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Nondrug therapies in atrial fibrillation: Evolving strategies in rhythm and rate control, Part 1

Learning Objectives

After reading this article, the reader should be able to: (1) describe the uses and limitations of current drug therapy for managing atrial fibrillation (AF); (2) discuss specific situations when nondrug therapies may be considered appropriate for rhythm or rate control; and (3) review the evidence supporting use of pacing and implantable cardioverter/defibrillator devices in specific patient types with AF.

James A. Reiffel, MD

This issue provides the first of a 2-part update on the role of nonpharmacologic therapy in the management of atrial fibrillation (AF). In recent years, nondrug strategies have emerged as the limitations of antiarrhythmic and anticoagulant drug therapy have become clear and as medical technology has grown more sophisticated and adaptable for the growing population of elderly patients with AF. These new nondrug options for common arrhythmias are increasingly in the public eye—from US Vice President Dick Cheney's implantable defibrillator to UK Prime Minister Tony Blair's catheter ablation procedure—a presage of the baby boom generation's likely growing interest in the dangers of age-related arrhythmias and the options for more permanent devices or procedure-based solutions. This newsletter is based on recent Grand Rounds presentations by James A. Reiffel, MD, Columbia University College of Physicians and Surgeons, New York.

Atrial fibrillation (AF), the most common sustained arrhythmia requiring treatment,[1] currently affects about 2.2 million to 2.3 million individuals in the United States.[2,3] The prevalence increases with age, from <0.5% in those younger than 50 years of age, to approximately 2% at ages 60 to 69 years, to about 9% to 10% in those 80 years or older,[1,2,4] an

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This special report was made possible by an educational grant from Reliant Pharmaceuticals, Inc. The opinions expressed herein are not attributable to the sponsor or to the publisher, editor, or editorial board of *Cardiology Review*. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made herein may indicate use of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information. This report contains discussions of the use of amiodarone for atrial fibrillation and of new catheters and energy sources for ablation, which are therapeutic indications not currently approved by the FDA. PROJ M425

association that, in conjunction with the aging of the baby boom generation, portends a doubling in the prevalence of AF over the next 20 years.[4]

Although many patients with AF are minimally or mildly symptomatic, all are at increased risk of profound hemodynamic deterioration, disabling heart failure (HF), hospitalization, and/or thromboembolic stroke.[5-7] The most common symptoms, none of which are specific to AF, include palpitations, fatigue, dizziness and syncope, exertional intolerance, dyspnea, and chest pain. Signs of HF and tachycardia-induced cardiomyopathy may also develop as a result of long-term sustained AF. Perhaps most critically, AF is also estimated to cause about 1 of every 5 of the 700000 new or recurrent strokes that occur in the United States every year.[2]

The current guidelines for antiarrhythmic drug therapy in patients with AF are driven to a large degree by the patient's cardiovascular status.

The presentation of AF varies from patient to patient not only in terms of pattern, severity, and symptoms, but also in terms of associated underlying structural heart disease. The nature of this underlying structural disease strongly influences the presentation of AF as well as the risk of thromboembolism and the potential benefits and risks of specific pharmacologic therapies. In fact, the current guidelines for antiarrhythmic drug therapy in patients with AF are driven to a large degree by the patient's cardiovascular status, including the presence or absence of HF, coronary artery disease, or hypertension with or without substantial left ventricular hypertrophy.[8] However, in applying these evidence-based treatment guidelines from the American College of Cardiology, American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC), cardiologists must also consider the patient's potential underlying etiology and triggers, the pattern of presentation (ie, paroxysmal, persistent, or permanent), the severity of symptoms related to reduced hemodynamic function, the risk factors for thromboembolism, and, of course, the patient's preferences.[9]

The dominant treatment issues in AF are the arrhythmia itself and the prevention of thromboembolism (Figure 1). Because of the difficulty of completely abolishing AF with procedures such as focal ablation, long-term anticoagulation therapy with warfarin or aspirin has become the standard to prevent stroke in patients with persistent AF.[10] Unfortunately, optimal anticoagulation dosing is difficult to maintain, and a new direct thrombin inhibitor, thought to be an easier-to-administer alternative to warfarin, was recently rejected by the US Food and Drug Administration because of as yet unsettled safety concerns. This continuing failure to uniformly reduce the stroke risk maintains the pressure on physicians to manage the dysrhythmia itself. For this, the 2 main options remain: (1) restoring and maintaining the sinus rhythm, and (2) allowing the AF to continue while ensuring that the ventricular rate is controlled.

