus rhythm. Similarly, beta blockers, verapamil, diltiazem, and digoxin are effective for control of ven-

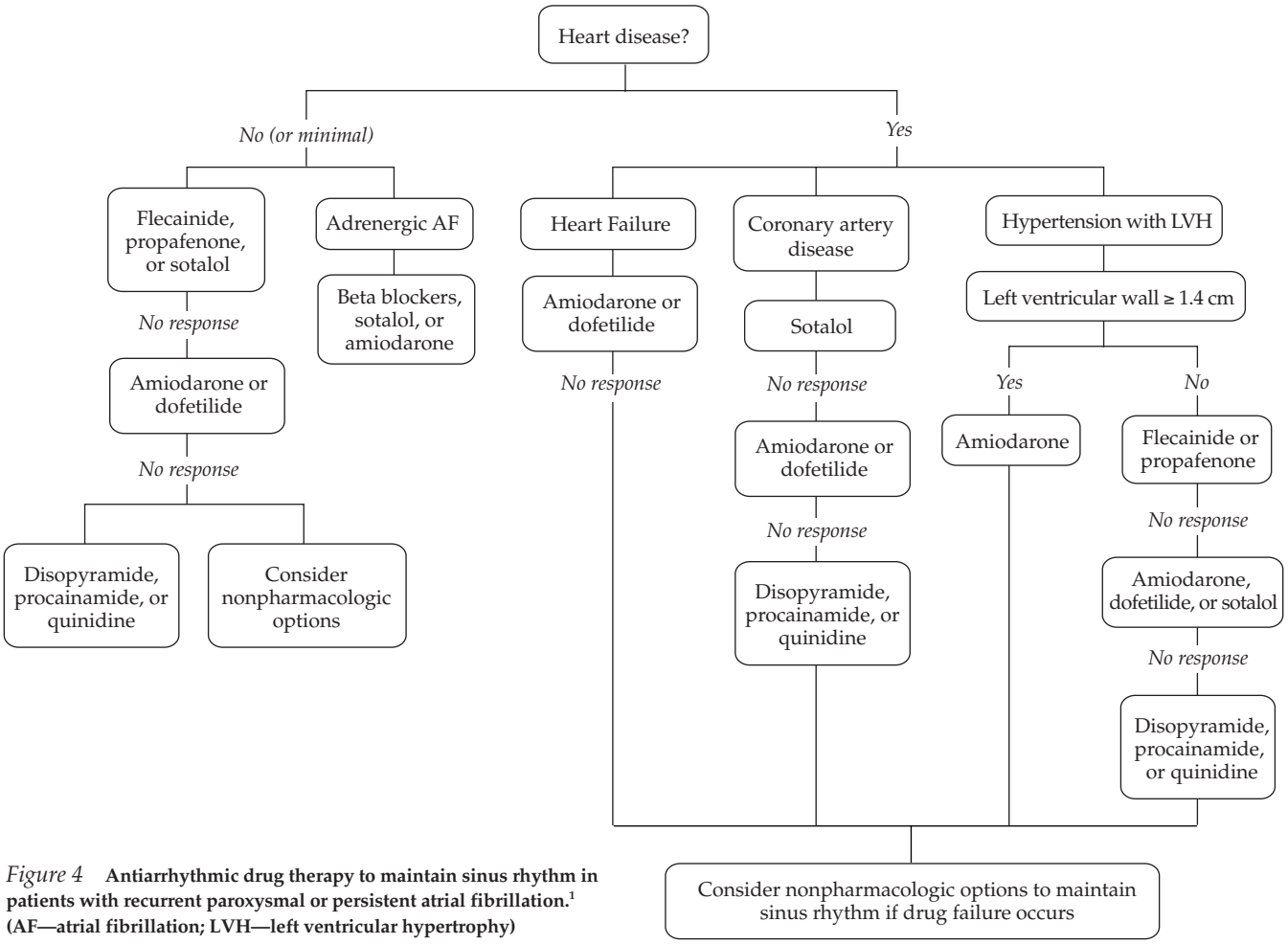

Figure 4 **Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation.[1] (AF—atrial fibrillation; LVH—left ventricular hypertrophy)**

tricular rate in patients with AF, but these medications have little role in AF cardioversion.

Electrical Cardioversion

DC cardioversion is the most effective mechanism for achieving sinus rhythm, with success rates of approximately 70% to 90%.[23,24] DC cardioversion has an even greater rate of success with atrial flutter, approximating 95%.[25] The efficacy of DC cardioversion can be optimized by enhancing delivery of energy to the atrial myocardium. This is achieved through a number of maneuvers:

- Electrode paddle positioning. Anteroposterior positioning is more effective than anterolateral positioning.[26] In addition, applying pressure to the paddles during conversion reduces transthoracic impedance, improving energy conduction.
- Timing of cardioversion. Application of the energy when the patient has fully exhaled reduces pulmonary resistance to the current.[27]
- Use of rectilinear biphasic energy. Traditional energy sources supply monophasic energy. Biphasic energy transfers more efficiently to atrial tissue, leading to higher cardioversion success rates and lower cumulative energy discharge.[28]

