Atrial Fibrillation

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Current Treatment Options in Cardiovascular Medicine 2001, **3:**261–276
Current Science Inc. ISSN 1092-8464

Opinion statement

- The conversion of atrial fibrillation (AF) to normal sinus rhythm should be attempted in patients who present with this condition, as long as the cure is not worse than the disease itself. In young patients with normal hearts, AF has a small impact on morbidity and mortality. The primary indication for conversion in this population is often symptoms. In contrast, in patients with diseased hearts or who are older than 65 years, maintaining sinus rhythm may have a favorable impact on stroke risk, ventricular function, and symptoms. In the absence of normal sinus rhythm, these patients should receive anticoagulants.
- Rate control is the preferred first-line strategy for asymptomatic patients and patients presenting with a history of long-standing, persistent AF, making conversion and maintenance of sinus rhythm unlikely. Rate control may be used in patients who develop AF during an acute systemic illness, which will likely terminate with time or therapy.
- Conversion to sinus rhythm should be considered in patients with a first episode of AF, as unconverted AF tends to perpetuate itself. Conversion can be attempted if the duration of AF is less than 48 hours or if the patient has received anticoagulants when the duration is not known. Other indications for cardioversion are prolonged episodes in patients with otherwise infrequent episodes of paroxysmal AF, and in patients who refuse to take anticoagulants or in whom anticoagulation is contraindicated.
- After the patient is converted to sinus rhythm, the decision to initiate chronic drug therapy should be based on the presence of other cardiac and medical diseases that increase the risk of recurrence and serious symptoms in case of recurrence (such as hypertrophic cardiomyopathy or mitral stenosis). It is acceptable to manage patients with new-onset AF and normal cardiac function with cardioversion alone and not initiate chronic antiarrhythmic therapy afterwards. However, in patients with abnormal hearts (coronary artery disease, hypertensive or mitral valvular heart disease, and cardiomyopathy) AF is likely to recur, and such patients should be placed on antiarrhythmic medication.

Introduction

Atrial fibrillation (AF) is widely acknowledged to be the most common sustained arrhythmia in humans worldwide. Its prevalence increases with age, and 84% of individuals with AF are older than 65 years. Its presence independently increases the risk of death [1]. AF is responsible for 75,000 strokes annually. Also, the treatment of AF is associated with a very significant financial burden. The management of AF is still challenging, and there is some controversy regarding the best strategy. The last few years have seen many advances in its management, aided by clinical trials, new drugs, and invasive technology.

The therapeutic goals in patients with AF are maintenance of normal sinus rhythm if possible; alleviation of symptoms and the improvement of quality of life; prevention of thromboembolism; and prevention of

the induction of more dangerous arrhythmias by AF. The current treatment options available are summarized in Table 1.

Firm clinical evidence is lacking to support either strategy of managing AF, rate control versus rhythm control. The PIAF (Pharmacological Intervention in Atrial Fibrillation) trial [2] showed similar symptom improvement and quality of life amongst patients randomized to either rate control or rhythm control with amiodarone and electrical cardioversion. Exercise tolerance was better in the rhythm control group, but hospital admissions and drug adverse effects were higher. The study was underpowered to assess for differences in survival, and because anticoagulation was not withdrawn in either group, changes in thromboembolic risk could not be assessed. The currently ongoing AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial is enrolling patients with persistent or paroxysmal AF with a duration of less than 6 months and at least one risk factor for stroke. Four thousand three hundred patients will be randomized to rate versus rhythm control (amiodarone, sotalol, or a class I antiarrhythmic drug) and followed for 3.5 years. The primary and secondary endpoints will be mortality and a composite of total mortality and disabling stroke, cost, and quality of life, respectively. Results are expected in 2002 [3].

Indications for hospitalization

- Newly diagnosed or known previous AF associated with hemodynamic compromise or other severe symptoms such as congestive heart failure (CHF), myocardial infarction (MI), unstable angina, syncope, or thromboembolism.
- Initiation of antiarrhythmic drugs such as dofetilide, amiodarone, and sotalol, or initiation of antiarrhythmic therapy in the presence of pro-arrhythmic risk factors such as left ventricular dysfunction. It is also preferable to initiate inpatient therapy in patients with persistent AF and suspected sinus or atrioventricular node dysfunction.
- When nonpharmacologic therapies such as bundle of His ablation and pacing, focal or linear ablation, or atrial defibrillator implantation are planned.

Treatment

Pharmacologic treatment

Rate control

- The adequacy of a patient's rate control is best assessed by a Holter monitor. It is important to consider ventricular response during both exercise and sleep and to not miss excessively rapid or slow rates. Rate control is desirable even in asymptomatic patients to prevent rate-related cardiomyopathy, as well as in those receiving antiarrhythmic medications.

Digoxin

Standard dosage	Intravenous: 0.5 mg initially, followed by 0.25 mg every 4 to 6 hours for two doses. Oral: 0.125 to 0.375 mg/d, based on creatinine clearance.
Contraindications	Accessory pathway, sinus and atrioventricular nodal disease, hypertrophic cardiomyopathy.
Main drug interactions	Digoxin levels are increased by amiodarone, verapamil, propafenone, quinidine, antibiotics, and spironolactone. Increased risk of heart block when used with other atrioventricular nodal blockers.
Main side effects	Tachy- and bradyarrhythmias, gastrointestinal and central nervous system side effects.