The medical options for rhythm and rate control were reviewed in the previous issue of *Arrhythmia Clinic*

(see September 2004 issue available at www.webcentral.uc.edu/cme). This supplement continues with a brief review of the inherent limitations of anti-AF drugs. The following is an expanded review of 2 key nonpharmacologic approaches—atrial pacing methods and atrial defibrillators—which have recently seen expanding, although still somewhat limited, use. The second part of this newsletter series will focus on surgical and radiofrequency catheter ablation procedures for the management of AF.

The complexities of managing AF with drugs

In attempting to control rate or rhythm, no single drug approach works for all patients with AF. Drug choices are driven by efficacy, tolerance, convenience, cost, interactions, and, most important, safety.[9,11] Control of ventricular rate is essential both for symptom reduction and the prevention or reversal of tachycardia-induced cardiomyopathy. The main choices for rate control are beta blockers, verapamil, diltiazem, and/or digitalis (especially in elderly or sedentary individuals). If these agents fail because of inefficacy and/or intolerance, atrioventricular (AV) node ablation, coupled with pacemaker insertion, becomes the therapy of choice.

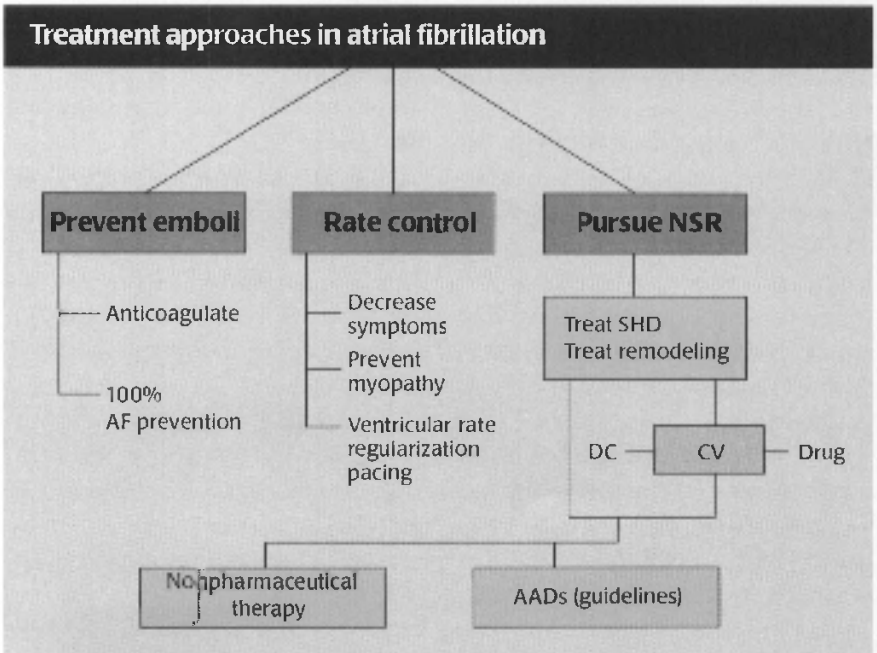
When patients with AF have significant symptoms that persist despite rate control, rhythm control is pursued to prevent development of recurrent AF. Currently, the main choices for maintaining sinus rhythm are propafenone, flecainide, sotalol, dofetilide, and amiodarone. Because efficacy rates with these agents are generally similar (slightly higher with amiodarone), the current guidelines emphasize safety considerations. In particular, the treatment algorithm is based on the presence or absence of underlying abnormal ventricular pathophysiologic states that can promote ventricular proarrhythmia, as well as on the potential for organ toxicity (eg, pulmonary fibrosis, agranulocytosis, lupus, hepatitis, optic neuritis) and nuisance effects.