Although numerous protocols have been validated, a reasonable protocol that uses monophasic energy to convert AF is to start at 200 joules (J), followed by 300 J, then by 360 J or 400 J.[29] For patients with atrial flutter, cardioversion is frequently achieved with 50 J of monophasic energy; therefore, the monophasic AF protocol can be modified for AF by starting with 50 J, followed by 100 J. If biphasic energy is utilized for AF, a protocol of 70 J or 100 J followed by 150 J and then by 200 J may be utilized.[28,30]

Although success rates are high with DC cardioversion, a number of risk factors for cardioversion failure have been identified. These include longer duration of AF (notably, greater than 1 year), older age, left atrial enlargement, cardiomegaly, rheumatic heart disease, and transthoracic impedance.[25,28] Pretreatment with amiodarone, ibutilide, sotalol, flecainide, propafenone, disopyramide, and quinidine have been shown to increase DC cardioversion success rates.[1] Transvenous cardioversion also may be successfully used for cardioversion for patients in whom transthoracic cardioversion fails.[31,32]

DC cardioversion of AF is extremely safe, typically resulting in no significant myocardial damage if cardioversion attempts are separated by at least 1 minute. Nevertheless, clinicians must give consideration to two types of adverse events[33,34]:

- Reprogramming or malfunction of permanent pacemakers or implantable cardioverter-defibrillators (ICDs). Electricity transmitted from endocardial wires to myocardium can lead to tissue scarring and an increased threshold for tissue capture.[35] In addition, cardioversion energy can erase or alter the programming of permanent pacemakers or ICDs. For that

Table 2 Drugs for Cardioversion of Atrial Fibrillation and Maintenance of Sinus Rhythm[10]

Medication	*Route*	*Time to Conversion*	*Precautions*	*Drug Interactions*	*Side Effects*	*Comments*
Amiodarone	Oral/ I.V.	Hours to weeks	—	Increases digoxin, procainamide, quinidine, and warfarin levels	Bradycardia, visual disturbances, nausea, constipation, phlebitis (I.V. form); hepatic, ocular, pulmonary, thyroid, neurologic toxicity	Safe for use in patients with left ventricular dysfunction; TdP/VT less common than with dofetilide, ibutilide, or sotalol
Dofetilide	Oral	Days to weeks	—	Levels increased by cimetidine and verapamil	—	Safe for use in patients with left ventricular dysfunction; associated with TdP
Ibutilide	I.V.	< 1 hr	Check serum potassium, magnesium levels; requires 4 hr of monitoring for TdP	—	—	Safe for use in patients with left ventricular dysfunction; associated with TdP; not used for maintenance of sinus rhythm
Sotalol	Oral	Incompletely studied; reduced efficacy or no proven efficacy for cardioversion of AF	May exacerbate CHF and/or COPD	—	Bradycardia	Use with caution in patients with reduced left ventricular function; associated with TdP
Flecainide	Oral	3 hr	Pretreat with AV nodal blocking agents* to avoid accelerated ventricular response; avoid in patients with heart failure, left ventricular dysfunction, or CAD	Levels increased by amiodarone	—	
Propafenone	Oral/I.V.	< 6 hr	Pretreat with AV nodal blocking agents* to avoid accelerated ventricular response; avoid in patients with heart failure, left ventricular dysfunction, or CAD; may exacerbate COPD	Increases digoxin and warfarin levels	Blurred vision, hypotension	Efficacy reduced in patients with structural heart disease
Quinidine	Oral/I.V.	2–6 hr	Pretreat with AV nodal blocking agents* to avoid accelerated ventricular response; avoid in patients with heart failure or left ventricular dysfunction	Increases digoxin levels; levels increased by verapamil	Hypotension, nausea, diarrhea, fever, hepatic dysfunction, thrombocytopenia, hemolytic anemia	Safety limits use in cardioversion; side effects limit use; associated with TdP
Disopyramide	Oral/I.V.	< 12 hr	Incompletely studied, reduced efficacy or no proven efficacy for cardioversion of AF; pretreat with AV nodal blocking agents* to avoid accelerated ventricular response; avoid in patients with heart failure or left ventricular dysfunction	—	Dry mucous membranes, constipation, urinary retention; significant reduction of left ventricular function	Side effects limit use; associated with TdP
Procainamide	I.V.	< 24 hr	Incompletely studied, reduced efficacy or no proven efficacy for cardioversion of AF; pretreat with AV nodal blocking agents* to avoid accelerated ventricular response; avoid in patients with heart failure or left ventricular dysfunction	—	Drug-induced lupus, vasculitides, blood dyscrasias, central nervous system disturbances	Reduced efficacy, side effects limit use; associated with TdP

*AV nodal blocking agents typically used are verapamil or diltiazem, and possibly digoxin.
AF—atrial fibrillation CAD—coronary artery disease CHF—chronic heart failure COPD—chronic obstructive pulmonary disease TdP—torsade de pointes VT—ventricular tachycardia

Table 3 Dosages of Drugs for Pharmacologic Cardioversion of Atrial Fibrillation and Maintenance of Sinus Rhythm[10,80]

