Overview of the Management of Atrial Fibrillation: What is the Current State of the Art?

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Management of Atrial Fibrillation. There are three fundamental approaches to the management of atrial fibrillation (AF): rate control, rhythm control, and anticoagulation. Selecting a course of treatment requires a thorough knowledge of these therapeutic alternatives. This article explores treatment options, including the relative benefits of rate control versus rhythm control, which are complicated by the lack of highly effective and safe antiarrhythmic drugs. Anticoagulation is also an important issue in AF management, and warfarin effectively reduces the incidence of thromboembolic events in AF patients. The use of warfarin, however, presents its own complications. We conclude that individualization of therapy is paramount when treating AF. *(J Cardiovasc Electrophysiol, Vol. 14, pp. S275-S280, December 2003, Suppl.)*

sinus arrhythmia, antiarrhythmic drugs, anticoagulants, atrial fibrillation, left ventricular dysfunction

Introduction

Atrial fibrillation (AF) is a complicated disease state that requires a multifaceted management approach. It is not an exaggeration to say that this disease requires as much clinical skill in management as any disorder that doctors treat. On one hand, we have learned that AF need not be treated aggressively in many patients, but we also know that AF frequently is complicated by disabling stroke, an outcome worse than death for most patients who experience this devastating and avoidable complication of the disease. Thus, as in no other condition, individualization of therapy is paramount, while still adhering, as best we can, to basic treatment dictums derived from well-designed and well-executed clinical trials.

In this article, we consider the three major components of AF treatment: rate control, rhythm control, and anticoagulation. Because other articles in this issue of the Journal review specific therapies, we confine this discussion to the broad categories, highlighting treatment options and the trial evidence to support them. For most of this discussion, atrial flutter will not be discussed separately unless there are specific data pertaining to that arrhythmia that are not applicable to AF as well.

Rate Control

The first step in the treatment of AF generally is control of the ventricular response rate. In elderly patients, especially those with conduction disease, rates may be well controlled at the onset of AF, but for the majority of patients with intact AV nodal conduction, some rate control medication is necessary. Which drug is used and how it is delivered depends on several factors, including the drug's pharmacologic profile, the urgency of the clinical situation, the patient's clinical stability, and concomitant drug therapy and medical conditions.[1,2] In general, rapidly acting calcium channel blockers or beta-blockers are administered intravenously when a clinical effect is needed quickly. It is important to note that only a minority of patients who develop AF have so much hemodynamic compromise that intravenous administration of AV nodal-blocking agents is necessary. In the majority, a short-acting oral beta-blocker or calcium channel blocker, with a short time to effect, may suffice, with longer-acting oral congeners reserved for long-term clinical use. Weaker AV nodal blockers, such as digitalis, are reserved as adjuvant therapy for patients whose AV nodes are diseased, when single-drug treatment does not suffice, or for management of heart failure.[3-6] The adequacy of rate control is difficult to define, but heart rates of <80 beats/min at rest with attainment of $<90\%$ of the maximum predicted heart rate with maximal exercise would be considered acceptable. Alternatively, criteria have been applied based on control of rate during a range of activities of daily living. It is critical, however, that optimization of heart rate be judged with the patient at rest and then during exertion, because the rate control effect of agents such as digitalis may be overcome by catecholamines, rendering the patient uncontrolled during a significant portion of her/his daily routine.[6,7] In those rare cases where conventional AV nodal-blocking agents are ineffective, such as in very ill patients, amiodarone may be useful because the drug's earliest effect, when administered intravenously, is negative dromotropism via its noncompetitive beta-adrenergic and calcium channel-blocking effects.[6] Careful rate control is paramount no matter which agent is used, because high heart rates over time may cause severe symptoms as well as profound left ventricular dysfunction in some individuals.[8,9] This is part of the rationale for considering AV nodal ablation and permanent pacemaker implantation in select patients who also may be suffering from severe symptoms caused by the rapidity and irregularity of their arrhythmia.[8] The relative benefits of rate