The prevalence of such side effects varies by drug class (Figure 2).[12] For example, organ toxicity is relatively higher with amiodarone whereas it is negligible with dofetilide, flecainide, propafenone, and sotalol. The proarrhythmic state known as torsade de pointes is mainly a consequence of class III and Ia antiarrhythmic drugs, whereas monomorphic ventricular tachycardias are associated more with class I (especially Ic) agents. Complicating drug selection even further, the proarrhythmic risk with the potassium-blocking drugs also depends on heart rate, ventricular hypertrophy, potassium and magnesium concentrations, baseline QT interval, sex, use of other QT-prolonging drugs, and renal and hepatic function.

Achieving efficacy without toxicity is a notoriously elusive goal in antiarrhythmic drug therapy. For example, although amiodarone is probably the most effective agent (40%-60% efficacy in maintaining long-term sinus rhythm) it is also the most toxic, with multiple class effects, multiorgan toxicity, drug interactions, and an overall 30% discontinuation rate.[12] The dose, duration of therapy, and patient type will affect amiodarone adverse event rates.[12]

By contrast, the class Ic agents generally produce no ventricular

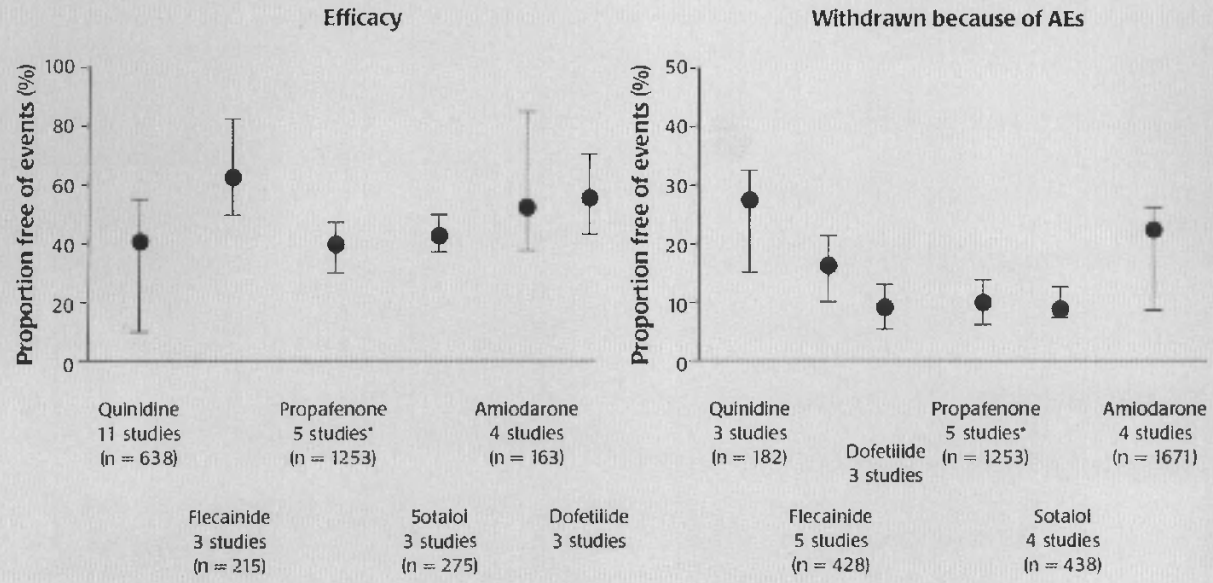
FIGURE 1



NSR = normal sinus rhythm; SHD = structural heart disease; AF = atrial fibrillation; DC = direct current; CV = cardioversion; AADs = antiarrhythmic drugs.

FIGURE 2

Selecting pharmacologic therapy for maintaining sinus rhythm: Can we achieve efficacy without toxicity?



