Is rate control or rhythm control preferable in patients with atrial fibrillation?

Rate Control Is Preferable to Rhythm Control in the Majority of Patients With Atrial Fibrillation

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". . .but to his surprise — the more he looked — the more Piglet wasn't there."

A.A. Milne, *The House at Pooh Corner*

The management of patients with atrial fibrillation has been the subjects of intense investigation over the past 2 decades. In the 1980s and early 1990s, large clinical trials of anticoagulant therapy for stroke prevention were performed. These consistently demonstrated that atrial fibrillation confers a significant and ongoing stroke risk and that anticoagulant therapy significantly reduces this risk.[1–10] Warfarin subsequently became a standard of therapy for patients with atrial fibrillation, whether paroxysmal, persistent, or permanent.

If patients with atrial fibrillation had a high stroke risk compared with those in sinus rhythm, then logic appeared to dictate that restoration and maintenance of sinus rhythm should reduce the likelihood of thromboembolism and hence obviate the need for long-term warfarin anticoagulation. Perhaps driven in part by this belief, new atrial antiarrhythmic drugs were introduced during this period, and there was an increasing use of such drugs among patients with atrial fibrillation.[11] A decade after the trials of anticoagulation in atrial fibrillation, several international trials were implemented to determine whether heart rate control would result in a similar outcome to the outcome after a strategy of restoration and maintenance of sinus rhythm.[12–15] Analysis of these trials demonstrated no benefit either in mortality or in a combined end point of mortality and morbidity. These results are generally interpreted as showing that either rate control or rhythm control is a suitable strategy in a patient with atrial fibrillation, and there has therefore been a rethinking of the appropriate way in which to treat a patient with atrial fibrillation when the options include control of either rate or rhythm. In the treatment of atrial fibrillation, as with most things in medicine, one size does not fit all, and it must be recognized that there are some patients in whom trials of pharmacological rate control may be ineffective for the complete control of symptoms. These patients most certainly deserve vigorous attempts at maintaining sinus rhythm; however, these patients represent a small minority of patients with atrial fibrillation and are not the topic of the current discussion. It is therefore my purpose in this debate to demonstrate that rate control, by virtue of its relative simplicity, is superior to rhythm control in the management of the majority of patients with atrial fibrillation and should therefore be the method of choice. Furthermore, as with Piglet, the well-known character from the children's story featured in the introductory quote to this argument, the more one looks in an attempt to prove the benefits of rhythm control over rate control, the more they are not there.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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TABLE 1. Summary of Features of Each Rate vs Rhythm Trial

Trial	n	Age, y	Mean Follow-Up	Primary End Point	Rate-Control Studies: End Point, Mortality	Rhythm-Control Studies: End Point, Mortality
AFFIRM	4060	69.7±9	3.5 y	Death	21.3%, 21.3% (At 5 y)	23.8%, 23.8% (At 5 y)
RACE	522	68±8	2.3 y	CV death, CHF, TE, bleeding, pacemaker, adverse drug reaction	17.2%, 7.0% (Study duration)	22.6%, 6.8% (Study duration)
PIAF	252	60.5±9	1 y	Improved dyspnea, palpitation, or dizziness	76%,* 2% (1 y)	70%,* 2% (1 y)
STAF	200	65.8±8	19.6 mo	Death, stroke, TIA, CPR, systemic embolus	6.1%, 4.9% (Annual)	5.5%, 2.5% (Annual)

CHF indicates congestive heart failure; CPR, cardiopulmonary resuscitation; CV, cardiovascular; TE, thromboembolism; and TIA, transient ischemic attack.
*End point represents improvement in symptoms (PIAF only).
Other than the AFFIRM trial, all trials recruited only patients with persistent atrial fibrillation.

Lessons From the Multicenter Trials of Rate Versus Rhythm Control

The results of the recently published trials of management strategies in atrial fibrillation have become a stimulus for the renewed debate concerning whether or not it is worthwhile to attempt to restore sinus rhythm (Table 1). As such, they deserve careful scrutiny to determine whether they have definitively answered the question of the best strategy or whether further trials, perhaps in specific patient subgroups, are needed.

AFFIRM Trial

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, performed in North America, evaluated mortality as a primary end point when the strategies of rate versus rhythm control in atrial fibrillation were compared.[12–15] Of the 4000 patients who were enrolled, no difference could be determined between these 2 strategies, although there was a trend toward a higher mortality rate in the rhythm-control group. The trial enrolled patients deemed to be at high risk for stroke on the basis of their age or underlying disease. It must be stressed that AFFIRM was a comparison of treatment strategies in a high-risk population with current or past atrial fibrillation. Patients with paroxysmal atrial fibrillation or those recently cardioverted from atrial fibrillation were eligible to participate, and this resulted in 52% of enrollees (1055/2027) who were randomized to rate control being in sinus rhythm at the time of randomization. Although many of these patients reverted transiently or permanently to atrial fibrillation during the study, it is conceivable that the failure to show a benefit of one or another strategy was related to a dilution of numbers by having patients in sinus rhythm in the rate-control group and patients who could not maintain sinus rhythm in the rhythm-control group. Despite these potential limitations, AFFIRM was a large study, and the strategy of attempted sinus rhythm maintenance showed no advantage either in the primary end point or in any prespecified secondary end points, including quality of life, stroke, or worsening functioning class.

RACE Trial

The Rate Control versus Electrical Cardioversion (RACE) trial, although smaller than AFFIRM (n=522), differed from it in only enrolling patients with persistent atrial fibrillation.[13] Eligibility required a patient to have had a prior cardioversion and to be back in atrial fibrillation at the time of randomization. Subjects were either randomized to a strategy of repeat cardioversion(s) and antiarrhythmic drugs to maintain sinus rhythm or to rate control, which was almost exclusively pharmacological. The primary end point was a composite of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker insertion, or severe side effects of antiarrhythmic drugs. The end point did not differ between the 2 groups at a mean follow-up of 2.3 years. Although it is unclear how many of the rate-control patients crossed over to the rhythm-control group, there were only 26 patients in the rate-control group who were in sinus rhythm at study end, 13 of whom had been cardioverted during the study for intolerable cardiovascular symptoms. Analysis of quality of life, a secondary end point in RACE, showed no difference between these 2 strategies.

Two much smaller pilot trials have also addressed rate versus rhythm control. The Strategies of Treatment of Atrial Fibrillation (STAF)[14] and Pharmacological Intervention in Atrial Fibrillation (PIAF)[15] trials were both pilot trials designed to test the feasibility of a larger trial. These both demonstrated very similar outcomes between rate and rhythm strategies but, in light of the AFFIRM and RACE trials, neither proceeded into a full-scale study.

Why Do Patients With Atrial Fibrillation Develop Symptoms?

Before treatment is prescribed for a patient with new-onset atrial fibrillation, a thoughtful analysis is required to examine why any symptoms or clinical deterioration might have occurred. Symptoms in a patient presenting with new-onset atrial fibrillation should not be attributed simply to the loss of the atrial contribution to ventricular filling, because other culprits may be the predominant factor, the most obvious of which is a rapid ventricular response associated with the

untreated arrhythmia. In the absence of AV nodal blocking agents, the mean resting ventricular response to atrial fibrillation is ≈110 to 125 bpm,[16–19] and this may increase considerably during exertion. As heart rate increases, the percentage of time spent in diastole is shortened. Because diastolic dysfunction is a feature of many diseases associated with atrial fibrillation,[20] a rapid ventricular rate can precipitate or aggravate heart failure. If the rate remains uncontrolled for a longer period of time, tachycardia-mediated cardiomyopathy may occur.[21] Although tachycardia-mediated cardiomyopathy is considered uncommon, there may be an unrecognized spectrum of subtle left ventricular dysfunction (diastolic as well as systolic) that is produced by atrial fibrillation. Thus, control of the ventricular rate should play a central role in the management of atrial fibrillation, because it can improve symptoms of heart failure by lengthening diastole, may decrease the likelihood of tachycardia-related systolic dysfunction, and can abolish the sensation of tachycardia or palpitations associated with the rapid rate. In addition to slowing the ventricular rate, the relative regularization of the ventricular response that may occur with such agents as verapamil or diltiazem,[22,23] or the absolute regularization that follows AV nodal ablation may also have some role in improving hemodynamics and providing a sense of wellbeing.[24–27]

Rhythm Control in Atrial Fibrillation: A Strategy That Is Difficult to Obtain Consistently

One reason rate control is a preferred strategy in atrial fibrillation is that rhythm control is not an easy goal to achieve in many patients. Why might this be so? As with many other forms of arrhythmia, atrial fibrillation is associated with and precipitated by a number of underlying types of heart disease. The abnormalities responsible for the maintenance of atrial fibrillation are complex and represent a combination of the primary pathology responsible for the arrhythmia[20] and cellular, subcellular and molecular changes that result from the fibrillation itself.[28–40] Although the underlying pathology both precipitates and perpetuates the arrhythmia, the secondary changes produced by atrial fibrillation may progress with time and lead to further likelihood of perpetuation ("atrial fibrillation begets atrial fibrillation"[41]). Simply restoring sinus rhythm does not affect the underlying pathology initially responsible for the arrhythmia, and it is therefore not surprising that atrial fibrillation has a high recurrence rate unless antiarrhythmic therapy is administered; however, as discussed below, the use of antiarrhythmic drugs is a 2-edged sword, because none of these drugs are free of side effects, and none comes close to having 100% efficacy.[42] Thus, before a patient is subjected to a potentially harmful agent to restore and maintain sinus rhythm, every effort should be made to ensure that heart rate during atrial fibrillation has been controlled adequately, because this may result in symptom improvement and obviate the need to use an antiarrhythmic drug.