Drug	*Dosage for Cardioversion*	*Daily Dosage for Maintenance of Sinus Rhythm*
Amiodarone	Oral, inpatient 1.2–1.8 g/day in divided doses until 10 g total, then 200–400 mg/day maintenance; or 30 mg/kg as single dose Oral, outpatient 600–800 mg/day in divided doses until 10 g total Intravenous/oral 5–7 mg/kg over 30–60 min, then 1.2–1.8 g/day continuous I.V. or in divided oral doses until 10 g total	100–400 mg
Dofetilide	Oral dosages for specified C_{Cr} values 500 μg b.i.d. for C_{Cr} > 60 ml/min 250 μg b.i.d. for C_{Cr} 40 to 60 ml/min 125 μg b.i.d. for C_{Cr} 20 to 40 ml/min Contraindicated for C_{Cr} < 20 ml/min	500–1,000 μg; dosage adjustment based on QTc
Ibutilide	I.V.: 1 mg over 10 min; repeat once, if necessary	Not available
Sotalol	Not effective for cardioversion	240–320 mg; dosage adjustment based on QTc; reduced dosing with renal insufficiency
Flecainide	Oral: 200–300 mg	200–300 mg; reduced dosing with renal insufficiency
Propafenone	Oral: 450–600 mg I.V.: 1.5–2.0 mg/kg over 10–20 min; reduced dosing with renal insufficiency	450–900 mg; reduced dosing with hepatic dysfunction
Quinidine	Oral: 0.75–1.5 g in divided doses over 6–12 hr I.V.: 1.5–2.0 mg/kg over 10–20 min	600–1,500 mg
Disopyramide	Oral: 200 mg q. 4 hr, up to 800 mg	400–750 mg; reduced dosing with renal insufficiency
Procainamide	I.V.: 100 mg q. 5 min, up to 1,000 mg	1,000–4,000 mg; reduced dosing with renal insufficiency or hepatic dysfunction

Note: Dosages given may differ from those recommended by the manufacturer; see Table 2 for guidance regarding medication selection and dosing adjustments.
C_{Cr}—creatinine clearance QTc—corrected QT interval

reason, all such devices should be interrogated before and after DC cardioversion. Distancing of paddles from implanted devices may limit these adverse events.

- Arrhythmias. Life-threatening arrhythmias are more common with pharmacologic conversion but can occur with DC cardioversion. Ventricular tachycardia and ventricular fibrillation can result from cardioversion in patients with hypokalemia or digoxin toxicity. Failure to synchronize DC energy with ventricular rhythm can lead to ventricular fibrillation if energy is applied during ventricular repolarization.

Finally, many patients with AF have underlying sinus node dysfunction that may require permanent pacing once cardioversion is completed.[36]

Pharmacologic Approaches to Maintaining Sinus Rhythm

Except for patients in whom the cause of AF is reversible, pharmacologic therapy likely will be required to maintain sinus rhythm after cardioversion. In approximately 50% of AF patients who undergo cardioversion to sinus rhythm, AF will return within 1 year if prophylactic drug therapy is not employed; AF will recur in approximately 75% of patients within 4 years.[24] Before prescribing medication to maintain sinus rhythm, the clinician must assess the patient for underlying cardiovascular disease [*see Table 1*]. The presence of heart failure, coronary artery disease (CAD), or hypertension with left ventricular hypertrophy has a critical impact on the selection of antiarrhythmic medications [*see Figure 4*].

Class I antiarrhythmics frequently suppress left ventricular function. Randomized clinical trials have demonstrated that amiodarone and dofetilide maintain sinus rhythm without reducing survival in AF patients with heart failure.[37-39] As a result, these two drugs have become first-line therapy in this patient subgroup. In patients with ICDs, sotalol may be used safely.[40,41]

Agents with beta-blocking properties are preferred for patients with CAD. Sotalol has the advantage of blocking both beta-adrenergic receptors and potassium channels. In addition, sotalol has been shown to reduce reinfarction rates after a myocardial infarction, and its use has been associated with a trend toward reduced mortality.[42] However, in patients with concomitant heart failure or reduced ventricular function, amiodarone or dofetilide is preferable.

Hypertension and left ventricular hypertrophy may affect drug selection. If the left ventricular wall thickness is 14 mm or greater, amiodarone is recommended.

Although these recommendations can be applied to the majority of patients with AF, a number of distinct clinical scenarios require a tailored approach. In patients who do not have structural heart disease but who experience AF during exercise or under adrenergic stimulation, beta blockers are the treatment of choice, followed by sotalol or amiodarone. Vagally mediated AF that is not associated with structural heart disease often re-

sponds to disopyramide, a vagolytic medication. Second-line therapy includes flecainide and amiodarone.

Combination therapy may be used when a single medication fails to maintain sinus rhythm. With the combination of medications comes the increased risk of drug-induced side effects, notably, torsade de pointes and heart failure. Monitoring of symptoms and the width of the QTc and QRS intervals is critical.

Monitoring of antiarrhythmic therapy ECG monitoring is necessary in all patients receiving antiarrhythmic medications for maintenance of sinus rhythm. If flecainide or propafenone is used, QRS widening should not exceed 150% of pretreatment QRS width. QRS width should be assessed during exercise ECG testing, typically within 3 days after starting the medication. With all antiarrhythmics except amiodarone, QTc width should not exceed 520 msec. In addition, renal function and levels of serum potassium and serum magnesium should be monitored periodically, because abnormalities in these levels may predispose to arrhythmias.