AEs = adverse events.
Source: Blitzer M, et al. *PACE.* 1998;21:590-602,742-752,1135-1145.
*Adapted/updated by Dr. Reiffel in October 2004 to include data from RAFT (Rythmol Atrial Fibrillation Trial) and ERAFT (European Rythmol/Rytmonorm Atrial Fibrillation Trial) studies.

proarrhythmia in the absence of underlying structural heart disease, no organ toxicity, and only a 10% discontinuation rate. Such class differences likely explain the results of a recent direct comparison of amiodarone versus propafenone in patients with AF in which the higher discontinuation rate of patients taking amiodarone canceled the slightly higher AF recurrence rate with propafenone, producing an overall benefit (efficacy without drug withdrawal) for 35 of the 72 patients taking amiodarone versus 39 of the 74 patients taking propafenone.[13]

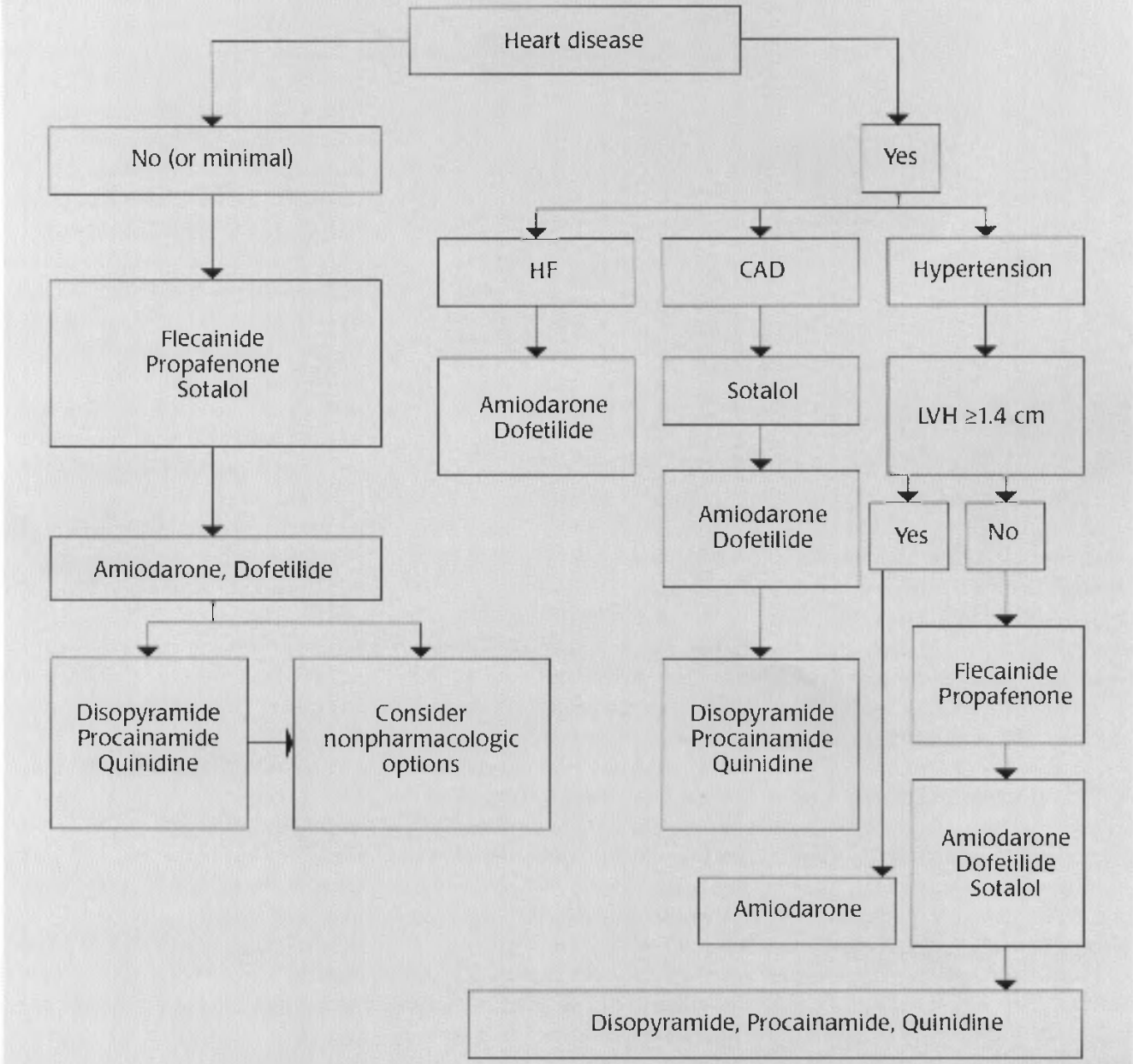
In fact, a multitude of drug differences must be carefully weighed before choosing and changing agents for sinus rhythm control. These include within-class distinctions, such as those between sotalol and dofetilide, as well as those between propafenone and flecainide in terms of beta blocker actions and drug interactions. Even alternative forms of the same chemical entity can produce key differences in dosage, dosing, and clinical utility, as seen with slow- and immediate-release forms of propafenone.