What Is the Optimal Heart Rate in Atrial Fibrillation?

Unfortunately, there is a lack of uniform definition of heart rate control in atrial fibrillation, although it is generally agreed that rate control must exist both at rest and during normal daily activities. Patients in atrial fibrillation demonstrate greater maximum and minimum heart rates during normal daily activities than do similar patients in sinus rhythm, and the assessment of an "optimal" heart rate in patients with atrial fibrillation must take into account the potential need for a slightly faster resting heart rate at rest than might be seen in sinus rhythm that results from the loss of the atrial contribution to ventricular filling. There have been several small trials of individual negative chronotropic agents for ventricular rate control in persistent atrial fibrillation that used exercise testing as a goal to determine optimal heart rate control. These studies have been reviewed recently by Bjerregaard and coworkers.[43] The predominant drugs studied were digoxin, various β-blocking agents, and the nondihydropyridine calcium channel blocking agents verapamil and diltiazem. β-Blocking agents and verapamil or diltiazem are more effective than digoxin for controlling heart rate, particularly during activity, although digoxin has a synergistic effect with each of the other classes of drugs. Few studies have directly compared the efficacy of heart rate control during daily activity with that during exercise using multiple drug regimens. Farshi et al[44] performed a crossover study in 12 patients treated with digoxin 0.25 mg/d, diltiazem CD 240 mg/d, atenolol 50 mg/d, or a combination of each of the latter 2 drugs with digoxin. Digoxin alone provided the least effective mean peak ventricular rate during exercise of 175 bpm and a daytime mean heart rate of 85±20 bpm. The combination of atenolol and digoxin resulted in a significantly lower peak heart rate during exercise than did the other therapies and was the most effective in blunting heart rate peaks during daily activities. Despite a mean decrease of 49 bpm during exercise compared with digoxin alone, the digoxin-atenolol combination had no effect on exercise tolerance compared with any other combination. This contrasts with some other studies of β-blocking agents in which vigorous blunting of peak heart rate was associated with a decrease in exercise tolerance. Thus, the use of currently available negative chronotropic agents results in reasonably good heart rate control in the majority of patients, although care must be taken not to overtreat.

The AFFIRM study was the first large study to attempt to formally define and institute criteria for a controlled ventricular response in atrial fibrillation.[12,45] Adequate rate control was defined not only as a controlled resting heart rate but also as the absence of excessive heart rate elevation with a modest level of exercise and/or during daily activities. Specifically, for the goal of adequate heart rate control to be achieved, patients were required to have a ventricular response of ≤80 bpm at rest and to have either a maximum heart rate of <110 bpm during a 6-minute walk on a flat surface or an average

heart rate during 24-hour ambulatory monitoring <100 bpm with no heart rate >110% of maximal predicted age-adjusted exercise heart rate. With these criteria, the overall success rate for heart rate control ranged from 38% with calcium channel blockers alone to 76% in a small group of patients who were treated with a combination of β-blocker, calcium channel blocker, and digoxin. The overall success rate for heart rate control 2 months after entering the AFFIRM study among patients who were in atrial fibrillation at the time of that visit was ≈63%, and control gradually improved throughout the study to a maximum of 86% at rest, 90% with exercise, and 78% overall at the 5-year mark.[45] Although these data may raise some concerns about the 22% to 37% of patients without "adequate rate control," the criteria for rate control were based on prospectively defined criteria. It is possible that this definition was too rigid and that patients who fell outside this definition of "rate control" were not harmed in any way. To attempt to answer this question, Cooper et al[45] analyzed patients in the rate-control arm of the AFFIRM study who were in atrial fibrillation both at baseline and at 2 months. Patients were grouped by quartile of achieved heart rate at rest and with exercise. The heart rate quartiles at rest (n=680) were 44 to 69, 70 to 78, 79 to 87, and 88 to 148 bpm, respectively, and with exercise (n=349), the rates were 53 to 82, 83 to 92, 93 to 106, and 107 to 220. No difference was found in survival free from cardiac hospitalization or in overall survival among quartiles, which suggests that at least in the median-term follow-up of the AFFIRM study, vigorous attempts at rate control to these predefined criteria may not have been necessary in every patient.[45] Therefore, rate control in atrial fibrillation may not necessarily require a rigid titration of medications to a particular heart rate goal, provided that prolonged periods of excessive or symptomatic tachycardia can be avoided.

Antiarrhythmic Drugs: An Armamentarium With a Plethora of Side Effects

Antiarrhythmic drugs have been used for many years to restore and maintain sinus rhythm; however, the use of these drugs has drawbacks, because none are free of side effects (cardiac or noncardiac), and none comes close to having 100% efficacy. Thus, their use requires a careful assessment of the risks and benefits of each agent and must be tailored to the individual patient's medical condition. Furthermore, no guarantee of safety or efficacy of any one drug in an individual patient can be given.

The currently available antiarrhythmic agents are associated with a plethora of significant side effects, both cardiac and noncardiac. Agents that prolong repolarization (predominantly the class 3 agents sotalol and dofetilide and class 1 agents such as quinidine, disopyramide, and procainamide) are associated with a risk of torsade de pointes, which may be fatal.[46–48] The absence of early proarrhythmia with these agents is no guarantee of freedom from late proarrhythmia, which may be precipitated by a fall in potassium, the development of bradycardia, or worsening renal function.[49] In the setting of prior myocardial infarction with ventricular ectopy, the use of the class 1C agent flecainide was associated with an increased risk of sudden death.[50] Although introduced after the Cardiac Arrhythmia Suppression Trial (CAST) study, propafenone has electrophysiological properties similar to flecainide, and it is likely that it would have had the same adverse effect. Thus, both propafenone and flecainide are considered to be contraindicated in patients with atrial fibrillation and ischemic heart disease.[51] The use of the 1C agents may also cause atrial fibrillation to organize to atrial flutter with a relatively slow atrial rate, resulting in 1:1 AV nodal conduction. Because of the "use-dependent" properties of these drugs (whereby their electrophysiological effect is heightened in the setting of an increased depolarization rate), atrial flutter with 1:1 conduction is commonly associated with a markedly widened QRS. This can result in ventricular dyssynergy and the potential for cardiovascular collapse. To minimize this occurrence, it is advisable to prescribe the class 1C agents in conjunction with an AV nodal blocking agent, thereby increasing the number of drugs a patient takes.

Amiodarone, the most effective atrial arrhythmic drug, also prolongs the QT interval but appears to have a very low risk of torsade de pointes. Unfortunately, the low risk of proarrhythmia with amiodarone is offset by its numerous side effects, which necessitated discontinuation in 18% of patients over 16 months in the Canadian trial of amiodarone for atrial fibrillation[52] and in up to 23% of patients in other clinical trials.[53] The long-term discontinuation rate is even greater owing to the cumulative toxicity of the drug. Pulmonary fibrosis due to amiodarone, although rare, is a serious complication. Although it often reverses after the drug is stopped, the fibrosis may progress, and fatal cases have been reported. Hypothyroidism is commonly induced by amiodarone, and amiodarone-induced hyperthyroidism, although less common, is a difficult to treat complication of this drug. Liver function test abnormalities are common, and on occasion, significant hepatotoxicity may occur. Perhaps the most common, troublesome, and potentially dangerous side effect of amiodarone is its interaction with warfarin. Amiodarone decreases total warfarin requirements, but because of its complex pharmacokinetics and an unpredictable time course, the international normalized ratio (INR) may suddenly elevate after apparently being stable for a number of weeks after the initiation of amiodarone in a patient taking warfarin.[54]

How Common Are Potential Contraindications to Atrial Antiarrhythmic Drugs?

The potential for side effects of atrial antiarrhythmic drugs is increased in the setting of comorbidities. In a study of 723 Canadian patients with paroxysmal atrial fibrillation entered into a prospective registry between 1991 and 1996, Humphries et al[55] noted that 56% had documented structural heart disease, including 22% with left ventricular systolic dysfunction. When they sought the presence of a clinical

TABLE 2. Stroke Rates in the 4 Rate vs Rhythm Trials

Trial	n	Stroke Rate, Rate-Control Trials, %	Stroke Rate, Rhythm-Control Trials, %	RR (95% CI)	*P*
AFFIRM	4060	5.7	7.3	1.28 (0.95–1.72)	0.12
RACE	522	5.5	7.9	1.44 (0.75–2.78)	0.44
PIAF	252	0.8	0.8	1.02 (0.73–2.16)	0.49
STAF	266	1.0	3.0	3.01 (0.35–25.3)	0.52
Total	5100	5.0	6.5	1.28 (0.98–1.66)	0.08

Data are modified from references 12 through 15 and from Verheught et al, presented at the American College of Cardiology 52nd Annual Scientific Sessions, Chicago, Ill, March 30 to April 2, 2003.

feature that was specified as a contraindication, warning, or precaution to a specific drug in the 1996 *Canadian Compendium of Pharmaceuticals and Specialties*, the percentage of patients who fell into at least 1 such category among the most commonly prescribed drugs (flecainide, quinidine, sotalol, amiodarone, and propafenone) ranged from 36% for quinidine to 58% for flecainide. Although, as the authors appropriately point out, these were only potential limitations to drug use and do not necessarily preclude therapy based on good clinical judgment, these data certainly underscore the complexities of prescribing antiarrhythmic drugs, even before the efficacy of the agents is entered into the equation.