Outpatient Initiation of Antiarrhythmic Drugs

In a subset of patients with AF, drugs for restoration and maintenance of sinus rhythm can be started safely in the outpatient setting. Advantages of this approach are elimination of the need for DC cardioversion, reduction of hospitalization time, and a decrease in early recurrences of AF after conversion to sinus rhythm. Although outpatient pharmacologic therapy to restore sinus rhythm is appealing, the concern for induction of life-threatening arrhythmias often precludes use of this approach.

Flecainide and propafenone may be initiated on an outpatient basis if the patient has no history of heart failure; if there is no left ventricular dysfunction; if the QRS width is normal; and if the QTc interval is not prolonged. Patients should have both a normal ECG (without any evidence of bradycardia, sinus node disease, or AV nodal disease) and a documented history of at least one episode of inpatient cardioversion with these medications during which no conduction abnormality was unmasked. Amiodarone and sotalol may be started in the ambulatory setting, provided there is no history of structural heart disease, left ventricular hypertrophy, reduced left ventricular function, bradycardia, sinus node or AV nodal conduction disease, hypokalemia, hypomagnesemia, or previous arrhythmias other than AF or atrial flutter. Flecainide, propafenone, amiodarone, or sotalol should not be started if the patient is also taking other medications that may prolong the QTc interval or predispose to electrolyte abnormalities. Dofetilide, disopyramide, procainamide, and quinidine typically should not be started in the ambulatory setting.[1]

Nonpharmacologic Approaches to Maintaining Sinus Rhythm

Several mechanical techniques offer the benefit of reducing the use of antiarrhythmics. The need for anticoagulation with these techniques remains uncertain, however.

Catheter-based ablation Radiofrequency energy emitted from intravascular catheters promotes the generation of endocardial scars to eliminate AF. These procedures focus primarily on elimination or isolation of ectopic foci, many of which are located in the pulmonary veins. Although these procedures have the potential to cure AF, many patients experience recurrence of AF. The risks of catheter-based ablation include thromboembolism, pulmonary vein stenosis, and cardiac perforation.[43]

Endovascular radiofrequency ablation is less suited to AF than to atrial flutter, which it can cure with minimal risks and a high rate of success. Ablation of atrial flutter typically involves creating a scar within the right atrium and therefore has a lower risk of complications than AF ablation of the pulmonary veins. Radiofrequency ablation for atrial flutter is curative in more than 90% of cases and should be considered primary therapy for these patients.[44]

Surgical ablation Surgical ablation of AF is similar in concept to catheter-based ablation. During open thoracotomy, linear lesions are created across atrial tissue to generate scars that will act as electromechanical obstacles, extinguishing the reentrant circuits needed for the maintenance of AF. There is a greater than 90% rate of success in eliminating AF with this procedure; however, approximately 25% of patients require a permanent pacemaker for sinus node dysfunction postoperatively.[45-47] This approach has an operative mortality of less than 1% but involves the morbidity of an invasive surgical procedure. The procedure is most often utilized when patients are undergoing cardiac surgery for other indications. The techniques utilized to generate the scars, as well as the location and number of scars created, continue to be modified to reduce surgical time while maintaining efficacy.

Atrial pacing In patients requiring ventricular pacing, the addition of atrial pacing reduces the risk of AF. However, the use of atrial pacing as the primary treatment to prevent AF has not been validated.[48-50]

Atrial defibrillators Implantable devices to detect and provide DC cardioversion for AF have been shown to successfully terminate AF in more than 95% of episodes.[51] Although promising, the use of atrial defibrillators is limited by the generation of pain associated with the release of the electrical shock, as well as the risks associated with device implantation (typically, bleeding and infection). As a result, atrial defibrillators have been used in patients who are unable to tolerate a strategy of ventricular rate control and whose condition is refractory to pharmacologic and ablative therapies.

CONTROL OF VENTRICULAR RATE

Ventricular rate control must be addressed both in the acute and the chronic setting. Medication selection in these scenarios is influenced by the rate of onset of the medication, its potential side effects, and its convenience of use.

Hemodynamically unstable patients with angina, myocardial infarction, heart failure, or symptomatic hypotension should be considered for acute conversion to sinus rhythm rather than rate control. In contrast, acute rate control can often be achieved rapidly in hemodynamically stable patients through the use of intravenous beta blockers, diltiazem, verapamil, or digoxin. Oral formulations of these medications are utilized for transition to long-term rate control [*see Table 4*]. More than one medication is often required to achieve ventricular rate control. Although digoxin is available orally and intravenously, its onset of action is at least 1 hour after infusion, so it is rarely sufficient for stand-alone therapy in the acute clinical setting.

Depending on the clinical scenario, specific agents may be more or less preferable for rate control. This is true of patients with reduced ventricular function, CAD, high sympathetic tone, pulmonary disease, and atrial flutter.

