Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 41, No. 10, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00331-0

EDITORIAL COMMENT

Rhythm Management in Atrial Fibrillation: Less Is More*

D. George Wyse, MD, PhD, FACC
Calgary, Alberta

The management of heart rhythm as part of the treatment of atrial fibrillation (AF) has been the subject of intensive investigation over the past two decades. Until recently, most physicians have believed that the initial approach to rhythm management should give primary consideration to restoration and maintenance of sinus rhythm (SR) (1). The potential benefits of restoration and maintenance of SR include, among others, relief of symptoms, improved exercise tolerance, prevention of stroke, less need for anticoagulant therapy, improved hemodynamic function, and prevention of tachycardia-induced cardiomyopathy (2). The negative aspects of this approach include the rather poor efficacy of the antiarrhythmic drugs (3) and the potential of these drugs to cause adverse effects, including death (4). The

See pages 1690 and 1697

balance between the benefit and risk of restoration and maintenance of SR, primarily with drug therapy, until this point in time has not been rigorously tested but rather assumed. Accordingly, the past two decades of research on pharmacologic rhythm management for AF have focused on the capability of restoring and maintaining SR, regardless of the recognized limitations, with the expectation that benefit would accrue from this approach. However, research on rhythm management for AF has evolved more recently, partly because of the demonstration of the remarkable efficacy of anticoagulation for the prevention of stroke in AF in the 1980s and 1990s (5), partly because of the limitations of drug therapy (3,4), and partly because of the recognition of the limitations of surrogate end points in trials of arrhythmia management (6). First, there has been the emergence of a number of nonpharmacologic therapies (7). Second, there has been an attempt to refocus on measuring clinical end points in studies of rhythm management of AF, rather than assuming SR restoration and maintenance is beneficial (6). And third, there has been a renewed interest in the strategy of heart rate (HR) control as a primary rhythm treatment modality as part of the management of AF, rather than using it only as a second choice or a temporary measure (8). In this issue of the *Journal*, two articles address important aspects of this last point (9,10).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiology, Department of Cardiac Sciences, University of Calgary and Calgary Health Region, Calgary, Alberta, Canada.

The STAF trial. Strategies of Treatment of Atrial Fibrillation (STAF) is the fourth randomized trial to be published comparing the strategy of rhythm control to the strategy of rate control for the rhythm management portion of the treatment of AF. It was preceded by the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial (11) and was concurrent with Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) (12) and RAte Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) (13). The primary end point of PIAF was the proportion of patients with improvement in symptoms (11). The primary end point of STAF was a composite including death, cardiopulmonary resuscitation, cerebrovascular event, or systemic embolus (9). RAte Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation used a somewhat similar composite end point (13). The primary end point in AFFIRM was total mortality (12). However, secondary end points in each trial are complementary to the primary end points of the others. Three of the four trials also reported on quality of life and all four reported on hospitalizations (9,11–13). None of the studies reported any advantage for the rhythm control strategy.

In STAF, no differences were found between the two treatment strategies with respect to the primary end point. An important aspect of the findings in STAF was that the proportion of patients assigned to the rhythm control strategy in whom SR could be maintained was low, only 23% after three years. Furthermore, at the time the primary events were detected in STAF patients in both treatment strategies, only one out of 19 was in SR. This last observation might lead one to conclude that if only SR could be successfully maintained, it would be a superior treatment to HR control. The STAF investigators, quite correctly, did not reach that conclusion. There are several reasons that conclusion remains a hypothesis to be tested. First, it is important to point out that the rhythm at the moment the event occurred could not be known with certainty in many of these patients. The first rhythm recorded when the patient receives medical attention is not necessarily the one present at the time of the event or immediately before the event. Second, in the AFFIRM trial, which included some patients ($<$30%) with paroxysmal AF, investigators were able to maintain SR in $>$60% of their patients over five years, and that trial also showed no advantage of the rhythm control strategy (12). Third, ease of maintenance of SR may itself be an independent predictor of a favorable outcome. This last point is illustrated in the dofetilide-AF results demonstrating a favorable outcome with SR versus AF in both the placebo and dofetilide-treated arms, but no survival advantage attributable to dofetilide (14). Finally, the potential adverse effects of the treatments for restoration and maintenance of SR cannot be ignored as a source of morbidity and mortality in the treatment of AF. Indeed, AFFIRM and RACE reported more frequent adverse drug effects in the rhythm control approach (12,13).