Table 1. Therapeutic strategies for atrial fibrillation

Rhythm control		Rate control		Prevention of stroke
Pharmacologic	**Nonpharmacologic**	**Pharmacologic**	**Nonpharmacologic**	
Procainamide	Catheter ablation	Beta-blockers	Atrioventricular nodal modification	Chronic warfarin or aspirin
Flecainide	Focal ablation in or around pulmonary veins	Digoxin	His bundle ablation with pacing	
Propafenone	Linear ablation (right atrium or left atrium alone) and biatrial ablation	Calcium channel blockers		
Sotalol	Pacing			
Amiodarone	Atrial defibrillator			
Dofetilide	Surgery			
Disopyramide				

Special points Digoxin is often ineffectual for rate control in patients with paroxysmal AF or denervated hearts and during exercise. Thus, its use in active and young patients is limited, but it is useful in older, sedentary patients and in those with concomitant left ventricular dysfunction.

Cost/cost-effectiveness A 30-day supply of generic digoxin (0.25 mg/d) costs $6; brand-name formulations cost $6 to $9.

Beta-blockers

Standard dosage Metoprolol (Lopressor; Novartis, East Hannover, NJ): 100 mg twice a day, up to 400 mg/d.
Atenolol (Tenoretic; AstraZeneca, Wilmington, DE): 100 mg/d, up to 200 mg/d.

Contraindications Bronchospasm, sinus bradycardia, high-grade atrioventricular block.

Main drug interactions Beta-blockers have an additive negative effect on conduction when given with other atrioventricular blockers.

Main side effects Bronchospasm, heart block, fatigue, depression.

Special points Beta-blockers are superior to digoxin for rate control during exercise and are effective in reducing the incidence of postoperative AF. Pindolol, a beta-blocker with intrinsic sympathomimetic activity, may obviate the need for a permanent pacemaker in patients with the so-called “tachy-brady syndrome” by preventing resting bradycardia and controlling rate during exercise.

Cost/cost-effectiveness A 30-day supply of generic metoprolol (50 mg twice a day) costs $27 to $32; brand-name metoprolol costs $42.

Calcium channel blockers

Standard dosage Diltiazem (Cardizem; Aventis, Parsippany, NJ): Intravenous dosage is a 0.25-mg/kg bolus (with an additional 0.35 mg/kg after 15 minutes if needed), followed by an infusion of 5 to 15 mg/h. The oral dosage is 60 to 90 mg three times a day, followed by 240 to 540 mg/d (sustained release).
Verapamil (Calan; Searle, Chicago, IL): Intravenous dosage is 5 to 10 mg.
Oral dosage is 240 to 480 mg/d in divided doses or once daily (sustained-release formulation).

Contraindications Accessory pathway, severe left ventricular dysfunction (verapamil), sinus or atrioventricular nodal disease (unless paced).

Main drug interactions Calcium channel blockers potentiate the effect of beta-blockers, digoxin, flecainide, and cyclosporine.

Special points There is some evidence suggesting that verapamil has a favorable effect on atrial electrical remodeling [4]. Diltiazem significantly reduced the incidence of clinically relevant atrial arrhythmias (including AF) compared with placebo when given to patients after thoracic surgery [5].

Cost/cost-effectiveness Verapamil: A 30-day supply of generic verapamil (240 mg/d) costs $10 to $38; brand-name verapamil costs $54.
Diltiazem: A 30-day supply of brand-name sustained-release diltiazem (240 mg/d) costs $62.

Rhythm control

- Table 2 shows antiarrhythmic agents preferred depending on the kind of cardiac disease the patient has. Complete suppression is uncommon during treatment for paroxysmal AF, but in the majority of patients, the duration and frequency of AF can be significantly decreased.
- Serious organ toxicity is rare with propafenone, sotalol, disopyramide, and flecainide. Thus, these agents should be used before more toxic drugs are used if proarrhythmia risk is low. For a patient at risk for proarrhythmia, the choice is limited to amiodarone and sotalol, in the absence of an implantable defibrillator.
- The safety and efficacy of amiodarone is supported by a study in which low-dosage amiodarone (200 mg or less per day) was more effective than sotalol or propafenone in reducing recurrent AF, with no difference in mortality, tolerability, or major events. The incidences of cardiac and noncardiac side effects of amiodarone were low in this study, which mirrors our experience [6]. We use it preferentially over sotalol in patients with structural heart disease and in cases of previously failed therapy.

Procainamide

Standard dosage Intravenous: 15 mg/kg, at a rate not exceeding 20 mg/min.
Oral (Procanbid; Monarch, Bristol, TN): Sustained-release procainamide, 50 mg/kg/d. A reduced dose is recommended for patients older than 50 years and those with renal or hepatic impairment.

Contraindications Left ventricular systolic dysfunction, coronary artery disease, history of torsades de pointes, prolonged baseline QTc, systemic lupus erythematosus, more than mild renal insufficiency.

Main drug interactions Potentiated by amiodarone, cimetidine, trimethoprim.

Main side effects Agranulocytosis, rash, gastrointestinal upset, drug-induced lupus.

Special points The efficacy of intravenous procainamide for acute conversion varies from 58% to 62%, and is less than that of ibutilide. It is especially valuable in patients who manifest pre-excitation during AF, as it prolongs the refractory period of the accessory pathway.

Cost/cost-effectiveness A 30-day supply of generic sustained-release procainamide (1500 mg/d) costs $29; brand-name procainamide costs $141. Generic intravenous procainamide (1000 mg) cost $6 to $28; brand-name procainamide costs $45.

Ibutilide

Standard dosage Patients heavier than 60 kg are given an initial 1-mg infusion of ibutilide (Covert; Pharmacia & Upjohn, Peapack, NJ) over 10 minutes; patients less than 60 kg are given 0.01 mg/kg for 10 minutes. A second similar dose may be given 10 minutes after completion of first one if arrhythmia does not terminate.