Table 4 Drugs for Ventricular Rate Control in Atrial Fibrillation[10]

Drug	*I.V. Loading Dose*	*I.V. Onset*	*I.V. Maintenance Dose*	*Oral Loading Dose*	*Oral Onset*	*Oral Maintenance Dose*	*Drug Interactions and Precautions*
Esmolol*	0.5 mg/kg over 1 min	5 min	5–20 μg/kg/min	Available in I.V. form only	—	—	—
Metoprolol*	2.5–5 mg over 2 min, up to 15 mg	5 min	Bolus every 4–6 hr	Not applicable	4–6 hr	50–200 mg daily in divided doses	—
Propranolol*	0.15 mg/kg over 1 min, repeat once	5 min	Bolus every 4 hr	Not applicable	1–1.5 hr	80–240 mg daily in divided doses	—
Diltiazem	0.25 mg/kg over 2 min	2–7 min	5–15 mg/hr	Not applicable	2–4 hr	120–360 mg daily in divided doses	Increases levels of digoxin, quinidine, simvastatin
Verapamil	75–150 μg/kg over 2 min	3–5 min	Bolus q. 3–6 hr	Not applicable	1–2 hr	120–360 mg daily in divided doses	Increases levels of digoxin, dofetilide, quinidine, simvastatin
Digoxin	0.25 mg q. 2 hr, up to 1.5 mg	2 hr	0.125–0.25 mg daily	0.25 mg q. 2 hr, up to 1.5 mg	2 hr	0.125–0.250 mg/day	Reduce dosing with renal insufficiency; levels increased by amiodarone, propafenone, quinidine, diltiazem, verapamil, spironolactone
Amiodarone	1.2–1.8 g/day until 10 g total	1–3 wk	720 mg/day up to 3 wk; limited data on continuous infusion beyond 3 wk	800 mg/day × 1 wk, 600 mg/day × 1 wk, 400 mg/day × 4–6 wk	1–3 wk	200 mg/day	Increases levels of digoxin, procainamide, quinidine, and warfarin

Note: Typical dosing regimens are provided; however, adjustments are necessary based on individual patient characteristics.
*Other beta-blocking medications may also be used.

Reduced Ventricular Function

Diltiazem and verapamil can significantly exacerbate left ventricular dysfunction and associated heart failure and so should be avoided in the acute setting. Beta blockers can also have this effect but are preferable for acute rate control. Intravenous esmolol has the advantage of rapid onset and clearance and so may be used to determine whether a patient with left ventricular dysfunction tolerates intravenous beta blockade. However, the large infusion of saline given with esmolol makes long-term intravenous use unattractive for patients with heart failure. If the patient tolerates intravenous esmolol, the clinician should consider changing to another intravenous beta blocker or to oral beta blockade. In addition, digoxin can be utilized in patients with left ventricular dysfunction without concern for exacerbating heart failure. Intravenous amiodarone may also be used in the subacute setting for rate control of patients with AF and reduced ventricular function.

Chronic rate control can be achieved through the oral administration of beta blockers. Bisoprolol, extended-release metoprolol, and carvedilol improve symptoms and survival in patients with systolic dysfunction and heart failure independent of atrial rhythm.[52-54] These medications should be first-line therapy for long-term rate control in these patients. If these medications are not tolerated, oral amiodarone should be considered. In addition, digoxin is effective and well tolerated in heart failure patients with AF.

Coronary Artery Disease

Beta blockers have been shown to reduce mortality in patients with CAD. Because of this additive benefit, beta blockers typically should be selected for CAD patients.

High Sympathetic Tone

The effects of digoxin are attenuated in patients with high sympathetic tone, so this agent rarely provides significant control of heart rate in acute, high sympathetic tone states.

Pulmonary Disease

Patients with asthma can experience significant exacerbation of their lung disease with the use of beta blockers. In these patients, diltiazem and verapamil should be used. Patients with chronic obstructive pulmonary disease without reactive airway disease may or may not tolerate beta blockers. Use of beta blockers in this population should be carefully monitored.

Atrial Flutter

It is often more difficult to achieve ventricular rate control in patients with atrial flutter than in those with AF. If rate control cannot be achieved easily in patients with atrial flutter, radiofrequency ablation should be reconsidered.

Monitoring Rate Control

Adequacy of rate control should be assessed both with the patient at rest and under stress. The history, physical examination, and ECG provide significant data for this assessment, but Holter monitoring and exercise stress testing also can be used. The ventricular rate should be maintained between 60 and 80 beats/min during rest and 90 to 115 beats/min during moderate exercise.[55,56] If rate control cannot be achieved with pharmacologic therapy, AV nodal ablation, combined with permanent pacemaker insertion, should be considered. In addition, permanent pacemaker insertion may be necessary for patients with AF who have labile responses to pharmacologic therapy to avoid episodes of symptomatic bradycardia.