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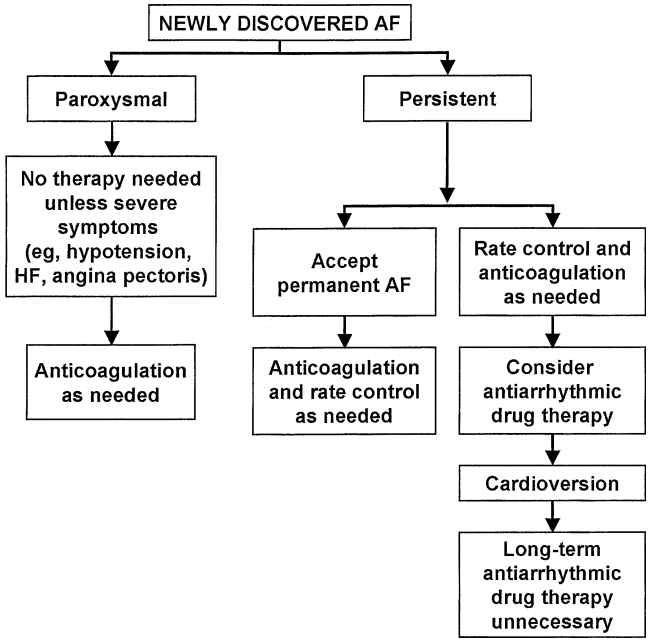

Figure 1. *An approach to the management of "new" atrial fibrillation, as previously published in the ACC/AHA/ESC guidelines.[10] (Reproduced with permission from Fuster V, Ryden LE, Asinger RW, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation); North American Society of Pacing and Electrophysiology: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary. Circulation 2001; 104:2118–2150.)*

control versus rhythm control will be considered in a subsequent section of this article.

Rhythm Control

The other broad strategy in AF management is maintenance of sinus rhythm (SR) (Fig. 1).[10] This approach has two parts: restoration of SR for patients whose AF is persistent, and chronic treatment to prevent AF recurrence. Conversion of AF to SR can be accomplished electrically or pharmacologically. Electrical conversion is well established, highly effective, and generally safe, especially when carried out electively. Emergent cardioversion is an uncommon event, because most patients can be rendered stable with acute rate control and measures to treat an underlying disease process. This is fortunate, because patients frequently are not prepared properly for cardioversion, having recently eaten and not being properly anticoagulated. In addition, emergent cardioversion is plagued with a very high relapse rate because the conditions that led to the arrhythmia still are present.[11,12] For elective cardioversion, with good technique including the use of biphasic waveform devices and adequate anesthesia, >95% of patients can be shocked into SR.[13–15] Unfortunately, early recurrence of AF and late relapses are not uncommon and occur as a consequence of concomitant cardiac or electrical disease and other factors, the most important of which may be the duration of the antecedent arrhythmia.[16,17] Prevention of early or late relapses usually requires predosing with antiarrhythmic drugs or beta-blockers.[5,6,11,12,18,19]

Pharmacologic conversion, although less effective, has the potential of better patient acceptance and wider applicability. It is important to note that, in general, drugs are more efficacious for converting AF of shorter than longer duration. In fact, very few drugs have been systematically studied and approved for this indication. Class IA and IC drugs have been used intravenously and orally with good reported success. The Class IC drugs appear to be effective and safe for termination of AF of relatively recent onset in patients with normal or nearly normal hearts, and they can be used either orally or parenterally.[20–22] However, the drugs approved for this indication are intravenous ibutilide and oral dofetilide, both Class III antiarrhythmic drugs. Ibutilide has no oral congener and thus is limited to acute therapy only. It appears to work better in patients with arrhythmias of relatively recent onset and has greater efficacy in atrial flutter.[23,24] Its principal liability is torsades de pointes, which occurs in 2% to 4% of patients and is more likely in women, the elderly, and patients with left ventricular dysfunction.[25–27] Dofetilide was approved for this indication based on its record of effectiveness in patients hospitalized for oral drug loading. Conversion to SR occurs in 30% of patients with persistent AF compared with a placebo conversion rate of about 1% to 3%.[28] As with ibutilide, dofetilide's principal liability is torsades de pointes, which fortunately happens early in dosing while the patient is under observation.[25,27,29]

Other drugs have been used for acute conversion of AF without convincing demonstration of effectiveness. Amiodarone has gained popularity for this indication. Although many previous studies were unconvincing as to amiodarone's efficacy for this indication,[30] more recent data have suggested that infusion of high doses for several hours might be useful.[31] Spontaneous conversions in this population occur with such variable frequency that carefully done, large, placebo-controlled trials are essential before any conclusions can be reached about the efficacy and safety of drugs for this indication. Amiodarone's peculiar pharmacokinetic profile makes such studies difficult to execute and to interpret.

Proper anticoagulation prior to and following cardioversion is a key item in its safe implementation. Fortunately, we now have good data on which to base firm recommendations about the proper use of anticoagulant therapy to prevent stroke and other thromboembolic events.[30] These recommendations will be presented in the section on anticoagulation later in this article.