Contraindications Hypersensitivity, history of drug-induced torsades de pointes, left ventricular dysfunction, QTc longer than 440 msec, uncorrected hypokalemia.

Table 2. Patient cardiac status and preferred rhythm-control drugs

Type of cardiac disease	Preferred drug	Avoid
Normal heart	Class IC agents	—
CAD	Sotalol, dofetilide, amiodarone	Class IC and IA antiarrhythmic agents
LVH	Propafenone	Class IA and IC (especially in presence of LVH with strain and QRS widening on ECG), and class III antiarrhythmic agents
Systolic dysfunction	Amiodarone and sotalol	Class IA and IC antiarrhythmic agents

CAD—coronary artery disease; ECG—electrocardiogram; LVH—left ventricular heart disease.

Main drug interactions All class IA and III antiarrhythmic drugs should be stopped for more than five half-lives before administration of ibutilide, and withheld for at least 4 hours afterwards after administration of ibutilide. There is potentiation of QT prolongation when given with other QT-prolonging drugs.

Main side effects Sustained polymorphic ventricular tachyrhythmia (1.5%), which usually occurs after the infusion is over, with a higher incidence in patients with a history of CHF. Nonsustained poly- or monomorphic ventricular tachyrhythmia occurs in 2.7% and 4.9% of patients, respectively. Bradycardia, hypotension, nausea.

Special points Overall efficacy is 25% to 40% at 1.5 hours, with cardioversion usually occurring in 30 to 60 minutes. It facilitates repeat direct-current cardioversion after initial failure [7], and is more effective for patients with AF of shorter duration. When given after cardiac surgery, efficacy was 44% at 1.5 hours, with about 65% of patients remaining in sinus rhythm at 24 hours [8]. Telemetry monitoring must be continued until the QTc normalizes or for at least 4 hours.

Cost/cost-effectiveness The cost for brand-name ibutilide (1 mg) is $221. A study has shown that ibutilide is more costly when compared with direct-current cardioversion ($280 versus $138 per patient) as first-line therapy. This likely is due to lower efficacy of ibutilide, and the need for electrical cardioversion after ibutilide failure [9].

Dofetilide

Dofetilide (Tikosyn; Pfizer, New York, NY) is indicated for both conversion to and maintenance of sinus rhythm.

Standard dosage 500 μg twice a day (when creatinine clearance rate is more than 60 mL/min), 250 μg twice a day (when creatinine clearance is between 40 and 60 mL/min), or 125 μg twice a day (when creatinine clearance is between 20 and 40 mL/min). Reduce dosage if the QTc increases more than 15% or absolute QTc is longer than 500 msec (550 msec in case of bundle block) 2 to 3 hours after the first dose. If the QTc is longer than 500 msec after the second dose, dofetilide must be discontinued.

Contraindications Severe renal (creatinine clearance less than 20 mL/min) or hepatic impairment, QTc longer than 440 msec, history of drug-induced torsades de pointes, heart rate less than 50 beats per minute, advanced atrioventricular block.

Main drug interactions Concomitant use of cimetidine, trimethoprim, and ketoconazole is contraindicated. Other QT-prolonging drugs and CYP3A4 isoenzyme inhibitors can potentiate its effects. Class I and II antiarrhythmic drugs should be withheld for three half-lives before administration; for amiodarone, 3 months before initiation.

Main side effects Increase in the incidence of torsades de pointes (0.9% to 3.3%), which is highest in the first 3 days after initiation. Headache, chest pain, dizziness.

Special points Dofetilide must be initiated with inpatient telemetry monitoring for at least 3 days. Its efficacy in converting AF was 30% at dosages of 500 μg twice a day in two randomized placebo-controlled trials that enrolled patients with AF of more than 1 week (50% had structural heart disease). At 6 and 12 months, efficacy was 52% and 46%, respectively, with a dosage-dependent effect. Its safety in patients with MI or CHF, with or without AF, was demonstrated in the DIAMOND (Danish Investigators of Arrhythmia and Mortality on Dofetilide) CHF and MI studies [10]. It is ineffective in patients with paroxysmal AF.

Cost/cost-effectiveness A 30-day supply of brand-name dofetilide (500 mg twice a day) costs approximately $108.

Azimilide

Standard dosage	A loading dose of 125 mg twice a day is given for 3 days, followed by 125 mg/d. The drug needs to be discontinued for QTc longer than 525 msec.
Contraindications	History of torsades de pointes or other polymorphic ventricular tachycardia, resting heart rate of less than 50 beats per minute, QTc of longer than 440 msec.
Main drug interactions	Avoid using concomitantly with azole antifungals, CYP3A4 enzyme inhibitors, and other QT-prolonging drugs.
Main side effects	Torsades de pointes.
Special points	A recent study compared different doses of azimilide with placebo in preventing recurrent AF in a patient population with a high prevalence of structural heart disease. When analyzed together, azimilide, in doses of 100 mg and 125 mg, was statistically better in increasing time to first recurrence of AF compared with placebo (60 days versus 17 days, $P = 0.005$). The drug was mainly initiated on an outpatient basis and was well tolerated, with only one case of torsades de pointes and three deaths in 291 patients [11]. It is not in routine use at present.
Cost/cost-effectiveness	Cost data are unavailable.