Safety of Negative Chronotropic Agents Compared With Antiarrhythmic Agents

In contrast to the common adverse effects of antiarrhythmic agents, the 3 main classes of negative chronotropic agents (digoxin, β-blockers, and the nondihydropyridine calcium channel blockers verapamil and diltiazem) have a good safety profile. The digitalis glycosides, of which digoxin is used almost exclusively, have been available for more than 2 centuries, and the outstanding clinical observations of Sir William Withering in the 18th century laid the foundation for the understanding of digoxin toxicity. With the introduction of the measurement of serum digoxin levels, classic digoxin toxicity decreased considerably. Digoxin has a synergistic negative chronotropic effect with drugs in the other classes,[44] and when used in appropriate doses and with recognition of the verapamil-digoxin interaction (which leads to elevated digoxin levels), it has proved to be a safe, useful, and enduring adjunct to ventricular rate control. β-Blockers and calcium channel blockers are similarly remarkably safe agents. Indeed, β-blockers have a well-known cardioprotective effect, and in selected cases of atrial fibrillation with left ventricular dysfunction, their use may be associated with an improvement in ejection fraction.[56,57] Although the calcium channel blockers demonstrate a negative inotropic effect in vitro, this is uncommonly seen in the clinical setting, provided that this class of drug is not given to patients with uncompensated heart failure.

Why Cannot Anticoagulation Be Discontinued in a Patient With a History of Paroxysmal or Persistent Atrial Fibrillation Once Sinus Rhythm Has Been Restored?

One argument in favor of the use of antiarrhythmic drugs in atrial fibrillation is that restoration of sinus rhythm may render unnecessary the need for continued anticoagulation. Until recently, it was considered safe to discontinue warfarin anticoagulation once a patient had been cardioverted from atrial fibrillation and had apparently remained in sinus rhythm for a period of 30 to 90 days. Some guidelines suggested that anticoagulation could be discontinued in such patients,[58] thereby implying an advantage of rhythm control over rate control in terms of the risks and inconvenience of long-term anticoagulation. The trials of rate versus rhythm control permitted discontinuation of anticoagulation in the rhythm-control group once sinus rhythm was (or at least appeared to have been) maintained; however, in each of the trials, the stroke/thromboembolism rate was the same or slightly higher in the rhythm-control group than in the rate-control group, with a difference that approaches statistical significance when the data are pooled (Table 2). This consistent demonstration that rhythm control is associated with an ongoing risk of thromboembolism underscores the need for warfarin to be continued for a longer period than was previously believed necessary after apparently successful cardioversion.

The risk of ongoing stroke among patients with a history of atrial fibrillation who subsequently appear to be in sinus rhythm is probably related to recurrent episodes of paroxysmal atrial fibrillation. The patient may be asymptomatic during recurrent episodes, but the atrial fibrillation retains the risk of thrombus formation and subsequent thromboembolism. In the Prevention of Atrial Fibrillation after Cardioversion (PAFAC) trial, 1182 patients with persistent AF were cardioverted and then randomized to receive either placebo, verapamil, or a combination of quinidine with verapamil.[59] Daily transtelephonic monitoring was performed in each patient for a mean follow-up of 266 days and a total of >191 000 ECGs. Recurrence of atrial fibrillation, documented by transtelephonic monitoring, occurred in 67% of

patients. Remarkably, the documented recurrence of atrial fibrillation occurred without symptoms in close to 70% of these patients.

Among patients with paroxysmal atrial fibrillation, even "successful" drug therapy may be associated with episodes of asymptomatic atrial fibrillation. The Suppression of Paroxysmal Atrial Tachyarrhythmias (SOPAT) trial was a sister study to PAFAC.[60] The design was similar, except that patients with paroxysmal arrhythmias (predominantly atrial fibrillation) were recruited. A total of 1012 patients with symptomatic paroxysmal atrial fibrillation were treated with either a combination of quinidine and verapamil, sotalol, or placebo. Daily transtelephonic ECG transmissions were performed for at least 1 minute for a total of >179 000 recordings. Atrial fibrillation was documented in 13 410 episode recordings (representing 7% of the total recordings), and fewer than half of the episodes were associated with symptoms. At the end of 1 year, approximately half of the drug-treated patients had experienced recurrences of symptomatic arrhythmia or had discontinued therapy owing to side effects. From these results, it is clear that antiarrhythmic therapy with these "classic" class 1A and class 3 agents is poorly effective for long-term maintenance of sinus rhythm and is associated with a high proportion of asymptomatic arrhythmia.

Thus, from the standpoint of antithrombotic therapy, clinical trials point to the need for continued warfarin anticoagulation in patients at risk of stroke. Because paroxysmal atrial fibrillation is as strong a risk factor for embolic stroke as persistent/permanent atrial fibrillation, warfarin anticoagulation should be continued indefinitely even when antiarrhythmic therapy is used, both because of the likelihood of silent episodes of paroxysmal atrial fibrillation and because of the poor long-term efficacy of most antiarrhythmic drugs for the maintenance of sinus rhythm.

Are There Any Proven Subgroups in Which Maintenance of Sinus Rhythm Produces Better Results Than Rhythm Control?

Symptoms may not be the only criterion for restoration of sinus rhythm, and it has been suggested that in a subgroup of patients with congestive heart failure, rhythm control may be superior to rate control. A recent retrospective study may throw some light on this question. Al-Khatib et al[61] performed a retrospective analysis of 1009 patients with atrial fibrillation and heart failure enrolled in the Duke University database between 1995 and 2001. All 1009 patients had a discharge diagnosis of atrial fibrillation along with clinical evidence of heart failure, some with an ejection fraction of <50%. Two thirds of the patients had, or had previously had, severe heart failure, defined as class III or class IV, and 30% were classified as having nonischemic cardiomyopathy on the basis of coronary angiography. Although therapy was nonrandomized and based on the preference of the treating physician, exactly half of the patients fell into the rhythm-control and rate-control groups, respectively. After adjustment for differences in baseline characteristics and medications, no significant differences in mortality were found between patients treated with rhythm control and those treated with rate control. Thus, within the limitations of a retrospective study, rhythm control failed to improve survival even in a group of patients with a high prevalence of severe congestive heart failure.

Quality of Life and Cost-Effectiveness

The AFFIRM trial primary end point was mortality, and the end point in RACE was a composite of mortality and serious events, yet neither trial demonstrated the superiority of rhythm control over rate control. Mortality and other morbid end points can be equivalent between 2 treatment strategies, yet quality of life may be superior in one or the other group. (Indeed, in some heart failure trials of positive inotropes, active therapy was associated with a higher mortality yet a better quality of life.[62]) Quality of life in the small PIAF study was assessed by the Medical Outcomes Short Form health survey (SF-36).[63] At baseline, scores on all 8 scales in both groups were reduced compared with normal subjects. At the end of the observation period, improvement was seen in both patient groups, and no difference was found between the rate- or rhythm-control strategy. The RACE investigators, who also used the SF-36 survey, obtained a very similar result.[64] Thus, no argument can be made that restoration of sinus rhythm improves quality of life.

In the absence of any proven benefit of a strategy of attempted restoration of sinus rhythm for a patient with atrial fibrillation, a comparison of cost-effectiveness of the 2 strategies is of interest. A detailed cost-effectiveness analysis from the RACE trial has shown the advantage of rate over rhythm control; the overall strategy of rate control was cheaper than that of rhythm control, and the cost saving per avoided end point was calculated as ≈25 000 Euros.[65] The AFFIRM investigators also performed a cost-effectiveness analysis. Patients in the rate-control group used fewer resources, such as hospital days, cardioversions, and emergency department visits. Utilizing a sensitivity analysis, the estimated cost savings per patient treated with rate control ranged from $2189 to $5481 per person.[66] Thus, in contrast to the absence of a difference in quality of life between the 2 strategies, rate control is a less costly strategy than rhythm control in the treatment of atrial fibrillation.

Might Catheter Ablation of Atrial Fibrillation Provide a Better Outcome Than Antiarrhythmic Therapy?

The criticism of antiarrhythmic drug therapy as the preferred therapy for atrial fibrillation is based on the side effects of these drugs. Therefore, if it were possible to maintain sinus rhythm without the use of antiarrhythmic drugs, might a primary approach stressing restoration of sinus rhythm become more attractive? Catheter ablation of atrial fibrillation, more precisely termed catheter-based isolation of the pulmonary veins, is an increasingly used procedure for patients with

symptomatic arrhythmia. It has been suggested that this technique is highly successful when performed by experienced operators, although the long-term efficacy is not perfect, and severe side effects can occur in a small minority of patients. In a nonrandomized study, Pappone et al[67] compared outcomes among 589 patients who had undergone radiofrequency ablation for atrial fibrillation with outcomes among 582 patients who had received drug therapy. The authors suggested that restoration of sinus rhythm by pulmonary venous isolation was associated with a subsequent survival rate equivalent to age-matched patients in the general population with atrial fibrillation. In contrast, patients treated with antiarrhythmic drugs had a worse survival than the same age-matched population. Although these data raise interesting questions, it is uncertain whether the 2 populations (ablation versus drug therapy) are precisely comparable, and it is hard to accept that they can be extrapolated to the vast majority of patients with atrial fibrillation. Most patients with atrial fibrillation have underlying structural heart disease, and on the basis of that disease alone, they would be anticipated to have a worse survival than randomly selected age-matched patients in the general population. This would suggest that the patients in the study by Pappone et al[67] do not represent the average patient with atrial fibrillation, and on the basis of this selected, nonrandomized population, it is premature to conclude that attempted maintenance of sinus rhythm by radiofrequency catheter pulmonary venous isolation has a salutary effect on mortality among patients with atrial fibrillation. Furthermore, there are few centers in the world that have the numerical experience with this procedure approaching that of the group in the study by Pappone et al,[67] and it is likely that the efficacy of the procedure is lower and its side effects are higher in centers that do not have dedicated, high-volume electrophysiological expertise.