JACC Vol. 41, No. 10, 2003
May 21, 2003:1703–6

It is also interesting to note a slight excess of stroke/systemic embolus in the rhythm control strategy compared with the rate control strategy in STAF. A similar observation was noted in AFFIRM (12) and RACE (13), but in no study was the difference significant. To some extent the use of anticoagulants in all trials was different in the two treatment strategies (greater anticoagulant use in the rate control arm), because of the belief by many that when SR is restored and maintained for at least one month, anticoagulation can be discontinued (2). Thus, it is tempting to attribute the observation of such a difference in thromboembolic events to the difference in anticoagulant use in the two treatment strategies. Indeed, this may be the major portion of the explanation. However, one could also hypothesize that alternating between AF and SR in partially successful rhythm management may be more likely to eject emboli from the heart than continuous AF. Whatever the explanation, it should be stressed that because of these uncertainties, anticoagulation should rarely be discontinued in high-risk patients (those with stroke risk factors) or in the persistent form of AF, even when the treating physician feels that SR has been restored and maintained. This is a new finding and seems contrary to current guideline recommendations (2), although it must be recognized that the guidelines are ambiguous on this point.

Although STAF did not report on quality-of-life measures, all three of the other trials found no difference in quality of life between the two treatment strategies. All four trials (9,11–13) did find that there are significantly more hospitalizations using the rhythm control strategy. Hospitalization has an important implication with respect to cost of the strategy. Although none of these studies has yet produced a published formal cost analysis, if it is indeed true that the cost of the rhythm control strategy is greater and there are no advantages attributable to it, then one could easily infer that the rate control strategy is the preferred initial approach, on the basis of cost-effectiveness, in patients such as those enrolled in the trials. At the very least, one is led to conclude that the rate control strategy should be considered as a primary therapy, not a second choice when rhythm control fails.

Given the strength and consistency of this emerging evidence, an important consideration is whether or not the results of these four trials apply to all patients with AF. To answer that question, one must look carefully at the type of patients enrolled in them, the therapies used, and any subgroup analyses available. In all four studies (9,11–13), patients were predominantly the elderly with persistent AF (2). Furthermore, only a minority had extensive structural heart disease. Finally, it is not possible from the available information to determine the reasons that eligible patients were not enrolled in the trials.

A number of potential biases arise in the enrollment of patients in most clinical trials. One of the strongest physician biases in the treatment of AF is that highly symptomatic patients need to be treated with the rhythm control strategy (1,15). To the extent that such a bias meant highly symptomatic patients were not enrolled in these trials comparing the rate control strategy to the rhythm control strategy, the results may not apply to highly symptomatic patients. However, because the final mode of therapy for the highly symptomatic patient is often the ablate and pace approach (16), it should be recalled that the ablate and pace approach is very effective for highly symptomatic patients and is part of the rate control strategy (17). There are virtually no young patients with highly symptomatic paroxysmal AF and minimal or no heart disease in these four trials. Therefore, the results do not apply to such patients, who are the primary type of patient currently having a pulmonary vein radiofrequency ablative procedure (18). It must also be recognized that these trials compared predominantly pharmacologic therapies. Perhaps greater use of nonpharmacologic therapies might have produced more favorable (or less favorable) results with respect to the rhythm control strategy. Finally, the AFFIRM trial is the only trial that is large enough to do subgroup analyses in order to generate hypotheses about enrolled patients in whom the rhythm control strategy might be preferable. The data do not reveal an advantage of the rhythm control strategy with respect to mortality for any of the prespecified subgroups in that study, although the point estimate of the hazard ratio is less than one for two groups: younger patients and those with congestive heart failure (12). Clearly, more data are needed on groups of patients and therapies underrepresented in these trials. In the meantime, the presumed superiority of the rhythm control approach should remain a presumption in groups that were not tested.