Amiodarone

Standard dosage	Conversion: 150 mg intravenous amiodarone (Cordarone; Wyeth-Ayerst, St. Davids, PA) over 10 minutes, followed by 1 mg/min intravenously for 6 hours, then 0.5 mg/min intravenously or 400 mg orally three times a day for 5 days. Maintenance: 400 mg/d for 1 month after a 5-day loading regimen, followed by 200 mg/d.
Contraindications	Severe sinus or atrioventricular nodal disease; severe lung, liver, or thyroid disease.
Main drug interactions	Potentiates procainamide, digoxin, warfarin, cyclosporine, and phenytoin. Other negative chronotropic agents may worsen bradycardia.
Main side effects	The most common side effects are hyperthyroidism (5% to 6%) or hypothyroidism (12%). Pulmonary fibrosis (0.5% per year, up to 3% to 12%), alveolitis, postoperative acute respiratory distress syndrome, hepatotoxicity, optic neuritis, corneal deposits, photosensitivity, peripheral neuropathy, proarrhythmia.
Special points	Intravenous amiodarone is less effective in producing early cardioversion than class I antiarrhythmic drugs. Amiodarone is useful for acute rate control in critically ill patients, as it is hemodynamically well tolerated. It is more effective than sotalol, propafenone [6], and flecainide for maintaining sinus rhythm.
Cost/cost-effectiveness	A 30-day supply of generic amiodarone (200 mg/d) costs $92; brand-name amiodarone costs $110. Intravenous brand-name amiodarone (150 mg) costs $84. By reducing the incidence of postoperative AF, oral amiodarone prophylaxis prior to cardiac surgery significantly reduced hospital length of stay and costs when compared with placebo ($18,375 ± $13,863 vs $26,491 ± $23,837; $P = 0.03$) [12•].

Flecainide

Standard dosage	Flecainide (Tambocor; 3M, St. Paul, MN), 100 mg twice a day; may be increased to 150 mg twice a day. Lower dosages for patients with a creatinine clearance less than 35 mL/min.
Contraindications	Known coronary artery disease, especially with previous MI; atrioventricular nodal or conduction system disease; left ventricular hypertrophy with strain or QRS widening; left ventricular dysfunction.
Main drug interactions	Potentiates digoxin and negative inotropic agents, and is potentiated by amiodarone and cimetidine.
Main side effects	Proarrhythmia, including incessant ventricular tachyrhythmias, especially with exercise. Tremor, edema, gastrointestinal upset.
Special points	A 300-mg oral bolus of flecainide is as effective as propafenone in converting AF to sinus rhythm at 3 hours (59% to 68%). Atrioventricular blockade must be instituted before starting flecainide, as it may convert AF to a relatively slow atrial

	flutter, which can conduct 1:1, simulating ventricular tachyarrhythmia. A single oral dose of 300 mg has been effective in converting AF of short duration, but otherwise it is indicated only for patients with paroxysmal AF.
Cost/cost-effectiveness	A 30-day supply of brand-name flecainide (100 mg twice a day) costs $143.

Propafenone

Standard dosage	Propafenone (Rythmol; Knoll Labs, Mount Olive, NJ), 150 mg every 8 hours; increase dosage at 3- to 4-day intervals to a maximum of 300 mg every 8 hours. Reduce dosage 20% to 30% for patients with hepatic impairment.
Contraindications	Left ventricular dysfunction, coronary artery disease, atrioventricular and conduction disease, bronchospastic conditions.
Main drug interactions	Potentiates digoxin, beta-blockers, warfarin, theophylline, and cyclosporine.
Main side effects	Proarrhythmia, dysgeusia, xerostomia, gastrointestinal upset, elevated antinuclear antibodies.
Special points	A single dose of 600 mg has up to 76% efficacy in converting AF by 8 hours. In the setting of a patient with a normal heart, patient-control, outpatient, single-dose therapy for terminating recurrences of AF is efficacious and cost effective. Propafenone has beta-blocking activity and therefore controls the ventricular rate even if AF recurs.
Cost/cost-effectiveness	A 30-day supply of brand-name propafenone (300 mg twice a day) costs approximately $147.

Sotalol

Standard dosage	Initial dose of sotalol (Betapace; Berlex, Richmond, CA) is 80 mg twice a day for patients with a QT shorter than 450 msec and a creatinine clearance of more than 60 mL/min, or 80 mg every day for creatinine clearance of 40 to 60 mL/min. The usual maintenance dosage is 160 mg twice a day.
Contraindications	Sinus and atrioventricular nodal disease, bradycardia (less than 50 beats per minute), baseline QTc longer than 450 msec, creatinine clearance less than 40 mL/min, asthma.
Main drug interactions	Class IA and III antiarrhythmic agents and other QT-prolonging drugs potentiate risk of torsades de pointes. Additive conduction abnormalities with other atrioventricular-blocking drugs.
Main side effects	Modest proarrhythmic risk in patients with or without structural heart disease. Fatigue, gastrointestinal and visual disturbances.
Special points	Although sotalol has low efficacy in causing cardioversion, it was effective in preventing recurrences of paroxysmal AF in about 50% of patients at 4.6 months in one study; multivariate analysis showed that sotalol efficacy is predicted by younger age, higher ejection-fraction, and absence of hypertension [13]. Sotalol is not indicated for patients with chronic AF and should be initiated in the hospital.
Cost/cost-effectiveness	A 30-day supply of brand-name sotalol (160 mg twice a day) costs $246.

Stroke prevention

Warfarin, aspirin

Standard dosage	Warfarin (Coumadin; DuPont, Wilmington, DE): Should be adjusted to an international normalized ratio (INR) of 2 to 3. Aspirin: 325 mg/d.
Contraindications	Warfarin: Risk of falls, recent or active bleeding, noncompliance, history of hemorrhagic stroke, pregnancy. Aspirin: Peptic ulcer, aspirin-sensitive asthma, hypersensitivity.
Main drug interactions	Warfarin: A number of drugs can increase (protein-bound drugs, antibiotics, amiodarone, and hepatic enzyme inhibitors such as cimetidine) or decrease (cholestyramine, vitamin K, barbiturates, phenytoin, rifampin) its action.