Does Radiofrequency Ablation Abolish the Likelihood of Asymptomatic Paroxysmal Atrial Fibrillation?

As noted above, paroxysmal atrial fibrillation is common among patients with prior persistent atrial fibrillation or prior episodes of paroxysmal atrial fibrillation even when sinus rhythm appears to have been maintained by antiarrhythmic drugs. For this reason, long-term warfarin is now recommended in most patients who have had 1 or more episodes of atrial fibrillation and who are considered to be at thromboembolic risk because of age or underlying heart disease. To date, no studies have evaluated the safety of discontinuing warfarin after (apparently) successful catheter ablation of atrial fibrillation. In an attempt to determine whether catheter ablation abolishes paroxysmal atrial fibrillation, Oral et al[68] recorded daily, randomly transmitted 3-minute ECG strips from 60 patients with a history of paroxysmal atrial fibrillation who had remained asymptomatic for at least 6 months after radiofrequency pulmonary vein isolation. Patients transmitted once-daily ECGs for a mean of 25 days and whenever they experienced symptoms that might represent arrhythmia recurrence. During the 1-month transmittal period, 7 patients (12%) developed symptoms and transmitted ECGs, all of which documented recurrent atrial fibrillation. Only 1 random asymptomatic transmission documented atrial fibrillation. On the basis of these results, the authors concluded that asymptomatic atrial fibrillation is uncommon among patients with paroxysmal atrial fibrillation who have undergone pulmonary venous ablation and who have remained asymptomatic for at least 6 months; however, these conclusions are questionable, because the duration of monitoring (3 minutes every 24 hours) would certainly have missed the vast majority of short episodes of asymptomatic atrial fibrillation. Furthermore, it is striking that 12% of subjects developed symptoms of atrial fibrillation once they had been given a monitor, despite apparent freedom from symptoms for a mean time greater than 1 year after ablation. As the authors point out, it is possible that participation in the clinical trial heightened patients' awareness of minor symptoms of atrial fibrillation, thereby making it more likely that they would transmit a recording. These observations, in my opinion, point to the likelihood of ongoing (albeit less symptomatic) episodes of atrial fibrillation in a significant number of patients after pulmonary venous ablation and underscore the probable need for continued anticoagulation in this group despite the clinical benefit gained from the procedure in terms of improvement of symptoms.

Ablate and Pace: The Optimal Rate-Controlling Procedure in Atrial Fibrillation?

Recent data from a trial of patients with an implantable defibrillator have indicated that permanent right ventricular pacing is more likely to be associated with the development of congestive heart failure than when patients are permitted to remain in sinus rhythm.[69] Because right ventricular pacing may increase left ventricular dyssynergy, and improvement of LV dyssynergy may decrease heart failure, concern has recently been expressed about the use of AV nodal ablation with right ventricular pacing for patients with atrial fibrillation and a poorly controlled heart rate. A meta-analysis of 21 studies of AV nodal ablation and pacemaker insertion performed for medically refractory atrial tachyarrhythmias (97% of which were atrial fibrillation) included 1181 patients and demonstrated improvement in quality of life, treadmill exercise duration, ejection fraction, and New York Heart Association class and showed a decrease in hospital visits.[70] Early concerns about the provocation of fatal polymorphic ventricular tachycardia after this procedure appear to be assuaged by the authors' finding of a low mortality on follow-up. As the authors of this meta-analysis point out, the use of baseline pacing rates of 80 to 90 bpm for 1 to 2 months after ablation appears to prevent this uncommon but serious proarrhythmic complication.

Further evidence that right ventricular pacing does not worsen left ventricular function in the majority of patients

with atrial fibrillation comes from the Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT).[71] Ninety-nine patients with permanent atrial fibrillation who had mild to moderate symptoms at the time of presentation and who also had an ability to successfully achieve rate control with pharmacological therapy were randomized to either pharmacological therapy or AV nodal ablation with right ventricular pacing. Not surprisingly, given the ability of all patients to achieve adequate pharmacological rate control and the presence of a mean baseline ejection fraction of 55% to 57%, exercise time did not differ between the 2 groups 12 months after randomization. According to the CAST quality-of-life questionnaire, patients with AV nodal ablation had a significant improvement in symptoms, but these results need to be interpreted cautiously because 2 other "arrhythmia nonspecific questionnaires" showed no difference in quality of life. Importantly, AV nodal ablation with pacing did not cause any deterioration in left ventricular function. Thus, the AIRCRAFT results confirm that pharmacological therapy is effective for symptom control and that rate regularization, such as occurs with ventricular pacing (and that is one of the purported benefits of sinus rhythm restoration), may play only a small part in symptom control. The difference in outcome in terms of quality of life between the prospective AIRCRAFT trial and the "ablate and pace" meta-analysis almost certainly represents different patient populations, with the AIRCRAFT patients being, by virtue of entrance criteria, less sick than the usual patients who are considered for ablation and pacing (ie, drug-refractory symptomatic atrial fibrillation, often with a decreased ejection fraction). For patients with a significantly reduced ejection fraction and refractory atrial fibrillation and for whom concern still exists that right ventricular pacing may not be the optimal mode, biventricular pacing, with or without AV nodal ablation, has been shown to be successful both in terms of rate control and in improving symptoms and ventricular function.[72,73]

Conclusions

Careful analysis of published data to date does not support a routine strategy of restoration of sinus rhythm in the majority of patients with atrial fibrillation. Large clinical trials have consistently shown that ventricular rate control is equally (or more) effective than rhythm control in terms of survival, quality of life, and multiple other end points. Currently available antiarrhythmic drugs have a relatively low efficacy in maintaining sinus rhythm and have the potential for serious cardiac and noncardiac side effects, which contrasts with the low side effect profile and (in the case of β-blockers) cardioprotective effect of rate-controlling agents. Catheter isolation of the pulmonary veins is quite effective in skilled hands in highly selected patients, but it is not proven to reduce the risk of thromboembolism, and the procedure has an uncertain long-term efficacy, particularly when episodes of asymptomatic atrial fibrillation are considered. In contrast, the well-established ablate-and-pace method for ventricular rate control in drug-refractory patients is a relatively simple and very safe procedure that is associated with a clear-cut improvement in the quality of life in previously symptomatic patients and that may be associated with an improvement in ejection fraction in patients with previously poorly controlled rate and impairment of ventricular function. Thus, in this era of increasing awareness of the side effects of antiarrhythmic drugs and the undocumentable benefit of restoration of sinus rhythm, the physician faced with a patient with atrial fibrillation should consider ventricular rate control first to fulfill the primary precept of all physicians: "First, do no harm."

References

1. The Boston Area Anticoagulation Trial for Atrial Fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323:1505–1511.
2. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet*. 1989;1:175–179.
3. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol*. 1991;18:349–355.
4. The Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation*. 1991;84:527–539.
5. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation: Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992;327:1406–1412.
6. European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255–1262.
7. Albers GW. Atrial fibrillation and stroke: three new studies, three remaining questions. *Arch Intern Med*. 1994;154:1443–1448.
8. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687–691.
9. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633–638.
10. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med*. 1998;158:1513–1521.
11. Naccarelli GV, Wolbrette DL, Khan M, Bhatta L, Hynes J, Samii S, Luck J. Old and new antiarrhythmic drugs for converting and maintaining sinus rhythm in atrial fibrillation: comparative efficacy and results of trials. *Am J Cardiol*. 2003;91(suppl D):15D–26D.
12. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
13. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ; Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
14. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U, for the STAF Study Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the

Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
15. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation: pharmacological intervention in atrial fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789–1794.
16. Falk RH, Knowlton AA, Bernard S, Gotlieb NE, Battinelli NJ. Digoxin for converting recent-onset atrial fibrillation: a randomized, double blind trial. *Ann Intern Med*. 1987;106:503–506.
17. Toivonen L, Kadish A, Kou W, Morady F. Determinants of the ventricular rate during atrial fibrillation. *J Am Coll Cardiol*. 1990;16:1194–1200.
18. Kawakubo K, Murayama M, Itai T, Ono S, Musha H, Ito H, Arai S. Heart rate at onset and termination of paroxysmal atrial fibrillation in apparently healthy subjects. *Jpn Heart J*. 1986;27:645–651.
19. Rawles JM, Metcalfe MJ, Jennings K. Time of occurrence, duration, and ventricular rate of paroxysmal atrial fibrillation: the effect of digoxin. *Br Heart J*. 1990;63:225–227.
20. Falk RH. Etiology and complications of atrial fibrillation: insights from pathology studies. *Am J Cardiol*. 1998;82:N10–N16.
21. Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol*. 1997;29:709–715.
22. Khalsa A, Olsson SB. Verapamil-induced ventricular regularity in atrial fibrillation: effects of exercise, isoproterenol, atropine and conversion to sinus rhythm. *Acta Med Scand*. 1979;205:509–515.
23. Klein GJ, Twum-Barima Y, Gulamhusein S, Carruthers SG, Donner AP. Verapamil in chronic atrial fibrillation: variable patterns of response in ventricular rate. *Clin Cardiol*. 1984;7:474–483.
24. Wasmund SL, Li JM, Page RL, Joglar JA, Kowal RC, Smith ML, Hamdan MH. Effect of atrial fibrillation and an irregular ventricular response on sympathetic nerve activity in human subjects. *Circulation*. 2003;107:2011–2015.
25. Wood MA. Trials of pacing to control ventricular rate during atrial fibrillation. *J Intervent Card Electrophysiol*. 2004;10:63–70.
26. Verma A, Newman D, Geist M, Greenhut S, Laslop J, DeBellis L, Freeman MR, Dorian P. Effects of rhythm regularization and rate control in improving left ventricular function in atrial fibrillation patients undergoing atrioventricular nodal ablation. *Can J Cardiol*. 2001;17:437–445.
27. Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, Harvey M, Strickberger SA, Man KC, Morady F. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol*. 1996;78:1433–1436.
28. Leone O, Boriani G, Chiappini B, Pacini D, Cenacchi G, Martin Suarez S, Rapezzi C, Bacchi Reggiani ML, Marinelli G. Amyloid deposition as a cause of atrial remodelling in persistent valvular atrial fibrillation. *Eur Heart J*. 2004;25:1237–1241.
29. Waldo AL. Mechanisms of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2003;14:S267–S274.
30. Khan IA. Atrial stunning: determinants and cellular mechanisms. *Am Heart J*. 2003;145:787–794.
31. Rocken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C, Roessner A, Goette A. Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. *Circulation*. 2002;106:2091–2097.
32. Brundel BJ, Henning RH, Kampinga HH, Van Gelder IC, Crijns HJ. Molecular mechanisms of remodeling in human atrial fibrillation. *Cardiovasc Res*. 2002;54:315–324.
33. Brugada R, Roberts R. Molecular biology and atrial fibrillation. *Curr Opin Cardiol*. 1999;14:269–273.
34. Schotten U, Duytschaever M, Ausma J, Eijsbouts S, Neuberger HR, Allessie M. Electrical and contractile remodeling during the first days of atrial fibrillation go hand in hand. *Circulation*. 2003;107:1433–1439.
35. Schotten U, Neuberger HR, Allessie MA. The role of atrial dilatation in the domestication of atrial fibrillation. *Prog Biophys Mol Biol*. 2003;82:151–162.
36. Ausma J, van der Velden HM, Lenders MH, van Ankeren EP, Jongsma HJ, Ramaekers FC, Borgers M, Allessie MA. Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the goat. *Circulation*. 2003;107:2051–2058.
37. Thijssen VL, van der Velden HM, van Ankeren EP, Ausma J, Allessie MA, Borgers M, van Eys GJ, Jongsma HJ. Analysis of altered gene expression during sustained atrial fibrillation in the goat. *Cardiovasc Res*. 2002;54:427–437.
38. Schotten U, Ausma J, Stellbrink C, Sabatschus I, Vogel M, Frechen D, Schoendube F, Hanrath P, Allessie MA. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. *Circulation*. 2001;103:691–698.
39. Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo AL. Pathophysiology and prevention of atrial fibrillation. *Circulation*. 2001;103:769–777.
40. Ausma J, Litjens N, Lenders MH, Duimel H, Mast F, Wouters L, Ramaekers F, Allessie M, Borgers M. Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. *J Mol Cell Cardiol*. 2001;33:2083–2094.
41. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.
42. Li H, Riedel R, Oldemeyer JB, Rovang K, Hee T. Comparison of recurrence rates after direct-current cardioversion for new-onset atrial fibrillation in patients receiving versus those not receiving rhythm-control drug therapy. *Am J Cardiol*. 2004;93:45–48.
43. Bjerregaard P, Bailey WB, Robinson SE. Rate control in patients with chronic atrial fibrillation. *Am J Cardiol*. 2004;93:329–332.
44. Farshi R, Kistner D, Sarma JSM, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33:304–310.
45. Cooper HA, Bloomfield DA, Bush DE, Katcher MS, Rawlins M, Sacco JD, Chandler M, for the AFFIRM Study Investigators. Relation between achieved heart rate and outcomes in patients with atrial fibrillation (from the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] Study). *Am J Cardiol*. 2004;93:1247–1253.
46. Mazur A, Anderson ME, Bonney S, Roden DM. Pause-dependent polymorphic ventricular tachycardia during long-term treatment with dofetilide: a placebo-controlled, implantable cardioverter-defibrillator-based evaluation. *J Am Coll Cardiol*. 2001;37:1100–1105.
47. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med*. 1992;117:141–150.
48. Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. *Am J Cardiol*. 2003;91(suppl D):39D–44D.
49. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. *Am Heart J*. 1986;111:1088–1093.
50. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321:406–412.
51. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, Halperin JL, Kay GN, Klein WW, Levy S, McNamara RL, Prystowsky EN, Wann LS, Wyse DG, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC Jr, Alonso-Garcia A, Blomstrom-Lundqvist C, de Backer G, Flather M, Hradec J, Oto A, Parkhomenko A, Silber S, Torbicki A, American College of Cardiology/American Heart Association Task Force on Practice Guidelines, European Society of Cardiology Committee for Practice Guidelines and Policy Conferences, North American Society of Pacing and Electrophysiology. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circulation*. 2001;104:2118–2150.
52. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med*. 2000;342:913–920.
53. Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol*. 1997;30:791–798.

54. Kurnick D, Loebstein R, Farfel Z, Ezra D, Halkin H, Olchovsky D. Complex drug-drug-disease interactions between amiodarone, warfarin and the thyroid gland. *Medicine (Baltimore)*. 2004;83:107–113.
55. Humphries KH, Kerr CR, Steinbuch M, Dorian P. Limitations to antiarrhythmic drug use in patients with atrial fibrillation. *CMAJ Can Med Assoc J*. 2004;171:741–745.
56. Meng F, Yoshikawa T, Baba A, Moritani K, Suzuki M, Satoh T, Yokozuka H, Murayama A, Ogawa S. Beta-blockers are effective in congestive heart failure patients with atrial fibrillation. *J Card Fail*. 2003;9:398–403.
57. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol*. 1944; 42:1944–1951.
58. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126: 429S–456S. Review.
59. Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N, Breithardt G. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J*. 2004;25:1385–1394.
60. Patten M, Maas R, Bauer P, Luderitz B, Sonntag F, Dluzniewski M, Hatala R, Opolski G, Muller H, Meinertz T. Suppression of paroxysmal atrial tachyarrhythmias: results of the SOPAT trial. *Eur Heart J*. 2004; 25:1395–1404.
61. Al-Khatib SM, Shaw LK, Lee K, O'Connor C, Califf RM. Is rhythm control superior to rate control in patients with atrial fibrillation and congestive heart failure? *Am J Cardiol*. 2004;94:797–800.
62. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F III, DeMets DL, White BG, for the Vesnarinone Trial Investigators. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med*. 1998;339:1810–1816.
63. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH, Pharmacological Intervention in Atrial Fibrillation Study I: impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation: results from a prospective randomized study. *Eur Heart J*. 2003;24: 1430–1436.
64. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ, Van Gelder IC, for the Race Study Group. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation: results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43:241–247.
65. Hagens VE, Vermeulen KM, TenVergert EM, Van Veldhuisen DJ, Bosker HA, Kamp O, Kingma JH, G. Tijssen JG, Crijns HJ, Van Gelder IC, for the RACE Study Group. Rate control is more cost-effective than rhythm control for patients with persistent atrial fibrillation: results from the RAte Control versus Electrical cardioversion (RACE) study. *Eur Heart J*. 2004;25:1542–1549.
66. Marshall DA, Levy AR, Vidaillet H, Fenwick E, Slee A, Blackhouse G, Greene HL, Wyse DG, Nichol G, O'Brien BJ, for the AFFIRM and CORE Investigators. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. *Ann Intern Med*. 2004;141:653–661.
67. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol*. 2003;42:185–197.
68. Oral H, Veerareddy S, Good E, Hall B, Cheung P, Tamirisa K, Han J, Fortino J, Chugh A, Bogun F, Pelosi F Jr, Morady F. Prevalence of asymptomatic recurrences of atrial fibrillation after successful radiofrequency catheter ablation. *J Cardiovasc Electrophysiol*. 2004;15:920–924.
69. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, for the DAVID Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA*. 2002;288:3115–3123.
70. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation*. 2000;101:1138–1144.
71. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol*. 2003;41:1697–1702.
72. Simantirakis EN, Vardakis KE, Kochiadakis GE, Manios EG, Igoumenidis NE, Brignole M, Vardas PE. Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation. *J Am Coll Cardiol*. 2004; 43:1013–1018.
73. Garrigue S, Bordachar P, Reuter S, Jais P, Kobeissi A, Gaggini G, Haissaguerre M, Clementy J. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study. *Heart*. 2002;87:529–534.

An Argument for Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

Peter Zimetbaum, MD

The age-old and common-sense argument that if you were born in sinus rhythm you should probably try to remain so has seemingly lost some vigor with the results of recent randomized studies.[1–6] These trials have convincingly demonstrated that in a select population of patients, a strategy of rhythm control with antiarrhythmic drugs confers no mortality benefit over a rate-control strategy. These studies have also demonstrated no quality-of-life benefit associated with a strategy of maintenance of sinus rhythm in this patient population.