The potential for drug interactions with antiarrhythmic agents must also be considered on a drug-by-drug basis; with amiodarone, propafenone, and quinidine, for example, known interactions include warfarin and digitalis. Amiodarone also has known interactions with about 50 other drugs, whereas dofetilide interacts with more than 20 drugs, including all QT-interval–prolonging drugs, and is contraindicated with verapamil.

As summarized in the previous issue of *Arrhythmia Clinic*, the ACC/AHA/ESC guidelines offer a logical antiarrhythmic treatment approach that attempts to balance many of the drug-specific and patient-specific factors just described.[8] Unfortunately, antiarrhythmic drugs do not always maintain sinus rhythm, and side effects also greatly limit their use in many patients.[14] Choice of the wrong agent for a specific patient can lead to bradyarrhythmias, ventricular tachycardia, syncope, cardiac arrest, or organ toxicity. The stubborn persistence of AF despite drug therapy plus the potential for serious or fatal

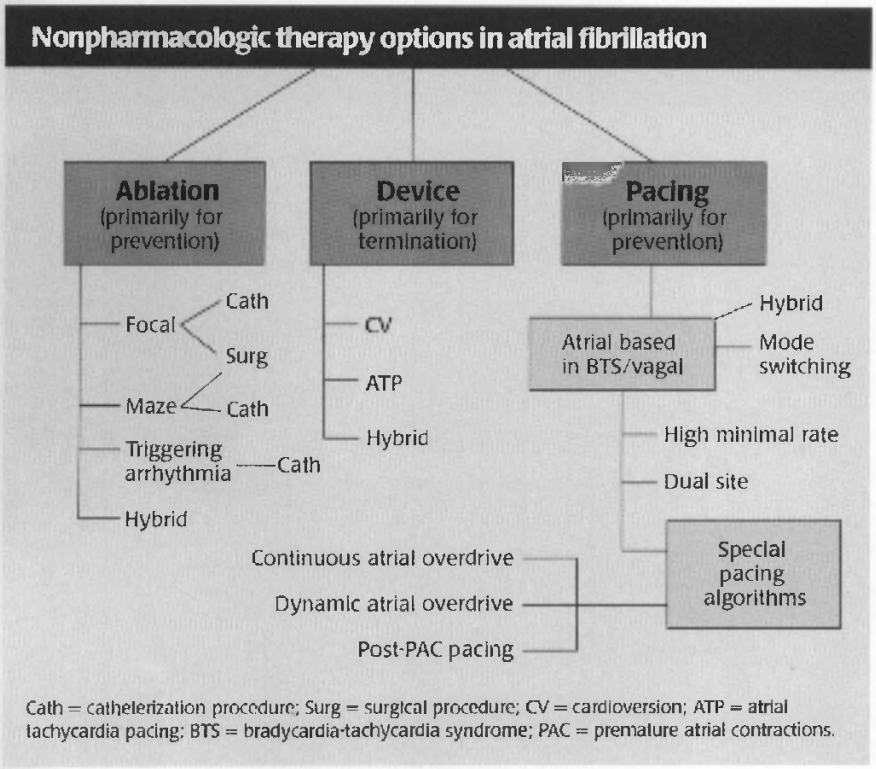
FIGURE 3

Guidelines for antiarrhythmic therapy in atrial fibrillation: When are nonpharmacologic options considered?



HF = heart failure; CAD = coronary artery disease; LVH = left ventricular hypertrophy.
Source: Fuster V, et al.[8]

FIGURE 4



Cath = catheterization procedure; Surg = surgical procedure; CV = cardioversion; ATP = atrial tachycardia pacing; BTS = bradycardia-tachycardia syndrome; PAC = premature atrial contractions.

side effects indicates that nondrug approaches must often be considered, especially in those with symptoms of HF. Recent insights into the mechanisms of AF and parallel advances in medical technology have resulted in an increasing use of nonpharmacologic treatments for AF.[15] As indicated in Figure 3, many clinicians today are switching to nonpharmacologic therapies earlier in the treatment algorithm.