Aspirin: Increased bleeding risk when taken with other antiplatelet agents (clopidogrel, ticlopidine) or anticoagulants (warfarin).

Main side effects Warfarin: Bleeding, skin necrosis, dermatitis, hepatic dysfunction.
Aspirin: Bleeding, peptic ulcer disease, worsening of asthma.

Special points The incidence of stroke in patients with AF who do not receive anticoagulants is approximately 5% per year, with the attributable risk increasing with age. Warfarin reduces stroke risk by approximately 68% compared with placebo, without any significant increase in major bleeding or intracranial hemorrhage if given carefully. The data for aspirin alone are far less striking, with only the SPAF1 (Stroke Prevention in Atrial Fibrillation) trial showing a significant benefit over placebo. A meta-analysis showed benefit of warfarin over aspirin, even though the individual trials did not. The combination of low-dosage warfarin and aspirin is not recommended (SPAF3) [14]. The risk of intracranial hemorrhage increases markedly with INRs of more than 4 to 5. Studies have suggested higher stroke rates in patients with an INR of less than 2. Thus, the recommended target INR is between 2 and 3. Table 3 shows the current recommendations for anticoagulant use in patients with AF [15••].

Warfarin is recommended for at least 3 weeks before and 4 weeks after electric or pharmacologic cardioversion. Embolic risk is low in patients undergoing cardioversion within 48 hours after onset of AF. The ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) pilot study demonstrated safety of transesophageal echocardiography-guided cardioversion in patients with AF of less than 48 hours duration [16]. Anticoagulation, however, must still be initiated immediately and continued for 4 weeks after cardioversion.

Cost/cost-effectiveness A 30-day supply of warfarin (5 to 10 mg/d) costs $20 to $29; cost are similar for both generic and brand-name forms. In one study, warfarin cost $8000 per quality-adjusted year of life saved for patients with nonvalvular AF and one additional risk factor for stroke. In the absence of any other risk factor, the expense with warfarin was much higher for patients of 65 years of age ($370,000 per quality-adjusted life-year). However, the expense decreased ($110,000 per quality-adjusted life-year) when 75-year-old patients were considered [17]. A study found transesophageal echocardiography-guided cardioversion to be more cost-effective than cardioversion following conventional 4 weeks of anticoagulation ($2774 vs $3070) [8].

Interventional procedures

Rate control

Atrioventricular node modification

Standard procedure Radiofrequency energy is applied to the mid or posterior septum along the tricuspid annulus in the same area as for ablation of a slow pathway. The rationale is to interrupt the inputs to the atrioventricular node, which have the shortest refractory period, without causing complete atrioventricular block, which would require permanent pacemaker placement.

Contraindications Because of the risk of inadvertent complete heart block, any contraindication for a permanent pacemaker constitutes a contraindication to this procedure.

Complications An incidence of complete heart block of up to 15% has been noted, which requires permanent pacing.

Special points In a study of 60 patients comparing atrioventricular node modification with atrioventricular node ablation, the former was less successful in achieving rate control, but was equally effective in improving patient readmission rates, symptoms, and exercise tolerance. The rate of late AF recurrence (more than 120 beats per minute) was 12% [19].

Cost/cost-effectiveness In a study by Knight *et al.* [20], the adjusted total costs at 1 year were significantly lower for the modification procedure ($19,389 ± $2002) compared with the ablation procedure ($28,485 ± $2023). The difference continued to be significant at 10 years.

Table 3. Recommendations for type of anticoagulation for stroke prevention

Warfarin	Warfarin or aspirin	Aspirin alone
Older than 75 years (regardless of sex)	One moderate risk factor	Age less than 65 years and no other risk factors
Hypertension (regardless of age)	Age 65 to 75 years	
Rheumatic mitral disease	Diabetes	
Poor left ventricular systolic function	Coronary artery disease	
Associated prosthetic valve		
More than one moderate risk factor		

Data *from* Albers *et al.* [15••].

Atrioventricular node ablation

Standard procedure The compact atrioventricular node/bundle of His is ablated. In some cases, a left-sided approach is needed and ablation is performed in the left septum just below the aortic valve. Patients who are candidates for atrioventricular ablation usually are intolerant of medications and have comorbidities.

Contraindications Any contraindication to placing a permanent pacemaker, such as uncontrolled infection.

Complications Polymorphic ventricular tachyrhythmias triggered by bradycardia-induced QT prolongation, as the paced rhythm following ablation is relatively slow compared with the heart rate before ablation. Faster pacing immediately after ablation and gradually reducing the paced rate can reduce this risk. Also, pacemaker complications such as infection and lead dislodgement.

Special points In the APT (Ablate and Pace Trial), the procedure was well tolerated in 157 patients [21]. Benefits noted were marked improvements in ejection fraction in 30% and significant improvements in exercise capacity and sense of well-being. Ventricular-inhibited pacing is associated with an increased risk of future conversion of paroxysmal AF to chronic AF; dual-chamber pacing is preferred, if possible. In a study of 585 patients, a low incidence of sudden death was noted on follow-up. This was associated with left ventricular dysfunction and coronary artery disease [22].

Cost/cost-effectiveness Jensen *et al.* [23] concluded that the cost of this procedure would be become equivalent with that of antiarrhythmic drugs and hospital admissions for uncontrolled ventricular rate at 2.6 years.