The question therefore remains, is there any reason to maintain sinus rhythm? The answer is "yes," given the fundamental observation that atrial fibrillation (AF) is an independent predictor of mortality in virtually every study that has monitored this end point.[7–13] Unselected population-based studies (most notably, the Framingham Heart Study)

TABLE 1. Randomized Trials of Rhythm vs Rate Control

Study	n	Age, y	Follow-Up, mo	Amiodarone at Some Point During Study, %	Sinus Rhythm, %	Warfarin, %	Thromboembolic Complications, %	Mortality,* %	QOL and Other Relevant Subgroup Analyses
AFFIRM[1]			42						Mortality reduction associated with sinus rhythm rather than treatment strategy
Rate control	2027	70±9		10	35	85	6	21	
Rhythm control	2033	70±9		70	63	70	7.5	24	
RACE[2]			27						No overall difference. Improved QOL in patients with AF-related symptoms
Rate control	256	68±9		NR	10	96–99	5.5	17	
Rhythm control	266	68±9		NR	39	86–99	7.9	13	
STAF[3]			22						QOL equivalent. Majority of adverse events occurred in patients during AF
Rate control	100	65±9		0	0	NR	0.6	5	
Rhythm control	100	66±9		0	NR	NR	3.1	2.5	
PIAF[4]			12						No difference in QOL. Improved 6-minute walk test in rhythm-control group.
Rate control	125	61±9		0	10	100	NR	1.6	
Rhythm control	127	60±10		100	56	100	NR	1.6	
Hot Café[7]			20						Improvement in exercise capacity and LVEF in rhythm-control group
Rate control	101	61±18		NR	NR	74	1	1	
Rhythm control	104	60±11		56	63.5	NR	2.9	2.9	

QOL indicates quality of life; NR, not reported; and LVEF, left ventricular ejection fraction.
*No significant difference in any study.

have identified an increased mortality risk associated with AF, particularly in women.[14] The Centers for Disease Control and Prevention analyzed national and state mortality statistics for patients with AF in 1999.[15] They identified 67 875 deaths in which AF was a contributing cause, with an age-adjusted death rate of 24.7/100 000 population. Patients aged ≥75 years represented 84% of these deaths and those aged ≥85 years represented 47.4%. Studies of selected populations with coronary and noncoronary cardiomyopathy, congestive heart failure, hypertrophic obstructive cardiomyopathy, and sinoatrial dysfunction have all demonstrated an increased mortality risk associated with AF.[7–13]

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the largest of the recent trials of rhythm control compared with rate control, demonstrated a statistically insignificant trend toward increased mortality in the rhythm-control arm (Table 1). Excess mortality in the rhythm-control arm was largely associated with noncardiovascular disease.[5] Further analysis of this study determined that the presence of AF at the time of study termination was a more potent predictor of mortality than treatment strategy.[6] This finding suggests that although sinus rhythm is preferable to AF, our methods of maintaining sinus rhythm may themselves contribute to overall mortality.

Why Doesn't Rhythm Control Reduce Mortality?

It seems obvious that the maintenance of sinus rhythm should be associated with reduced mortality. AF is associated with increased risk of stroke, congestive heart failure, and cardiomyopathy and may be associated with tachycardia-induced tachyarrhythmias. Strategies for rhythm control have not shown a reduction in overall mortality for a multitude of reasons. These trials have been performed in patient groups at high risk for stroke but have not mandated the continuation of anticoagulation. A major contribution of these studies has been to show the importance of continued anticoagulation regardless of the use of antiarrhythmic therapy. This imperative likely exists because these medications do not confer complete suppression of AF. In fact, studies of rhythm control versus rate control have shown at best a 60% suppression of AF in the rhythm-control group (Table 1). Indeed, the Strategies of Treatment of Atrial Fibrillation multicenter pilot study (STAF), which randomized 200 pa-

tients to a strategy of rhythm control versus rate control, found that all but 1 of the end points of death or thromboembolism reached in the rhythm-control group occurred during AF.[3]

The best available agent for rhythm control is amiodarone. In the Canadian Trial of Atrial Fibrillation, amiodarone was compared with propafenone and sotalol for suppression of AF. Amiodarone was associated with a 35% rate of AF recurrence at 16 months compared with a 63% rate of recurrence with the other study drugs.[16,17] The rates of stroke and intracranial hemorrhage were less in the amiodarone-treated group than in the other antiarrhythmic therapies.

Antiarrhythmic medications are also associated with a significant risk of proarrhythmic and noncardiovascular toxicities. The careful use of these medications as demonstrated in AFFIRM can minimize this risk but does not eliminate it entirely.[17] The problem lies with incomplete data for the effects of rhythm control in large groups of AF patients not represented in current clinical studies and the profound limitations of the tools currently available to maintain sinus rhythm.

Can We Generalize the Results of Rate Versus Rhythm Control Trials to All AF Patients?

AF is unlikely to be one disease. It is likely that lone AF in the 50-year-old male with vagal triggers is a very different disease in both mechanism and natural history than the same arrhythmia in a 75-year-old with longstanding hypertension and congestive heart failure. It seems logical that the apoptosis and fibrosis that naturally occur with aging would lead to different mechanisms of AF that are age dependent. Concomitant disease may further complicate the underlying substrate.

Randomized controlled trials have largely represented patients with at least 1 risk factor for stroke who were candidates for participation in a randomized trial. In general, younger patients with lone and highly symptomatic AF, the elderly over 80 years of age, and those patients with concomitant congestive heart failure were not included. These neglected groups constitute a significant proportion of patients with AF. Lone AF represents 15% to 20% of the AF population, and those over the age 80 years represent 35%.[18] Consequently, at least 50% of the 3.3 million adults who will have AF in the United States by the year 2025 will not be represented in the previously cited trials. It is inappropriate to generalize the results of AFFIRM and other such rhythm- versus rate-control trials to this large group of patients. Should we relegate the asymptomatic 50-year-old male with a normal heart and persistent AF to chronic AF? One could argue that we won't make him feel better by restoring sinus rhythm; however, we may prevent the progressive atrial remodeling (electrophysiological and anatomic) that occurs with chronic AF. These chronic changes that occur with the development of chronic AF will likely disqualify this patient from or reduce the effectiveness of developing and potentially curative therapies.

Methods for maintenance of sinus rhythm are particularly important in the elderly. The risk of AF-related stroke increases with age, with 1 in 4 strokes occurring in those >80 years of age directly attributable to AF.[19] The absence of stroke reduction associated with rhythm control strategies is likely related to the ineffectiveness of these therapies. Specifically, all available antiarrhythmic drugs are associated with at least a 25% to 50% yearly recurrence of AF.[16] These recurrences often occur with a controlled ventricular response and are asymptomatic. The elderly represent a group both at high risk of stroke and frequently intolerant of warfarin. Elderly patients who are started on warfarin therapy at the time of AF diagnosis frequently have it discontinued owing to the development of a risk of falls, bleeding, or difficulty with medication compliance. The effective suppression of AF in this group may reduce the risk of stroke. The combination of amiodarone and a pacemaker in the setting of sinoatrial dysfunction often proves a very effective method of AF suppression.[20]

The congestive heart failure population is another underrepresented group in currently analyzed clinical trials. The increased mortality associated with AF in patients with left ventricular dysfunction and congestive heart failure has been demonstrated conclusively.[21] Amiodarone has been shown to reduce mortality in patients with congestive heart failure who were converted to sinus rhythm in the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trial.[22] A similar finding was demonstrated in the DIAMOND (Danish Investigation of Arrhythmia and Mortality on Dofetilide) study, in which restoration and maintenance of sinus rhythm with dofetilide in patients with AF and congestive heart failure was associated with a reduction in mortality and hospitalization rates.[23] In the AFFIRM study, the subset with preexisting congestive heart failure (23% of population) demonstrated a trend toward improved mortality in the rhythm-control arm. The HOT CAFÉ (Rate Control vs Rhythm Control in Patients With Nonvalvular Persistent Atrial Fibrillation: The Results of the Polish How to Treat Chronic Atrial Fibrillation Study) study noted a significantly increased mean left ventricular fractional shortening in the rhythm-control group compared with the rate-control group.[7] The potential benefits of improved left ventricular function in the absence of clinical congestive heart failure will likely require longer follow-up to realize the absolute benefits of rhythm control. A definitive answer to the question of the importance of maintaining sinus rhythm in patients with congestive heart failure should be provided by the Canadian Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial.[24]

Nonpharmacological Therapies

Nonpharmacological therapies to maintain sinus rhythm represent the most hopeful option for reducing the mortality and morbidity of AF. The percutaneous isolation of the pulmonary veins to isolate triggers of AF, in some instances coupled

TABLE 2. Selected Studies of Percutaneous AF Ablation

Site, Study Type	N, Patient Type	Procedure	Repeat Procedure, n	Follow-Up, mo	Success Off AADs, %	Adverse Events	QOL/Other Findings
Milan[25]	589	PVI	NR	30	80	8%	Normalized QOL and reduction in mortality with ablation
Nonrandomized	589, PAF and chronic AF, >2 AAD failures	AAD			42	19%	
Michigan[26]	40	PVI	18	6	67	0	NR
Randomized	40, PAF	PVI+lines	0		88	0	
Bordeaux[27]	58 with CHF	PVI±lines	29	12 ±7	69	1 Stroke	Improved QOL, LVEF, CHF irrespective of heart rate before procedure
Nonrandomized	58 without CHF; PAF and chronic AF		27		71	1 Pericardial tamponade in each group	
Milan[28]	280	PVI	28	12	76	4 Pericardial tamponades (2 per group)	NR
Randomized	280, PAF and chronic AF	PVI+lines	11		83		

AAD indicates antiarrhythmic drug; QOL, quality of life; PVI, pulmonary vein isolation; NR, not reported; PAF, paroxysmal AF; lines, ablation lines in left atrium (in addition to pulmonary vein isolation); CHF, congestive heart failure; and LVEF, left ventricular ejection fraction.