Nonpharmacologic therapy

The major types of nondrug therapies for AF are atrial pacing, cardioverter-defibrillator devices, and surgical or catheter ablation procedures (Figure 4). These therapies are so rapidly evolving that even the 2001 ACC/AHA/ESC guidelines offer only minimal guidance on when and how to employ them. Accordingly, a revision of these guidelines is planned for the near future.

To assist practitioners, the mechanisms, potential indications, clinical evidence, and practical implications of the pacing and arrhythmia-terminating devices are outlined in the following sections. Also presented are several case studies illustrating how empiric clinical judgment remains of paramount importance in applying the current broad AF guidelines to individual patients. As highlighted in these AF patient vignettes, it is often the subtle or changeable "nonalgorithmic issues" that determine the choice of drug, nondrug, or combination therapy required for a patient with AF at a particular time. Similar background and case-based discussion of the latest surgical and catheter ablation procedures will be presented in the next issue of *Arrhythmia Clinic*.

Pacing. In addition to the pacing that is required in conjunction with AV node ablation (to be discussed in Part 2), various atrial pacing techniques have now been tested in patients with vagotonic AF, sick sinus syndrome, bradycardia, and a range of other AF conditions, to reduce symptoms, reduce recurrences of paroxysmal AF, and/or enhance drug therapy. Although the clinical data of the past decade are mixed,[16-20] the bulk of these studies support use of atrial-based pacing in patients with vagotonic AF or sinus node disease—especially if a relatively high minimal rate (eg, 80 bpm) is used, often in combination with antiarrhythmic drug therapy.[21-24] If nothing else, use of atrial-based pacing in this latter category of patients will allow higher doses of antiarrhythmic drugs.[1]

Atrial pacing may alter AF pathophysiology and/or symptoms by eliminating 2 prominent triggers of AF—pauses followed by escape beats and premature atrial contractions—and by generally smoothing the pulse after AF starts. In an attempt to enhance suppression of paroxysmal AF, pacing methodologies are now also being tested at novel atrial sites (eg, multisite, septal, coronary sinus ostium, Bachmann's bundle) and with special pacing software algorithms (eg, dynamic atrial overdrive, post-premature atrial contractions). These new sites and algorithms may reduce AF triggering pauses, prevent pause-related electrophysiologic alterations, reduce the total atrial conduction time, and make atrial depolarization and repolarization less heterogeneous. These new pacing methodologies are being evaluated in ongoing studies,

such as the Atrial Fibrillation Therapy (AFT) study, the Dual Site Atrial Pacing for Paroxysmal Atrial Fibrillation (DAPPAF) study, and the SYNchronous BI-Atrial PAC(E)ing (SYNBIAPACE) study, which have been reviewed elsewhere.[15,25] Additional potential advantages of pacemakers for patients with AF include remote evaluation of symptoms via telemetric interrogation and the incorporation of mode-switching algorithms for AF and flutter.

Although promising and worthy of further study, pacing solutions alone will likely provide >10% of AF patients with a long-term solution over the next decade. Given the potential of pacing both as prevention and as termination therapy, however, hybrid therapy involving pacing is likely to be a more common solution than defibrillation in coming years.

Other devices. For patients with intermittent but severe symptoms of AF, internal cardioversion may soon play a larger role. The latest iterations of atrial implantable cardioverter/defibrillators (ICD) now provide synchronized defibrillation and low-energy cardioversion as well as antitachycardia pacing. The devices can be activated automatically or by the patient. In addition to those with infrequent but recurrent and significantly symptomatic or persistent AF, candidates for such devices may include patients with spontaneous or drug-mediated atrial flutter or those with other types of initiating arrhythmias responsive to antitachycardia pacing.