Rhythm control

Pacing

Standard procedure Biatrial synchronization: Two atrial leads are used, one in the high right atrium and the other in the proximal, medial, or distal coronary sinus. The mode is either overdrive of the intrinsic atrial rate or triggering of left atrial pacing when intrinsic activity is noted by the right atrial lead.
Dual-site right atrial pacing: Active fixation leads are placed in the high right atrium (usually appendage) and within or at the ostium of the coronary sinus. Either two unipolar or two bipolar leads are used, with each method having unique issues related to sensing and threshold. Both triggered and inhibited pacing modes have been studied.

Contraindications The same contraindications as for a pacemaker, such as uncontrolled infection.

Complications Lead dislodgement (lower incidence with the use of active fixation and better lead designs), pneumothorax, infection.

Special points The SYNBIAPACE (Biatrial Synchronous Pacing for Atrial Arrhythmia Prevention) study showed no difference in time until the first recurrence of AF with biatrial synchronization compared with single-site right atrial pacing. Dual-site pacing shows more promise [24]. The DAPPAF (Dual Site Atrial Pacing to Prevent Atrial

Fibrillation) trial showed overdrive dual-site pacing to be safe, more effective, and better tolerated than overdrive single-site and support pacing in patients with symptomatic AF and bradycardia pacing indications. This beneficial effect of pacing was noted only amongst patients on antiarrhythmic drugs, suggesting an interaction [25]. Both temporary biatrial overdrive and right atrial pacing has been shown to reduce the incidence of postoperative AF.

Cost/cost-effectiveness No figures are available in the literature specifically for dual-site pacing. The cost for the pacemaker and implantation is $17,700; Dual-site pacing incurs the additional cost of a coronary sinus lead (approximately $1500).

Focal atrial fibrillation ablation

Standard procedure Therapeutic anticoagulation for at least 3 weeks prior to this procedure is essential. Multielectrode catheters are placed in the high right atrium, bundle of His, and coronary sinus for recording and pacing. After transseptal puncture, the activated clotting time is kept at longer than 250 seconds with heparin boluses. Two 8-F sheaths, the longer one for the right pulmonary vein, are positioned by torquing them into the right and left upper veins. Selective biplane angiography is performed, in sinus rhythm or during adenosine-induced asystole. For pulmonary vein mapping, one or two 6-F deflectable multipolar catheters or a steerable loop decapolar catheter (Lasso; Biosense Webster, Diamond Bar, CA), 15 to 20 mm in diameter, is positioned in the pulmonary veins through the sheath, which is then withdrawn into the right atrium. Standard quadripolar 4-mm tip catheters and Chilli catheters (Cardiac Pathways Corporation, Sunnyvale, CA) have been used for ablation. If spontaneous atrial premature beats triggering AF are not noted at baseline or when isoproterenol is given, AF is induced by burst pacing, adenosine, or vagal maneuvers. Depending on the P wave morphology of the observed triggering atrial premature beats, the superior or inferior veins are mapped to determine the point of earliest activation (a sharp, high-amplitude pulmonary vein potential that clearly precedes the P wave of the triggering atrial premature beat). Alternately, when using a Lasso catheter, multiple arrhythmogenic veins usually can be identified based on the presence of pulmonary vein potential, and ablation can be directed to the bipoles that show the earliest activation. During ablation in the ostial or proximal vein, the mapping catheter is pushed distally. This latter approach, described by Haissaguerre *et al.* [26], is based on the theory that "electrophysiologic breakthroughs" occur preferentially at one or more segments of the pulmonary vein. Additional ablation is often required at breakthrough sites at other bipoles after the initial ablation. The power for ablation is kept at less than 30 W for 30 to 60 seconds, with a target temperature of 50° C to 60° C. Patency of the targeted vein is confirmed by angiography before working on another vein. After ablation, aggressive attempts to induce AF are performed. Patients are monitored on telemetry for 2 to 5 days after the procedure, given anticoagulants, and discharged while on warfarin. Long-term follow-up is done by transtelephonic electrocardiogram and Holter monitoring and by clinic visits.

Contraindications Absolute: The presence of left atrial thrombus, contraindications for anticoagulation.

Complications Pulmonary vein stenosis (defined as more than 50% narrowing), was associated with the use of higher-power settings (45 to 50 W) in six of 90 patients in a series by Haissaguerre *et al.* [27]. The incidence of stenosis was nine of 225 patients in the series by Shah *et al.* [28••]. Most stenoses involved the left inferior pulmonary vein at the most distal ablation site. Stenosis may be asymptomatic or cause exertional dyspnea, hemoptysis, and pulmonary hypertension. Balloon angioplasty can be successful for treatment. No stenoses were noted when power was less than 30 W. Other complications include hemopericardium, pericardial effusion, air embolism, cerebrovascular accident or transient ischemic attacks (more common in patients with a patent foramen ovale), cough, and significant pain.

Special points It is now widely recognized that paroxysmal AF can be focally triggered. Almost 100% of paroxysmal AFs have a focal origin, most of which are in the pulmonary veins [29••]. Initially, focal ablation was limited to subjects with drug-refractory AF and electrocardiographic evidence for such foci. However, focal ablation is now attempted in almost all patients with frequent drug-resistant paroxysmal AF at

experienced centers. The current focus is on ostial ablation, because it has a lower risk of vein stenosis than distal ablation. In the 220 patients reported by Shah *et al.* [30], the disconnection of pulmonary veins was performed with 100% success (40% of patients required a second procedure). Seventy percent of the patients were free of AF without antiarrhythmic medications and some were taken off anticoagulants. In the remaining 30%, 15% responded to previously ineffective antiarrhythmic drugs, and the other 15% required right atrial linear ablation [30]. Procedure time varies between 2 to 2.5 hours, and is longer for nonpulmonary vein foci. Multiple arrhythmogenic pulmonary veins are associated with lower success rates. Natale *et al.* [31] recently reported high success rates with ostial ablation, mainly in patients with paroxysmal AF, but also in those with persistent and chronic AF. Pulmonary vein stenosis was noted with distal but not ostial ablation, even though the latter required more ablation sites [31]. Schartzman *et al.* [32] concluded that targeting only one vein resulted in a high failure rate of 50%.