with linear lesions to modify the atrial substrate for arrhythmia perpetuation, has proven increasingly successful. It is premature to call this procedure curative, but rates of significant reduction in AF frequency approach 70% to 80%[25–28] (Table 2). A recent study of pulmonary vein isolation coupled with left atrial linear lesions in patients with impaired left ventricular function (left ventricular ejection fraction <45%) and congestive heart failure reported a 78% rate of sinus rhythm maintenance at 12 months of follow-up.[27] There was a significant improvement in left ventricular ejection fraction, a decrease in left ventricular dimensions, and improvement in exercise capacity and quality of life. These findings were present in patients regardless of the adequacy of rate control before ablation, determined by a 48-hour Holter study. This observation raises the question of whether factors other than ventricular rate (eg, irregularity of rhythm, loss of atrial contribution to filling) contribute to congestive heart failure.[29] These findings are consonant with results of Pappone et al,[25] who showed improved survival and quality of life after pulmonary vein isolation. Unqualified enthusiasm for the percutaneous management of AF must be tempered by the 1% risk of stroke, 4% risk of pulmonary vein stenosis, and development of left atrial–esophageal fistula associated with this procedure.[30,31] The surgical approach to sinus rhythm maintenance is also rapidly evolving. Variations on the operative MAZE procedure have consistently demonstrated 80% reductions in the recurrence of AF. This procedure is generally reserved for patients already undergoing CABG or valve surgery.[32]

Costs and Quality of Life

There is no question that we need to reduce the healthcare costs associated with AF. In a retrospective analysis of 3 federally funded US databases, approximately 350 000 hospitalizations, 7 million office visits, and 542 000 emergency department visits were attributable to AF annually.[33] Overall, total inpatient and outpatient costs for AF were approximately $6.42 billion. The cost analysis of the AFFIRM study found the rate-control strategy to be more cost-effective than the rhythm-control strategy.[34] A large percentage of the costs comprised hospital admissions. Improvements in methods for rhythm control that lead to long-term suppression or cure of AF will undoubtedly prove cost-effective compared with long-term rate control, particularly in young individuals. The real cost savings associated with long-term maintenance of sinus rhythm will be achieved over decades with reductions in congestive heart failure and stroke and improvement in function that will translate into more work days and better quality of life.

There is currently no uniformly accepted AF-specific tool with which to assess quality of life.[35] Application of less specific tools has in composite demonstrated no improvement in quality of life in rhythm- versus rate-control studies; however, the Rate Control versus Electrical Cardioversion (RACE) study has demonstrated that as with the issue of mortality, quality of life is better in patients who maintain sinus rhythm, regardless of which study arm of a protocol they are assigned.[36] Recent data from the Sotalol Amiodarone Atrial Efficacy Trial (SAFE-T) demonstrated a significant improvement in quality of life and exercise capacity associated with the maintenance of sinus rhythm.[36a]

We Need a New Paradigm for the Prevention and Treatment of AF

Studies demonstrating no survival advantage to sinus rhythm maintenance over AF must be regarded as an indictment of our treatments more than a rationale for acceptance of continuous AF. The fundamental conclusion we should derive from the current state of the debate of rhythm versus rate control is that we need a new paradigm for our thinking about patients with AF. First, we need to target prevention. Next, we need to improve our methods of management to improve efficacy, safety, and quality of life for patients while reducing costs to the healthcare system.

Prevention

It is possible that improved management of hypertension will reduce the number of patients predicted to have AF in the coming decades. ACE inhibitors and angiotensin II type 1 receptor blockers have been demonstrated to reduce the development of atrial fibrosis and atrial remodeling.[37] In a pooled analysis of randomized controlled trials of ACE inhibitors and angiotensin II type 1 receptor blockers, the incidence of new-onset and recurrent AF was significantly reduced in patients taking these medications.[38] Whether the use of antialdosterone agents, which have been associated with decreased atrial fibrosis, will prove to be an additional preventative therapy needs to be tested.

Better and Safer Medications

There is a need for antiarrhythmic drugs with better efficacy and greater safety. Current strategies include the development of antiarrhythmic drugs with effects limited to atrial tissue to reduce the development of ventricular arrhythmias.[39,40] Genetic screening of patients to prospectively identify ion channel abnormalities that may predispose to proarrhythmic toxicity of antiarrhythmic medications may prove feasible and may help direct therapy of AF.

Better Surveillance

Frequent interrogation of atrial diagnostic parameters in implanted devices can provide information about the frequency and duration of AF recurrences. Ultimately, we will be able to monitor these device patients on a continuous basis through wireless technology. Those at high risk for anticoagulation-related complications or those on the lower-risk side for stroke who still meet requirements for anticoagulation (eg, 65 years old with treated hypertension) may be maintained safely with no warfarin but with antiarrhythmic medications. If recurrences are documented, anticoagulants can be administered until sinus rhythm is restored. The development of rapidly acting anticoagulants with efficacy and safety equivalent to warfarin will make such an approach very practical. It is likely that for some patients (eg, those with diffuse atheromatous disease), AF is a marker but not the sole risk factor for stroke, and anticoagulants should never be stopped. This approach will need to be tested in a randomized controlled study but is needed given the limitations of chronic anticoagulation in this population.

Better and Safer Procedures

Safer and more efficacious refinements of the percutaneous procedure for AF ablation are under constant development. New energy sources will likely reduce the risk of pulmonary vein stenosis and provide more complete electrical isolation of the pulmonary veins.

A completely epicardial approach to the MAZE procedure holds great promise. A thoracoscopic-guided procedure with the avoidance of cardiopulmonary bypass, pulmonary vein stenosis, and stroke risk associated with an endocardial catheter-based procedure, coupled with the potential stroke risk reduction of a left atrial appendectomy, may prove a successful strategy for AF management.[41]

Evaluation of Cost-Effective Management Strategies

We need to test and implement management strategies to reduce the costs associated with AF. This involves improved compliance with anticoagulation guidelines to reduce the incidence of thromboembolic complications. Strategies to avoid unnecessary hospital admissions for components of AF management, including cardioversion and antiarrhythmic drug initiation, have proved safe and highly effective.[42–45]

As Sir Thomas Lewis noted in 1912, “Most hearts which develop fibrillation of the auricles maintain this mechanism to the end of the chapter; it is essentially a chronic and terminal malady. But from time to time transient attacks are seen, and in some patients paroxysms of fibrillation of a few hours, days or weeks duration are noted. The affection, when it takes this form, is generally classed as paroxysmal tachycardia.”[46] He went on to say, “There is no ailment in which such success can be achieved, no other cardiac disease which may be so speedily benefited, as the well-managed case of auricular fibrillation. As a direct result of active treatment the moribund may be restored and many years may be added to their lives.” Sir Lewis was referring to the use of digoxin for rate control of chronic AF. He did not have high hopes for the maintenance of sinus rhythm, let alone a curative solution for AF. Nearly a century later, we have not improved much on Lewis’ original characterization of AF. We now recognize the importance of isolated atrial ectopy, particularly arising from the pulmonary veins in the initiation of paroxysmal AF.[47] We are just beginning the process of targeting our therapies to the diverse mechanisms of this disease. The generalization of one management strategy for AF would represent a step back we should not be willing to take. Ultimately, a combination of the above strategies may bring us full circle to what our common sense has always told us: if you were born in sinus rhythm, you should probably try to remain so.

References

1. Wyse DG, Waldo AL, Domanski MJ, Rosenberg Y, Schron E, Kellen J, Greene H, Mickel M, Dalquist J, Corley S. Comparison of rate control