The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). Now that the rate control strategy has been elevated to the position of a primary treatment for AF, we need to know a lot more about it than we do at the present time. Research on the rate control strategy is currently sparse, to say the least. It is useful to dissect out some of the aspects of HR control in the management of AF before a discussion of the Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). Many understand effective HR control to be the prevention of excessive HRs. Some even understand that excessive HRs need to be assessed during rest and activity. However, fewer have acknowledged that good rate control also encompasses the absence of chronotropic incompetence and some effort at regularization of the HR. Finally, we need to identify patient groups that will benefit the most from the best HR control therapies that we can deliver. The AIRCRAFT (10) addresses this last question.

Few data exists about the first few issues in rate control. Some data exist about the appropriateness of a resting HR $<$80/min (19). To my knowledge, no data exists that objectively defines appropriate upper limits of HR during activity or data that objectively defines chronotropic incompetence for patients with AF. There are data that have

highlighted the importance of regularity of the heartbeat in patients with AF (20). Most physicians would probably acknowledge that with respect to all these aspects of "good" HR control, the ablate and pace approach currently represents our best attempt at HR control. The AIRCRAFT examines this approach in a particular subset of patients that has not previously been examined.

The AIRCRAFT enrolled patients with few symptoms and well-preserved ventricular function who were already judged to have adequate pharmacologic HR control (10). Co-primary end points were left ventricular function assessed by echocardiography and functional capacity on a graded treadmill test. Secondary end points included HR control itself and quality of life assessed by questionnaire. There were no differences between the effect of the two treatments on the ventricular systolic function and the duration of exercise during the treadmill tests. However, peak HRs and quality of life were better in the ablate and pace treatment group. There are some issues to be noted, however, with respect to these findings. The first is that a lot of patients assigned to the ablate and pace approach (15 of 49) did not receive that treatment, primarily because they were already doing well. If one considers that a major objective of treating AF is to relieve symptoms, it is not too surprising that patients who are already feeling quite well would ultimately not want to accept a relatively invasive therapy. Furthermore, one interpretation of the noted improvement in quality of life is that perhaps these patients did not feel as well as they thought, and they indeed felt better after the ablate and pace treatment. It is important to note, however, that the therapies could not be blinded for the two approaches used in the AIRCRAFT. Accordingly, an improvement in quality of life in the ablate and pace treatment arm must be viewed with skepticism.

The authors did not feel that the lack of blinding could explain their findings (10). However, a useful comparison is two recent trials of pacing for vasovagal syncope. In the first trial, patients were randomized to a pacemaker or no pacemaker (open-label) and the point estimate for the relative risk reduction of syncopal episodes was highly significant and >85% (21). However, when the same investigators repeated the study implanting a pacemaker in all subjects and randomizing whether or not pacing was "on" or "off" (blinded), the relative risk reduction was not significant and closer to 25% (unpublished data, presented as a Late Breaking Clinical Trial at NASPE 2002). Therefore, implanting a pacemaker can indeed have a powerful placebo effect. Finally, a lower peak HR with exercise is a surrogate end point and in itself is less meaningful (7).

With respect to their primary end point, the AIRCRAFT investigators recognized the importance of baseline left ventricular function and stratified on the basis of left ventricular ejection fraction <0.45 and ≥ 0.45. However, the range of left ventricular ejection fractions available for the analysis was limited. Observational studies had already suggested that ventricular function would only be improved with this treatment modality when ventricular systolic function was already substantially reduced at enrollment (16). Thus, it is not too surprising that no difference was noted between apparently good pharmacologic HR control and the ablate and pace approach in this population with well-preserved systolic function. Thus, in summary the AIRCRAFT is a negative trial, showing no benefit of the ablate and pace approach in this patient subgroup. The authors correctly conclude that the ablate and pace approach is not indicated for this purpose.