Chronic maintenance of SR remains the major challenge in this realm. To date, we have not seen the development of any antiarrhythmic drug with sufficient efficacy and safety to allow us to administer it with confidence to a broad sample of patients. It is important to remember that even with optimal therapy, drug treatment is rarely "curative." In most cases, the most we should expect is a reduction in the frequency, duration, and severity of the events, which may be adequate in some patients to improve their quality of life and to allow them to pursue their usual activities.[32] In addition, antiarrhythmic drugs have the potential for toxicity. The best we have been able to do is to describe safety and efficacy in carefully defined patient populations to allow physicians to prescribe one or another agent depending on the individual patient profile. For example, it is important to distinguish between paroxysmal and persistent AF, because the former frequently causes severe symptoms in young active

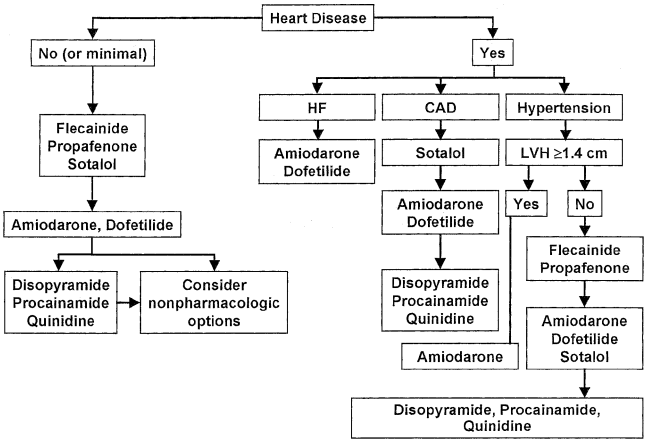

Figure 2. *A pharmacologic approach to maintenance of sinus rhythm, as previously published in the ACC/AHA/ESC guidelines.[10] (Reproduced with permission from Fuster V, Ryden LE, Asinger RW, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation); North American Society of Pacing and Electrophysiology: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary. Circulation 2001; 104:2118-2150.)*

individuals whereas the latter may become less noticed and more amenable to a conservative strategy of rate control only. The latest guidelines issued by our professional organizations have grouped patients by type of heart disease and presented what might be considered first-line and alternative drug therapy based on that classification (Fig. 2).[10] For example, in the realm of congestive heart failure, the drugs best studied for efficacy and safety are clearly dofetilide and amiodarone, which makes those two agents the preferred therapy for patients with severe left ventricular dysfunction. It appears from good trial data that neither drug is associated with deterioration of left ventricular function in these patients, nor does either agent predispose patients to lethal proarrhythmia once they have been started carefully and as long as rigid dosing guidelines are adhered to. Similarly, sotalol, dofetilide, and amiodarone are featured for patients with ischemic heart disease based on good data from randomized clinical trials that the drugs were safe in such patients, and with effectiveness not diminished in comparison to patients without coronary artery disease.[33-35] Many more agents have been examined in patients with normal hearts, multiplying the therapeutic alternatives for those patients. Although highly useful for clinical purposes, schema such as these point out the limitations of the chemical agents currently on the market and the need for better comparative information. It also is clear that we need better antiarrhythmic drugs with less attendant cardiac and organ toxicity. In fact, several new agents are under active investigation that have greater specificity for atrial electrophysiology or have novel mechanisms of action to circumvent the problems engendered by blocking standard ion currents. Whether these agents will make it to market and what impact they will have on AF management remain to be seen.[6] It is clear that new antiarrhythmic drugs will be held to a high standard of safety and will need to be studied comprehensively in patients with a broad spectrum of cardiac disease in order to be able to provide physicians with the best prescribing information.

Finally, it is important to note that nonantiarrhythmic drugs may play an important role in rhythm control. For many of these agents, the magnitude of the treatment effect may be modest, but if applied to a very large at-risk population, the dividends could be significant. For example, emerging data suggest that drugs that interfere with the renin-angiotensin system may limit atrial fibrosis and at the same time reduce the frequency of AF when used in patients after myocardial infarction. Widespread use of these agents, which also control hypertension, the most common cause of AF, would be expected to reduce the disease burden.[36] Studies to confirm this benefit are in progress.

Rate Versus Rhythm Control

The lack of highly effective and safe antiarrhythmic drugs prompted several investigators to ask the question whether maintenance of SR is actually preferable to allowing AF to persist. Obviously, the question is valid only for patients who have minimal or no symptoms while in rate-controlled AF, because severe symptoms would prompt the physician to recommend rhythm reversion. It should be clear that this is not a new idea. For decades, experienced clinicians allowed AF to persist, based on the premise that antiarrhythmic drugs are not safe, particularly in the elderly, and could place the patient in more danger than the arrhythmia itself.[37,38] For example, all antiarrhythmic drugs depress the conduction system, including the sinoatrial node, and many patients with AF have concomitant conduction disease. Thus, insistence on maintenance of SR could mandate a pacemaker implantation, which would be avoided if AF is allowed to persist.