Table 5 Data Collection for Assessment of Thromboembolic Risks and Need for Antithrombotic Therapy in Atrial Fibrillation

Characteristic	*Comments*
Age	
Sex	
History of hypertension	Patients with medically treated hypertension are considered hypertensive for risk-stratification guidelines
Diabetes mellitus	Irrespective of control with insulin or oral medications
Coronary artery disease	
Heart failure	Past or current
Hyperthyroidism	Treatment varies depending on whether currently euthyroid
Rheumatic heart disease	Defined as involving the mitral valve
Previous thromboembolism	Includes strokes, transient ischemic attacks, and other emboli
Prosthetic heart valves	
LVEF less than 35%	

LVEF–left ventricular ejection fraction

ANTITHROMBOTIC THERAPY

AF (including paroxysmal, permanent, and chronic forms) is associated with an increased risk of stroke and other embolic phenomena. The risk of stroke for an individual AF patient varies according to the presence or absence of a number of thromboembolic risk factors. These factors can be garnered from the baseline history, physical examination, laboratory evaluation, ECG, and transthoracic echocardiogram; assessment of these thromboembolic risk factors can serve to guide antithrombotic therapy [*see Table 5*].

Current ACC/AHA/ESC guidelines for anticoagulation recommend the use of aspirin or warfarin [*see Table 6*]. Clinical trials have shown that both aspirin and warfarin significantly reduce AF-related strokes in high-risk patients.[57-59] Warfarin reduces the risk of stroke by greater than 60%, whereas aspirin reduces stroke risk by 19%. However, the increased benefits of warfarin must be counterbalanced by the increased risk of hemorrhage.[60] Use of lower-intensity warfarin in combination with aspirin provides no additional stroke prevention over aspirin alone, and the combination of full-dose warfarin with aspirin further increases the risk of intracranial hemorrhage.[61,62] After warfarin therapy is started, the international normalized ratio (INR) of prothrombin time should be measured at least weekly until stable dosing is reached, and monthly thereafter [*see 1:XVIII Venous Thromboembolism*].

Atrial Flutter

Although clinical trial data are limited, epidemiologic studies demonstrate that the risk of stroke with atrial flutter, although less than that with AF, remains elevated.[63] As a result, use of warfarin and aspirin in atrial flutter should be based on the current AF guidelines.

Elderly Patients

Patients who are 75 years of age or older are at increased risk for both stroke with AF and bleeding with AF anticoagulation.[64] As a result of these increased risks, anticoagulation must be tightly monitored in elderly patients, with a goal of maintaining the INR at 2.

Surgical Procedures

Anticoagulation may need to be discontinued in patients scheduled for elective surgical procedures. AF anticoagulation can be discontinued for up to 1 week for surgical procedures in patients without mechanical heart valves. In patients with mechanical valves, the practice has been to discontinue warfarin 1 week before surgery but to maintain anticoagulation with either unfractionated or low-molecular-weight heparin (LMWH). However, current case reports suggest that LMWH may not provide sufficient anticoagulation for patients with mechanical valves, irrespective of concomitant AF.[65] Until further data become available, intravenous unfractionated heparin should be utilized.[66]

Anticoagulation and Cardioversion

Cardioversion from AF or atrial flutter to sinus rhythm—whether it occurs spontaneously or is accomplished with drugs or electricity—is associated with a 1% to 5% risk of thromboembolism. Therefore, strategies for cardioversion of AF should include consideration of anticoagulation; the anticoagulation may start before cardioversion, extend after it, or both [*see Figure 5*].

If warfarin anticoagulation (to an INR of 2 to 3) is used for 3 to 4 weeks before and after cardioversion, the risk of stroke is reduced to 0.5% in the immediate follow-up period.[36,67,68] For that reason, anticoagulation before cardioversion has been strongly advocated.

TEE has been validated as an alternative mechanism to gauge the risk of thromboembolism at the time of cardioversion and immediately afterward. If TEE reveals no evidence of thrombus in the left atrium or left atrial appendage, cardioversion can be performed immediately, with a risk of thromboembolism comparable to that in patients pretreated with 3 to 4

Table 6 ACC/AHA/ESC Recommendations for Antithrombotic Therapy in Atrial Fibrillation Based on Underlying Risk Factors[10]

Patient Characteristics	*Antithrombotic Therapy*
Age < 60 yr, no heart disease (lone atrial fibrillation)	Aspirin, 325 mg daily, or no therapy
Age < 60 yr, heart disease but no risk factors	Aspirin, 325 mg daily
Age ≥ 60 yr but no risk factors	Aspirin, 325 mg daily
Age ≥ 60 yr with DM or CAD	Warfarin (INR, 2.0–3.0); consider addition of aspirin, 81–162 mg daily
Age ≥ 75 yr, especially in women	Warfarin (INR, 2.0)
Heart failure	Warfarin (INR, 2.0)
LVEF ≤ 0.35	Warfarin (INR, 2.0–3.0)
Thyrotoxicosis	Warfarin (INR, 2.0–3.0)
Hypertension	Warfarin (INR, 2.0–3.0)
Rheumatic heart disease (mitral stenosis)	Warfarin (INR, 2.5–3.5 or possibly higher)
Prosthetic heart valves	Warfarin (INR, 2.5–3.5 or possibly higher)
Prior thromboembolism	Warfarin (INR, 2.5–3.5 or possibly higher)
Persistent atrial thrombus on TEE	Warfarin (INR, 2.5–3.5 or possibly higher)