Several relatively small and short-term trials have documented the success of implantable atrial defibrillators in safely converting episodes of AF. In clinical trials of the Atrioverter (InControl, Redmond, Wash), the first implantable atrial defibrillator, conversion to normal sinus rhythm was reported in >90% of patients with AF who were refractory to drug therapy (Table).[26,27]

Similar efficacy has been reported with the Jewel AF (Medtronic, Minneapolis, Minn), a device with dual-chamber sensing and pacing as well as defibrillation capability in both the atrium and ventricle.[28] This device discriminates atrial from ventricular tachyarrhythmias and is capable of delivering antitachycardia pacing.

In many of the ongoing trials, the devices are being tested in conjunction with antiarrhythmic drugs in an effort to improve efficacy or patient acceptance (eg, by reducing the potential harm of proarrhythmic effects and by enhancing pace termination of drug- or ablation-mediated flutter rather than shock termination of AF). These devices are also likely to be used in the expanding population of patients with AF who undergo ablative procedures.

Hybrid therapy involving pacing is likely to be a more common solution than defibrillation in coming years.

Although the preliminary data with implantable atrial defibrillators are promising, long-term outcomes are lacking, and the energy levels needed for cardioversion are still painful and intolerable for many patients. Thus, a suitable patient for an implantable atrial defibrillator must not only have infrequent episodes of significantly symptomatic AF, he or she must also have the capacity to sustain the discomfort associated with cardioversion shock. The indications for these devices are likely to evolve over time.

An intriguing, but still theoretical, rationale for ICD use by patients with AF involves the alteration of the natural history of recurrences. This hypothesis states that early and repeated cardioversion will reduce the incidence of AF recurrences. For

TABLE

Results with an implantable atrial defibrillator

- Multicenter trial (19 centers, 9 countries) of Atrioverter
- 51 patients (40 men, 11 women) with mean LVEF 0.58 ± 0.11
- Not responsive to antiarrhythmic drug therapy: mean number of AADs at entry: 3.8
- Followed for 72 to 613 days after device implantation
- Result: 96% of 227 AF episodes in 41 patients successfully converted to sinus rhythm
- 27% needed multiple shocks because of early AF recurrence

LVEF = left ventricular ejection fraction; AADs = antiarrhythmic drugs; AF = atrial fibrillation.
Source: Wellens H, et al. *Circulation.* 1998;98:1651-1656.

years, cardiologists have recognized that AF duration before cardioversion affects the probability of post-cardioversion recurrence.[29] Recent evidence in goat models indicates that lengthier episodes of AF are associated with electrophysiologic changes and a reduced likelihood of spontaneous cardioversion.[30] Human data now show that prompt cardioversion can lengthen the interval to AF recurrence.[31]

Initial concerns about intolerance to ICDs in patients with AF have lessened as device designs and programs have improved. As with pacemakers, however, defibrillator and antitachycardia pacing devices as monotherapy are likely to be appropriate for <10% of the AF population requiring treatment.

Conclusion

In years to come, drugs will remain first-line therapy for most patients with AF. Atrial pacing devices and defibrillators will have an increasing but limited role in treating patients with very specific conditions. By contrast, ongoing enhancements in ablation techniques will lead to these procedures assuming a progressively larger role in AF management—perhaps accounting for as much as 30% to 50% of first-line AF therapy by 2010. (These ablation techniques will be discussed in Part 2 of this newsletter series.) In years to come, hybrid therapeutic approaches involving drugs—including safer agents and more convenient new formulations of older agents—together with pacing, ICDs, and ablation, will become the norm.

Even today, the sheer heterogeneity of AF patient types makes a single algorithm or treatment approach unrealistic.[9] As nondrug therapies continue their rapid evolution and clinical uptake, clinicians will be even more challenged to create and maintain consensus guidelines that reflect the latest evidence. Decision making in AF therapy will increasingly rely on the empiric judgments of well-informed clinicians.

CASE 1 Report

Presentation

The patient is a 77-year-old man with a 7-year history of initially paroxysmal and more recently persistent atrial fibrillation (AF) and hypertension. He has been taking aspirin for the past 5 years and a beta blocker for the past 3 years. He has had 2 elective electrical cardioversions over the past 2 months. No antiarrhythmic drug therapy has been tried yet.

- Presents 48 hours after last cardioversion again with AF, reports palpitations, fatigue, mild lightheadedness, and anxiety about increasingly persistent AF.
- Stress-echocardiography done 6 months ago as part of his hypertension follow-up showed left ventricle 1.1 cm thick, normal left ventricular ejection fraction (LVEF), and no ischemia.
- Electrocardiogram (ECG) within normal limits except for AF.