Four randomized studies that have been completed and reported have examined this question.[39-41] Although the studies are of varying size and used different methods and endpoints, the overwhelming message from all of them is that, aside from symptom control, there does not appear to be an advantage for rhythm control in terms of quality of life, mortality, hospitalization rates, or any other endpoint examined.[41] In fact, in many of the analyses, the advantage went to the more simple strategy of rate control. Although there are a number of caveats in the interpretation of these data (including patient selection bias, inefficiencies in SR retention, and relatively short follow-up periods), it is now axiomatic that letting elderly patients remain in SR for a few years is not inimical to their outcome and may be preferred to exposing those individuals to the hazards of antiarrhythmic drug therapy and repeated cardioversions. Although some of these randomized trials permitted nonpharmacologic therapy for SR maintenance, too few of those patients were so treated to allow any conclusions as to whether a nondrug approach would alter the studies' overall conclusions.

Anticoagulation

By far, the most important issue in AF management is anticoagulation.[10,42] It now is clear that avoidance of stroke renders AF treatment an exercise in symptom reduction rather than an attempt to preserve life and prevent major disability. Fortunately, a number of large, well-done clinical trials

TABLE 1
Anticoagulation Trials in Atrial Fibrillation

Trial	Reference	Year Published	No. of Patients	Interventions
Large published trials				
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I)	468	1989	1,007	OA, ASA, placebo
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II)	487	1998	677	OA, ASA, OA* + ASA, OA*
Stroke Prevention in Atrial Fibrillation I (SPAF I)	32	1991	1,330	OA, ASA, placebo
Stroke Prevention in Atrial Fibrillation II (SPAF II)	488	1994	1,100	OA, ASA
Stroke Prevention in Atrial Fibrillation Ill (SPAF Ill)	438	1996	1,044	OA, OA* + ASA
Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)	456	1990	420	OA, control
Canadian Atrial Fibrillation Anticoagulation (CAFA)	489	1991	378	OA, placebo
Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)	469	1992	571	OA, placebo
European Atrial Fibrillation Trial (EAFT)	439	1993	1,007	OA, ASA, placebo
Studio ltaliano Fibrillazione Atriale (SIFA)	490	1997	916	OA, indobufen
Minidose Warfarin in Nonrheumatic Atrial Fibrillation	491	1998	303	OA, OA*
Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF)	461	1999	729	OA, OA*, ASA
Small or pilot trials				
Harenberg et al.	492	1993	75	LMW heparin, control
Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF)	493	1996	285	ASA, placebo
Subgroups with AF in other trials				
European Stroke Prevention Study II (ESPS II)	494	1997	429	ASA, dipyridamole, placebo
Ongoing or unpublished AF trials				
French Aspirin Coumarin Collaborative Study		—	—	OA, OA + ASA
Swedish Atrial Fibrillation Trial		—	—	—
Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF)		—	—	OA, thrombin inhibitor

AF = atrial fibrillation; ASA = aspirin; LMW = low molecular weight; OA = oral anticoagulation; OA* = low-dose oral anticoagulation.
Adapted and reproduced with permission from Hart RG, Benavente O, McBride R, Pearce LA: Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. Ann Intern Med 1999;131:492-501.

have proven that warfarin is effective in dramatically reducing the incidence of thromboembolic events in patients with valvular and nonvalvular AF (Table 1).[10,42] Warfarin, however, is a complex drug, and the incidence of major bleeding associated with its use is not inconsequential. Thus, physician and patient acceptance and its applicability to high-risk populations have all been major issues limiting its general application. In addition, strict guidelines must be followed at each phase of the disease's management in order to obtain the benefits that have been described in clinical trials. For example, patients with recent-onset arrhythmia (<48 hours) must have a continuously therapeutic level of anticoagulation (international normalized ratio [INR] >2.0) for 3 to 4 weeks prior to an elective drug or electrical conversion.[10,43] Alternatively, such patients may undergo a transesophageal echocardiogram and simultaneous anticoagulation with heparin followed by warfarin and cardioversion if the study indicates the absence of left atrial clot.[44,45] Although the studies supporting these recommendations were not necessarily well controlled or randomized, their results are well accepted and adopted as standard of care.