An alternative is the isolation of all pulmonary veins, by creating circular lesions more than 5 mm from the ostia around each pulmonary vein. Pappone *et al.* [33] described this procedure using CARTO (Biosense Webster), a nonfluoroscopic electroanatomic mapping system. Long-term success rates were 85%, with 62% of the patients taken off antiarrhythmic drugs. No pulmonary vein stenosis was noted. Overall procedural times were long (290 ± 58 minutes) but fluoroscopy time was reduced with CARTO (25 ± 3 minutes).

Another novel technique, still in its early stages, is ostial pulmonary vein isolation using a saline-filled balloon catheter, with an ultrasound transducer near the tip. Natale *et al.* [34] targeted at least three veins in all patients after initial mapping, and reported a 60% success rate at 35 ± 6 weeks. No pulmonary vein stenosis was noted. Limitations were long procedure time and failure in veins with large ostia.

Cost/cost-effectiveness Focal ablation is not routinely performed in the United States, and is done under institutional review board protocol. According to our data, the cost should be similar to those charged for a standard ablation procedure ($10,500).

Linear ablation

Standard procedure The initial attempts to create linear lesions have used a catheter-drag technique in the right atrium using a standard ablation catheter. Ablation lines are created in the atrial septum connecting the cavae via the fossa ovalis and the coronary sinus os; the inferior vena cava to tricuspid valve annulus isthmus; transversely from the fossa ovalis to the lateral edge of the tricuspid valve; or some variation.

Kay recently described a left atrial catheter maze procedure [35]. A stiff, preshaped, 12-electrode steerable catheter for the left atrium with simultaneous application of radiofrequency energy to all 12 poles was used. A transesophageal echocardiogram is performed before ablation in the left atrium, and therapeutic anticoagulation is essential for 4 to 6 weeks before and after the procedure. Kay [35] also used a glycoprotein IIb/IIIa inhibitor in addition to heparin after transseptal puncture, with a procedural activated clotting time between 225 to 250 seconds. The ablation lines connected the left and right superior pulmonary veins to the mitral annulus, the two superior pulmonary veins, and were also made along the roof of the left atrium.

Procedural transesophageal echocardiogram is useful to verify catheter apposition with the atrial wall. An electroanatomic guiding system such as CARTO may be used to document lesion creation.

Contraindications Absolute: Atrial thrombus, contraindications to anticoagulation.

Complications Complications of ablation in the right atrium include transient sinus node dysfunction, the need for a permanent pacemaker, pulmonary embolism, and acute respiratory distress syndrome. Complications of ablation in the left atrium include hemopericardium (10%), small atrial septal defects (45% of which close by 1 month), cerebrovascular accident, pericardial tamponade, phrenic nerve injury, and air embolism.

Special points Linear ablation lesions aim to nonsurgically compartmentalize the atrium and thus reduce the number of propagating wavelets, which are essential to maintain AF. Right atrial ablation alone, right atrial followed by left atrial ablation, and single-stage biatrial lesion production have been attempted. Results of isolated right atrial ablation have been disappointing. In a series by Haissaguerre *et al.* [36], the immediate success rate was 40%, but AF remained inducible in the majority of patients. Many required reablation of ectopic atrial foci, which caused sustained postprocedure atrial arrhythmias. At 9 months, 15% of patients were free of AF, 20% improved, and the remainder showed no improvement. Left atrial ablation, performed in the patients for whom right atrial ablation had failed, resulted in better immediate and long-term success rates (60%). The procedure duration and fluoroscopy times were long, averaging 2.8 to 6.4 hours and 0.5 to 1.5 hours, respectively [36]. Schartzman *et al.* [37] reported a high failure rate after isolated right atrial ablation using CARTO guidance, with only 19% of the patients free of AF at 2 years.

In the past, enthusiasm for left atrial linear ablation declined after frequent incidence of cerebrovascular accident and pulmonary vein stenosis. In the series by Kay [35], the majority of the patients had chronic drug- and cardioversion-refractory AF. Initial right atrial linear ablation was performed with no success in the majority. Left atrial linear ablation was performed in the patients who failed to respond to right atrial ablation, with good results. In some patients, focal activity from the pulmonary veins was noted after left atrial linear ablation. These patients underwent additional ostial pulmonary vein ablation, after which many of the patients were free of AF when given previously ineffective antiarrhythmic drugs.

Cost/cost-effectiveness Linear ablation is not routinely performed in the United States, and is done under institutional review board protocol. According to our data, the cost may be similar to those charged for a standard ablation procedure ($10,500). Actual costs very from institution to institution.

Atrial defibrillator

Standard procedure For the Metrix 3020 (Guidant, St. Paul, MN), leads are implanted in the right atrium, coronary sinus, and right ventricle. For the Jewel AF device (Medtronic, Minneapolis, MN), atrial and ventricular pace-sense and high-voltage leads are implanted. Sensing and synchronization are essential to ensure appropriate and safe shocks.

Contraindications Active infection, patients who are not psychologically prepared to deal with receiving multiple shocks.

Complications Lead dislodgment, pocket infection, and device migration.

Special points Evidence suggests that early defibrillation favorably affects electromechanical remodeling and decreases left atrial size and AF burden in patients with chronic AF (but not paroxysmal AF).