Drug treatment

- Antiarrhythmic drug therapy is added before the third direct-current cardioversion in an attempt to suppress recurrent AF.
- Because there is no underlying structural heart disease other than hypertension and no LV hypertrophy associated with the hypertension, propafenone or flecainide are appropriate choices.
- Beta blocker continued.
- Switch to warfarin for anticoagulation because of increased risk factors (eg, age and hypertension).

Follow-up and consideration of nondrug therapy

- Recurrences are infrequent (3 paroxysmal AF episodes, all <3 hours) and apparently well tolerated over the next 7 months.
- Echocardiogram shows no loss of LV function 3 months after cardioversion.
- However, patient now presents to emergency department with extreme fatigue and sinus rate of 36; testing reveals sick sinus syndrome.
- Atrial pacemaker with interatrial septal pacing is implanted.
- With the sinus node dysfunction treated, his drugs are maintained and the propafenone dose is increased to try to further reduce his paroxysmal AF.
- The patient has been kept in sinus rhythm and free of bradycardia for the next year.

Comment: Elderly patients often develop sick sinus syndrome as a consequence of AF drug therapy. Data support using atrial-based pacing in patients with sick sinus syndrome.[21,22]

CASE 2 Report

Presentation

A 46-year-old man has a 5-year history of episodes of paroxysmal AF at night and after large meals when much wine has been served. He has no structural heart disease or hypertension. He is currently taking a statin for high cholesterol and a selective serotonin reuptake inhibitor for mild depression. His primary care physician added a beta blocker 3 months ago, and recently referred him for evaluation of AF after 1 week of almost nightly AF episodes.

Initial evaluation and treatment

- History reveals that alcohol is not always a precipitant of AF episodes (he has eliminated all drinking except 1 glass of wine on Friday and Saturday evenings).
- No evidence of sick sinus syndrome or hyperthyroidism.
- Patient is fatigued, associated with loss of sleep caused by paroxysmal AF symptoms.
- Preliminary diagnosis after further tests including Holter ECG analysis: paroxysmal AF related to heightened vagal tone.
- One year of treatment with disopyramide without beta blocker is only partially effective in preventing recurring self-terminating episodes, despite increasing doses of the antiarrhythmic agent.

Follow-up and consideration of nondrug therapy

- Accelerating rate of recurrences, growing patient anxiety, and fatigue lead to consideration of atrial pacing in conjunction with vagolytic antiarrhythmic drug.
- Atrial pacemaker is inserted and disopyramide is continued.
- Episodes of AF now 1 to 2 per month and self-terminating in <30 minutes.

Comment: The vagal stimulation that can accompany sleep or postprandial states can shorten the refractory period of atrial myocardium and lead to paroxysmal AF.[1] Certain drugs, such as quinidine and disopyramide, with or without atrial pacing appear to be effective in AF of neurogenic origin.[23]

CASE 3 Report

Presentation

A 54-year-old man with hypertrophic obstructive cardiomyopathy presents with syncope and pulmonary edema triggered by AF. He has been taking an angiotensin-converting enzyme inhibitor and a beta blocker. The AF has recurred 3 times in 2 years, manifesting as lightheadedness and congestive heart failure after 6 hours, despite rate control.

Initial evaluation and treatment

- ECG and echocardiogram confirm severe LV hypertrophy with a hyperdynamic but stiff left ventricle.
- Amiodarone is added but then discontinued 8 months later because of chest film changes and the onset of neuropathic symptoms.
- His severe LV hypertrophy contraindicates use of sotalol, dofetilide, or class I antiarrhythmics.

Follow-up and consideration of nondrug therapy

- An implantable cardioverter defibrillator capable of atrial and ventricular pacing and defibrillation is implanted.
- Recurrent AF, which continues at 1 to 2 episodes per year, is treated with elective, patient-initiated shock conversion, each done 1 hour after sedation with diazepam.

Comment: The tolerance for AF is impacted by the properties of the ventricle. For patients with infrequent and very poorly tolerated AF, cardioversion with an implanted device may be beneficial.

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