Chronic anticoagulation is a more complex issue. First, it is clear that aspirin, although effective, is grossly inferior to warfarin for this indication and should be used only in patients who cannot take warfarin.[10] Although routinely used in "low-risk" patients, the rationale for this practice is nil. Patients with atrial flutter require warfarin anticoagulation, as do AF patients based on their relative risks of atrial clot formation and stroke in large series.[46] Although we try to differentiate risk based on AF burden, there are no data concluding that patients with paroxysmal AF are at less risk for stroke than patients with persistent AF. Whether relative frequency of AF within the paroxysmal category is a risk stratifier has not been determined.

It is very clear that risk for stroke in AF can be quantified based on a number of clinical characteristics, including age, sex, cardiac function, and associated clinical conditions such as diabetes and hypertension (Table 1).[10,47,48] For high-risk individuals, we now believe that warfarin anticoagulation should never be discontinued once initiated. This recommendation comes from several lines of evidence. We know that many patients do not know when they are having AF. Asymptomatic relapses may predispose to stroke. In fact, the first presenting symptom of AF is stroke in a sizable percentage of elderly patients.[49] Recently, the randomized studies of rate versus rhythm control reported a disturbingly high incidence of strokes in patients in the rhythm control arm of the trials whose anticoagulation either was stopped or was at an inadequate level.[40] The reason for this is not clear but could have been due to AF recurrences during which symptoms were masked by drugs that slow the ventricular response to AF if they do not suppress it, rendering stroke more likely. In any case, guidelines that in the past advocated cessation of anticoagulation in patients maintaining SR for several weeks after conversion may have to be restricted to patients who have AF without stroke risk factors.

What also is clear is that warfarin alternatives are desperately needed. To date, evidence supporting the efficacy of alternative therapy has been lacking. Heparins, including recently some low-molecular-weight heparins, have been found useful in association with the transesophageal cardioversion strategy discussed earlier, but they have not been well studied otherwise.[50,51] The need for parenteral administration greatly diminishes their clinical applicability in any case. Recently, we have seen encouraging results from trials in which direct thrombin inhibitors have been compared with warfarin in patients with nonvalvular AF.[52] These drugs have the potential advantage of a shorter half-life, permitting faster onset

and offset, fewer drug interactions, and empiric dosing without the need for monitoring coagulation status. Given the dire nature of the clinical outcomes in these trials, placebo controls are not possible. Positive controlled studies versus warfarin, even those with a noninferiority endpoint, mandate the inclusion of a very large number of at-risk patients, with double dummy and phantom INR-based dose adjustments and scrupulous safety monitoring. The ability to use simpler drugs for this indication would have far-reaching consequences and could revolutionize our approach to patients with low-to-intermediate risk of stroke, including those with compliance issues. The preliminary results have been very encouraging, and we anticipate that anticoagulation of patients with AF soon will be simplified.

Conclusion

Management of AF is a highly complex task that requires a thorough knowledge of several therapeutic alternatives, careful individualization of therapy, and patience on the part of the physician and patient. The search for better treatment alternatives continues because of the burden of this arrhythmia in our population and the limitations of what is currently available. Although many of these new treatments will come to fruition, AF will remain a challenge for clinicians for years to come. It deserves the attention it has received and will receive from the scientific and clinical communities.

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Discussion

Dr. Prystowsky: What percent of people were not enrolled in AFFIRM because the clinician felt they specifically needed to be in sinus rhythm?

Dr. Waldo: We don't know. There were about 3,300 patients followed who opted not to be in AFFIRM, and two thirds of those who opted not to participate made the decision on their own. The other third did not participate because of a decision by the physician.

Dr. Packer: There is a bit of a problem on the whole ablation scene because people keep coming in and thinking that after AFFIRM and RACE we shouldn't be ablating anybody because it doesn't matter. These are totally different patients.

Dr. Naccarelli: As an AFFIRM investigator, there may have been some bias against randomizing the most symptomatic patients. However, a number of the patients randomized in our center were very symptomatic. Some of these very symptomatic patients were randomized to rate control and subjectively did well with complete abolition of their symptoms. However, rate control is probably not for everybody, and there is a large group of patients who probably are not candidates for rate control and may be for pharmacologic suppression or even nonpharmacologic abolition of their atrial fibrillation.

Dr. Packer: I'm not even going as far as saying that they're not a candidate for rate control. We don't know about those patients who were not in the trial.

Dr. Prystowsky: My own approach is to control the heart rate before making a decision on symptoms. But often patients have their rate well controlled by the time they are referred to me, and they are still quite symptomatic and want to be in sinus rhythm. The message of AFFIRM for me is if a person is in an older age group, they can have an option of rate control. We shouldn't forget that we have minimal data on younger patients without a high stroke risk regarding long-term effects of AF.