and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
2. Van Gelder I, Hagens V, Bosker H, Kingma J, Kamp O, Kingma T, Said S, Darmanata J, Timmermans A, Tijssen J, Crijns J. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
3. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. Randomized trial of rate-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
4. Hohnloser S, Kuick Karl, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomized trial. *Lancet*. 2000;356:1789–1794.
5. Steinberg J, Sadaniantz A, Kron J, Krahn A, Denny D, Daubert J, Campbell B, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco E, Greene L. Analysis of cause specific mortality in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Circulation*. 2004;109:1973–1980.
6. The AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 3004;109: 1509–1513.
7. Villareal R, Hariharan R, Liu B, Kar B, Lee V, Elayda M, Lopez J, Rasekh A, Wilson J, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol*. 2004; 43:742–748.
8. Crenshaw B, Ward S, Granger C, Stebbins A, Topol E, Califf R. Atrial fibrillation in the setting of acute myocardial infarction: the GUSTO-I experience: Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1997;30:406–413.
9. Wong C, White H, Wilcox R, Criger D, Califf R, Topol E, Ohman E. New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO-III experience. *Am Heart J*. 2000;140:878–885.
10. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998;158:229–234.
11. Dries D, Exner D, Gersh B, Domanski M ,Waclawiw M ,Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol*. 1998;32:695–703.
12. Olivotto I, Cecchi F, Casey S, Dolara A, Traverse J, Maron B. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation*. 2001;104:2517–2524.
13. Glotzer T, Hellkamp M, Zimmerman J, Sweeney M, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich F, Lee K, Lamas G. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke. *Circulation*. 2003;107:1614–1619.
14. Benjamin E, Wolf P, D'Agostino R. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98: 946–952.
15. Atrial fibrillation as a contributing cause of death and Medicare hospitalization: United States, 1999. *MMWR Morb Mortal Wkly Rep*. 2003;52: 128–131.
16. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B, for the Canadian Trial of Atrial Fibrillation Investigators. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med*. 2000;342:913–920.
17. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol* 2003;42:20–29.
18. Go A, Hylek E, Phillips K, Chang Y, Henault L, Selby J, Singer D. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors In Atrial Fibrillation Study. *JAMA*. 2001;285:2370–2375.
19. Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
20. Essebag V, Hadjis T, Platt R, Pilote L. Amiodarone and the risk of bradyarrhythmia requiring permanent pacemaker in elderly patients with atrial fibrillation and prior myocardial infarction. *J Am Coll Cardiol* 2003;41:249–254.
21. Wang T, Larson M, Levy D. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925.
22. Deedwandia PC, Singh B, Ellenbogen K, Fisher S. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). *Circulation*. 1998;98:2574–2579.
23. Pederson O, Bagger H., Keller N, Marchant B, Kober L, Torp Pederson C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish Investigation of Arrhythmia and Mortality on Dofetilide (diamond) study. *Circulation*. 2001;104:292–296.
24. Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial. *Am Heart J*. 2002;14:597–607.
25. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol*. 2003;42:185–197.
26. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, Veerareddy S, Pelosi F, Morady F. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. *Circulation*. 2003;108:2355–2360.
27. Hsu L, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie J, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation of atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2372–2378.
28. Pappone C, Manguso F, Vicedomini G, Gugliotta F, Santinelli O, Fero A, Gulletta S, Sala S, Sora N, Paglino G, Augello G, Agricola E, Zangrillo A, Alfieri O, Santineeli V. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation. *Circulation*. 2004;110:3036–3042.
29. Stevenson W, Stevenson L. Atrial fibrillation and heart failure: five more years. *N Engl J Med*. 2004;351:2437–2438.
30. Saad E, Marrouche N, Saad C, Ha E, Bash D, White R, Rhodes J, Prieto L, Martin D, Saliba W, Schweikert R, Natale A. Pulmonary vein stenosis after catheter ablation of atrial fibrillation: emergence of a new clinical syndrome. *Ann Intern Med*. 2003;138:634–638.
31. Pappone C, Oral H, Santinelli V, Vicedomini G, Lang C, Manguso F, Torracca L, Benussi S, Alfieri O, Hong R, Lau W, Hirata K, Shikuma N, Hall B, Morady F. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. *Circulation*. 2004;109: 2724–2726.
32. Gaynor S, Diodato M, Prasad S, Ishii Y, Schuessler R, Bailey M, Damiano N, Bloch J, Moon M, Damiano R. A prospective, single-center clinical trial of a modified Cox maze procedure with bipolar radiofrequency ablation. *J Thorac Cardiovasc Surg*. 2004;128:535–542.
33. Coyne KS, Grandy S, Paramore C, Mercader M, Zimetbaum P. Resource use and costs associated with atrial fibrillation in the US. *Circulation*. 2004;110(suppl III):III-826. Abstract.
34. Marshall D, Levy A, Vidaillet H, Fenwick E, Slee A, Blackhouse G, Greene H, Wyse G, Nichol G, O'Brien B. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. *Ann Intern Med*. 2004;141: 653–661.
35. Coyne K, Margolis M, Grandy S, Zimetbaum P. The state of patient-reported outcomes in atrial fibrillation: a review of current measures. *Pharmacoeconomics*. In press.
36. Hagens V, Ranchor A, Van Sonderen E, Bosker H, Kamp O, Tijssen J, Kingma JH, Crijns H, Van Gelder I. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation: results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43:241–247.

36a. Singh B, Singh S, Reda D, Tang X, Lopez B, Harris C, Fletcher R, Sharma S, Atwood J, Jacobsen A, Lewis D, Raisch D, Ezekowitz M. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med.* 2005; 352:1861–1872,

37. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and

structural remodeling in atrial fibrillation. *J Am Coll Cardiol*. 2003;41:2197–2204.
38. Madrid A, Peng J, Zamora J, Marin I, Bernal E, Escobar C, Munos-Tinoco C, Rebollo J, Moro C. The role of angiotensin converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases. *Pacing Clin Electrophysiol*. 2004;27:1405–1410.
39. Roden D. Antiarrhythmic drugs: past, present and future. *J Cardiovasc Electrophysiol*. 2004;26:57C–66C.
40. Roy D, Rowe B, Steill I, Coutu B, Ip J, Phaneuf D, Lee J, Vidaillet H, Dickinson G, Grant S, Ezrin A, Beatch G. A randomized, controlled trial of RSD 1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol*. 2004;44:2355–2361.
41. Salenger R, Lahey S, Saltman A. The completely endoscopic treatment of atrial fibrillation: report on the first 14 cases with early results. *Heart Surgery Forum*. 2004;7:E554–E558.
42. Hauser T, Josephson ME, Zimetbaum P. Safety and feasibility of a clinical pathway for the outpatient initiation of antiarrhythmic medications in patients with atrial fibrillation and flutter. *Am J Cardiol*. 2003;91:1437–1441.
43. Kim M, Morady F, Conlon B, Kronick S, Lowell M, Bruckman D, Armstrong W, Eagle K. A prospective, randomized, controlled trial of an emergency department-based atrial fibrillation treatment strategy with low-molecular-weight heparin. *Ann Emerg Med*. 2002;40:187–192.
44. Zimetbaum P, Reynolds MR, Ho KK, Gaziano T, McDonald MJ, McClennen S, Berezin R, Josephson ME, Cohen DJ. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. *Am J Cardiol*. 2003;92:677–681.
45. Botkin SB, Dhanekula LS, Olshansky B. Outpatient cardioversion of atrial arrhythmias: efficacy, safety, and costs. *Am Heart J*. 2003;145:233–238.
46. Lewis T. Auricular fibrillation. In: *Clinical Disorders of the Heart Beat: A Handbook for Practitioners and Students.* London, England: Shaw and Sons; 1912:71–90. Chapter 6.
47. Haissaguerre M, Shah D, Takahashi A, Hocini M, Quiniou G, Garrigue S, LeMouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in pulmonary veins. *N Engl J Med*. 1998;339:659–666.

Response to Zimetbaum

Rodney H. Falk, MD, FRCP

"He thought he saw an argument that proved he was the Pope, he looked again and found it was a mottled bar of soap."

Lewis Carroll, "The Mad Gardener's Song"

As in the poem above, my opponent's arguments do not bear up to careful scrutiny. "Common sense" may decree that being born in sinus rhythm is a reason to try and remain in it, but the era of controlled clinical trials is littered with discarded common sense arguments, from the idea that suppression of ectopic beats would decrease sudden death risk[1] to the concept that positive inotropic drugs decrease mortality in heart failure.[2,3] So it is now with atrial fibrillation. The controlled trials have consistently demonstrated no benefit of attempts to maintain sinus rhythm over rate control in any primary or secondary end point evaluated.

Studies demonstrating that atrial fibrillation is associated with an increased mortality[4] do not prove that restoration of sinus rhythm will reduce mortality. Rather, they suggest that atrial fibrillation is a marker of more severe disease, as underscored by the observation that atrial fibrillation during an acute myocardial infarction is associated with a higher 1-year mortality rate than among those never experiencing the arrhythmia, despite the fact that most patients revert to sinus rhythm before hospital discharge.[5] Drawing conclusions from uncontrolled studies is also unreliable, as has repeatedly been learned when controlled trials have overturned firmly held beliefs.[6,7] With regard to heart failure, described as an "underrepresented group," the AFFIRM results clearly show no benefit of a strategy of rhythm control in 939 heart failure patients, whereas those without heart failure had a statistically significant better survival in the rate-control group, as did, among others, patients with coronary artery disease and those over age 65 years.[8] Thus, although there are some highly symptomatic patients with atrial fibrillation who may benefit from restoration of sinus rhythm, the majority can, and probably should, be allowed to remain in atrial fibrillation with adequate anticoagulation unless future data tell us otherwise.

References

1. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman AL, Greene HL. Mortality and morbidity in patients receiving encainide, flecainide or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.
2. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML. Effect of oral milrinone on mortality in severe chronic heart failure: the PROMISE Study Research Group. *N Engl J Med.* 1991;325:1468–1475.
3. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F, DeMets DL, White BG; Vesnarinone Trial Investigators. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure: *N Engl J Med*. 1998;339:1810–1816.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death. *Circulation*. 1998;98:946–952.
5. Wong C-K, White HD, Wilcox RG, Criger DA, Califf RA, Topol EJ, Ohman M. New atrial fibrillation after acute myocardial infarction

predicts death: the GUSTO-III experience. *Am Heart J*. 2000;140: 878–885.
6. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605–613.
7. Borzak S, Ridker P. Discordance between meta-analyses and large-scale randomized clinical trials: examples from the management of myocardial infarction. *Ann Intern Med*. 1995;123:873–877.
8. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825–1833.

Response to Falk

Peter Zimetbaum, MD

The debate of rhythm compared with rate control for atrial fibrillation is born from antiarrhythmic therapies with poor efficacy and high rates of adverse effects. As Dr Falk points out, in select populations (representing ≈50% of the atrial fibrillation population), randomized data have failed to define a mortality, cost-savings, or quality-of-life advantage to a strategy of sinus rhythm maintenance. These studies have clearly found that the presence of sinus rhythm (regardless of the strategy) is associated with a lower mortality than the presence of atrial fibrillation. It is not surprising that quality-of-life measures have not identified an advantage to sinus rhythm maintenance strategies. It is likely that most patients with severe atrial fibrillation–related symptoms would not be referred for enrollment in a study with randomization to rate control. In RACE, patients with atrial fibrillation–related symptoms had improved quality of life in the rhythm-control arm. Importantly, we have not yet validated a quality-of-life tool with sufficient specificity for atrial fibrillation to fully evaluate this critical issue in the diverse populations of atrial fibrillation patients. The controversy surrounding this issue should be viewed as a call to improve our methods of prevention and therapy not as a justification to accept rate control as a final common pathway for all patients with atrial fibrillation.