Summary. What is the simple lesson from these two quite different studies? It seems obvious that in the two situations explored in these two trials, the main finding is that for many patients "less is more." In the case of the STAF trial, the implication is that extensive effort to restore and maintain SR is not warranted for many elderly patients with persistent AF. In the case of the AIRCRAFT, the ablate and pace approach is not warranted for improvement of ventricular function unless ventricular function is already reduced, and it cannot improve symptoms when pharmacologic rate control is well tolerated and the patient is doing well with respect to symptoms.

Reprint requests and correspondence: Dr. D. George Wyse, Division of Cardiology, Department of Cardiac Sciences, University of Calgary and Calgary Health Region, Room G009, Health Sciences Center, 3350 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1. E-mail: dgwyse@ucalgary.ca.

REFERENCES

1. Falk RH. Atrial fibrillation. N Engl J Med 2001;344:1067–78.
2. Fuster V, Ryden LE, Asinger RW, et al. 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 for Developing Guidelines for the Management of Patients With Atrial Fibrillation). Circulation 2001;104:2118–50.
3. Nichol G, McAlister F, Pham B, et al. Meta-analysis of randomized controlled trials of the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation. Heart 2002;87:535–43.
4. Murgatroyd FD, Camm AJ. Maintenance of sinus rhythm in patients at risk of atrial fibrillation. In: DiMarco JP, Prystowsky EN, editors. Atrial Arrhythmias. State of the Art. Armonk, NY: Futura Publishing Company Inc., 1995:253–79.
5. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. Ann Intern Med 1999;131: 688–95.
6. Wyse DG. Selection of endpoints in atrial fibrillation studies. J Cardiovasc Electrophysiol 2002;13:S47–52.
7. Saksena S, Domanski M, Benjamin EJ, et al. Report of the NASPE/NHLBI Round Table Study Group on future research directions in atrial fibrillation. J Intervent Cardiac Electrophysiol 2001;5:345–64.
8. NHLBI Working Group on Atrial Fibrillation. Atrial fibrillation: current understandings and research imperatives. J Am Coll Cardiol 1993;22:1830–4.
9. Carlsson J, Miketic S, Windeler J, et al. 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;41:1690–6.
10. Weerasooriya R, Davis M, Powell A, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). J Am Coll Cardiol 2003;41:1697–702.

11. Hohnloser SH, Kuck H-H, Lilienthal J, for the PIAF Investigators. Rhythm or rate-control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomized trial. Lancet 2000;356:1789–94.
12. The AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347: 1825–33.
13. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834–40.
14. Pedersen OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy. Circulation 2002;104:292–6.
15. Brodsky MA, Chun JG, Podrid PJ, et al. Regional attitudes of generalists, specialists, and subspecialists about management of atrial fibrillation. Arch Intern Med 1996;156:2553–62.
16. Kay GN, Ellenbogen KA, Guidici M, et al. The ablate and pace trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker insertion for the treatment of atrial fibrillation. J Intervent Card Electrophysiol 1998;2:121–35.
17. Brignole M, Gianfranchi L, Menozzi C, et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. Circulation 1997;96:2617–24.
18. Haissaguerre M, Jais P, Shah DC, et al. Electrophysiological endpoint for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000;101:1409–17.
19. Rawles JM. What is meant by a "controlled" ventricular rate in atrial fibrillation? Br Heart J 1990;63:157–61.
20. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. Am J Cardiol 1996;78:1433–6.
21. Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent pacing for the prevention of vasovagal syncope. J Am Coll Cardiol 1999;33:16–20.