ACC/AHA/ESC—American College of Cardiology/American Heart Association/European Society of Cardiology CAD–coronary artery disease DM—diabetes mellitus INR—international normalized ratio LVEF–left ventricular ejection fraction TEE–transesophageal echocardiography

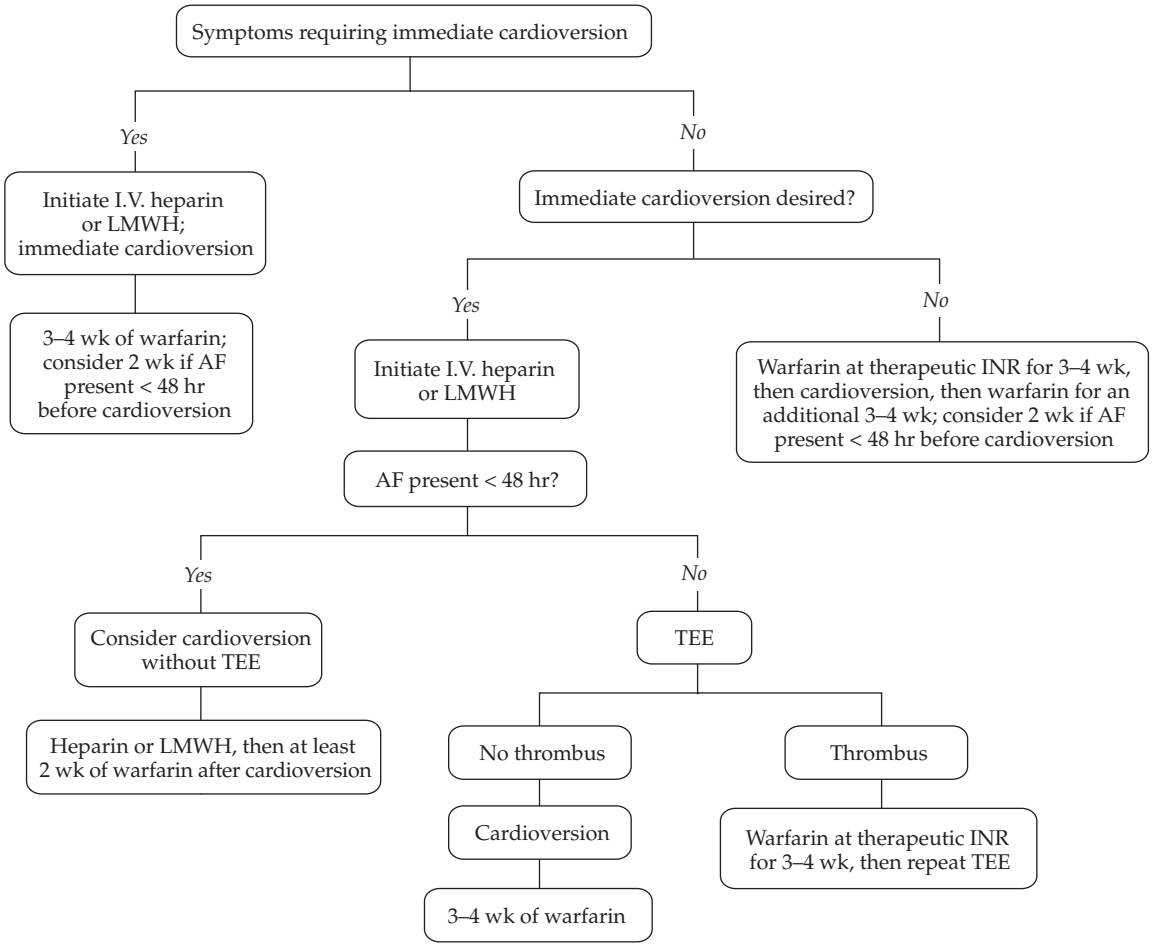

Figure 5 **Cardioversion and anticoagulation strategy for atrial fibrillation. Symptoms that frequently require cardioversion include hypotension, altered mental status, heart failure, pulmonary edema, angina, and myocardial infarction. Adjustment of warfarin intensity and therapy duration is based on individual patient characteristics; the anticoagulation goal is typically an INR of 2–3. (AF—atrial fibrillation; INR—international normalized ratio; LMWH—low-molecular-weight heparin; TEE—transesophageal echocardiography)**

weeks of warfarin therapy.[69] This approach allows for immediate cardioversion; however, because cardioversion frequently results in so-called stunning of left atrial and left atrial appendage tissue (a condition that may predispose to thrombus formation), warfarin anticoagulation is required for 3 to 4 weeks after cardioversion, even when TEE performed before cardioversion showed no thrombus. If TEE does identify thrombus, cardioversion should be postponed for 3 to 4 weeks of anticoagulation therapy with warfarin, after which TEE should be repeated.