In a study of 163 patients with no ventricular arrhythmia, the Metrix 3020 was effective 85% of the time. Patient tolerability was 4.2 ± 3.2 (on scale of 1 to 10, with 10 being best) for successful therapy [38]. The Jewel AF is a combined atrial and ventricular defibrillator. In a study of 221 patients, it had a high sensitivity for arrhythmia detection and an overall success rate of 75% [39]. Early reinitiation of AF is a problem, with an incidence of approximately 30%. Most recurrences are within the first minute after conversion and are predicted by a large left atrial size. Postshock high-rate pacing and ablation of pulmonary vein triggers may decrease its occurrence.

These devices may be indicated in patients with infrequent but long-lasting paroxysmal AF, drug-refractory persistent AF, and in those requiring a ventricular implantable cardiac defibrillator, as approximately 20% of such patients will develop AF.

Cost/cost-effectiveness The Jewel AF device costs $25,000. The Metrix 3020 is no longer used.

Surgical therapy

Modified Cox maze III

Standard procedure The procedure is usually performed under cardiopulmonary bypass, though recently it has been done off bypass. The chest is approached through a median sternotomy, and transmural incisions are made so as to isolate the pulmonary veins but to preserve conduction from the sinoatrial node to the atrioventricular node, which activates the remaining atrial tissue, thereby preserving atrial transport function. Both appendages are excised and a cryolesion is made across the coronary sinus posterior to the mitral valvular ring [40•].

Contraindications Coexistent cardiac diseases, which greatly increase the risk of left ventricular dysfunction. A high mortality has been noted when the maze procedure is combined with myomectomy.

Complications Postoperative complications: Atrial arrhythmias, fluid retention (treated with aggressive diuresis).
Long-term complications: Inappropriate sinus tachycardia.

Special points At present, the maze I and II procedures are not performed. The maze III procedure is indicated for medically refractory AF in patients undergoing cardiac surgery, especially with a history of previous embolism. Its advantages are a high success rate (more than 90%); low operative mortality in experienced hands, even when combined with valve or bypass surgery; low postoperative stroke rates (0.7%), which decline further on follow-up; preservation of atrial transport; and low incidence of pacemaker requirement. Postoperatively, patients are usually not anticoagulated (unless otherwise indicated) because the risk of stroke is low after the removal of the left atrial appendage (which is the main source of emboli), even if left atrial function remains abnormal.

Cost/cost-effectiveness It is difficult to define the cost of the maze procedure alone, as it is almost always done with other cardiac surgery. The cost is approximately $6000.

Radial incision approach

Nitta *et al.* [41] have used this approach in a small number of patients. Incisions are made, which radiate from the sinoatrial node towards the atrioventricular annuli, parallel to the atrial coronary arteries. It is felt to be technically easier and result in better postoperative atrial transport function.

Open-chest radiofrequency ablation

This technique has been reported by Melo *et al.* [42], who performed epicardial radiofrequency ablation, to isolate the pulmonary veins using a heptapolar catheter, during concomitant bypass surgery. Some of the procedures were done off-pump. The procedure time was short (32 ± 10 minutes) and there was no morbidity or mortality. Seven out of nine patients were free of AF at 6 months.

Other therapies

Direct-current cardioversion

Standard procedure External cardioversion: Either anterior-apex or apex-posterior positioning can be used. Initial energy used can be 360 J, or 200 J in incremental increases. The delivery of energy should be synchronized to the R wave, as delivery on the T wave can trigger ventricular fibrillation. In a study comparing a rectilinear biphasic waveform external defibrillator with the standard damped sine-wave monophasic waveform defibrillator, the former increased cumulative efficacy of cardioversion from 79% to 94% [43]. The energy levels used were between 70 and 170 J. The biphasic defibrillator was especially useful in patients with a high transthoracic impedance of more than 70 ohms.
Internal cardioversion: This is best accomplished by delivery of a biphasic 3/3 msec shock between catheters in the right atrium and coronary sinus.

Contraindications Direct-current cardioversion is contraindicated in patients with digitalis toxicity or at high risk for postshock asystole, unless pacing capability is available.

Main side effects Ventricular fibrillation: to minimize the risk, shock delivery should be synchronous to the QRS and avoided during rapid RR cycles (less than 300 msec). Other risks are skin burns, postshock bradycardia or pauses, and those related to invasive procedures (for internal cardioversion).

Special points External defibrillation has efficacy rates of 67% to 94%. Cardioversion failure may be due to a high defibrillation threshold due to increased thoracic impedance (patients with voluminous lungs or large chests) or AF of long duration due to atrial remodeling. Internal defibrillation has greater efficacy compared with external cardioversion, with AF duration being the most important predictor of defibrillation threshold. Internal fibrillation is indicated for failed external cardioversion or in patients who are not good candidates for general anesthesia or sedation, as it can be accomplished with little or no sedation.

Cost/cost-effectiveness In deciding on the cost-effectiveness of electrical versus pharmacologic cardioversion, factors such as the need for hospital admission, prolonged telemetry monitoring (in case of ibutilide), and costs of sedation and anesthetist services need to be considered.

Emerging therapies

- Improved methods of both focal and linear ablation and mapping, which allow higher success, lower risk, improved patient tolerance, and shorter procedure and fluoroscopy times. Examples include the use of ultrasound balloon and cryoablation catheters for pulmonary vein isolation, and loop catheters with multiple coil electrodes for linear ablation.
- Development of implantable devices that allow local cardiac drug delivery for immediate arrhythmia termination.
- Improved lead and device designs to decrease the defibrillation threshold and thus increase the tolerability of implantable atrial defibrillators.
- Atrial fibrillation prevention using targeted cellular therapies.

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