Cardioversion without 3 to 4 weeks of warfarin pretreatment and without TEE assessment can be considered if the cardioversion can be done within 48 hours of the onset of AF or if the patient is started on heparin within 48 hours of AF initiation. Limited data suggest that LMWH may be used instead of intravenous unfractionated heparin, allowing both simplified dosing and transition to warfarin therapy on an outpatient basis.[70] This strategy should be most strongly considered in AF patients with significant symptoms of cardiac compromise, including hemodynamic instability, angina, myocardial infarction, heart failure, and shock. The need for anticoagulation after cardioversion in this scenario is unclear, but considering that more than 95% of postcardioversion thromboemboli occur within 10 days after cardioversion, at least 2 weeks of warfarin therapy should be strongly considered if the patient has no contraindications.[71]

Even if heparin was not started until more than 48 hours after the onset of AF, immediate cardioversion also may be necessary if the patient has symptoms of cardiac compromise. Unlike patients who present less than 48 hours after onset of AF, patients with AF of longer duration should receive 3 to 4 weeks of warfarin therapy after cardioversion.

Prolonged anticoagulation after cardioversion should be considered in patients at high risk for both AF recurrence and thromboembolic complications. Atrial flutter is associated with a risk of thromboembolism in the setting of elective cardioversion and should be treated in the same manner as AF.[67]

Ximelagatran

Ximelagatran is a direct thrombin inhibitor that can be administered orally. In the Sport Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation–III (SPORTIF III) trial, which was an open-label comparison of adjusted-dose warfarin and fixed-dose ximelagatran, there were no significant differences in rates of stroke, systemic thromboembolism, bleeding, or death with

the two drugs.[72] The SPORTIF V trial will compare the two drugs in a double-blinded format. Ximelagatran offers a wider therapeutic window than warfarin and requires no monitoring with coagulation studies. If the equivalence of ximelagatran with warfarin is confirmed, the ease of use of this medication will likely lead to its replacing warfarin for many patients with AF. Future studies will be required to determine whether ximelagatran can be applied to specific settings in which warfarin therapy has been validated.

TREATMENT IN SPECIFIC CLINICAL SCENARIOS

Cardiac Surgery

AF occurs after 25% of all coronary artery bypass surgeries and after more than 60% of combined coronary artery bypass and mitral valve surgeries.[73] Additional risk factors in these cases included advanced age, male sex, preoperative atrial arrhythmias, left atrial enlargement, chronic lung disease, and previous cardiac surgery.[74] AF after cardiac surgery leads to a significant increase in length of hospital stay and cost.[75] A number of prophylactic therapies to prevent postoperative AF have been examined and validated, including use of beta blockers, sotalol, amiodarone, and postoperative temporary atrial pacing.[76] The incremental cost of prophylactic therapy must be balanced against the potential savings achieved by reducing length of stay if AF is prevented. Unless contraindicated, beta blockers should be given to all patients scheduled for cardiac surgery. Sotalol, amiodarone, and biatrial pacing should be considered if patients are at high risk for postoperative AF because of additional risk factors.

Anticoagulation should be given if AF occurs after cardiac surgery and lasts longer than 48 hours. Although sinus rhythm returns spontaneously within 6 weeks in 95% of patients with postoperative AF, pharmacologic or DC cardioversion is often performed, particularly in patients who are symptomatic or hemodynamically unstable.[77] Medications to maintain sinus rhythm or to achieve ventricular rate control can be selected on the basis of patient characteristics.

Acute Myocardial Infarction

In patients with acute myocardial infarction, AF is an independent predictor of mortality and stroke. Immediate DC cardioversion should be performed in patients with severe hemodynamic compromise or persistent ischemia. If rate control is possible, digoxin can be combined with a beta blocker if left ventricular function is preserved. Because of the thromboembolic risk, heparin should be given acutely and followed with warfarin if AF persists or significant left ventricular dysfunction develops.

Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White syndrome (WPW) in association with AF can be a life-threatening condition. The bypass tract of WPW may allow rapid conduction of atrial activity to the ventricles, precipitating hemodynamic compromise or ventricular fibrillation. In the acute setting, DC cardioversion should be pursued if hemodynamic compromise is present. If the patient is hemodynamically stable, the clinician may consider pharmacologic cardioversion to sinus rhythm with intravenous procainamide or ibutilide.[78] Agents that slow AV conduction are contraindicated, including digoxin, diltiazem, and verapamil. Beta blockers should be used rarely and with extreme caution. Once stabilization is achieved, catheter ablation of the WPW bypass tract should be pursued in all symptomatic WPW patients with AF.

Hyperthyroidism

Hyperthyroidism may cause AF and is associated with an increased risk of stroke. Hence, these patients require anticoagulation. Rate control should be attempted with beta blockers, supplemented with diltiazem, verapamil, or digoxin as needed. Warfarin should be given while the patient is thyrotoxic. Once the euthyroid state has returned, use of aspirin or warfarin should be based on underlying risk factors.

Hypertrophic Cardiomyopathy

AF in patients with hypertrophic cardiomyopathy is associated with a high risk of death and stroke.[79] Warfarin therapy is recommended (INR, 2 to 3).

Pulmonary Disease

In patients with pulmonary disease, hypoxia and other metabolic disturbances frequently initiate AF. Initial therapy focuses on treating the underlying lung disease. Beta blockers, propafenone, sotalol, and adenosine are contraindicated in patients with reactive airway disease. Diltiazem or verapamil, with or without digoxin, should be utilized for rate control in these patients.

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