Atrial Fibrillation Therapies – Rate or Rhythm Control?

a report by
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Atrial fibrillation (AF) is a rhythm disturbance of the atria that results in irregular, chaotic, ventricular waveforms, varying from bradyarrhythmia to tachyarrhythmia. Essentially, all forms of AF therapy can be divided into two categories – restoration and maintenance of normal sinus rhythm, or control of the ventricular rate while permitting on-going fibrillation of the atria. Although pharmacologic therapies for rate control and rhythm control have been available for over four decades, only in the past few years have controlled trials, designed to guide the clinician in selecting a treatment strategy, been undertaken. Recently completed trials in conjunction with new mechanistic insights provide new guidance in the treatment of patients with AF.

Rate Control or Rhythm Control

There are three main goals to attain when treating a patient with AF, regardless of whether the rate control or rhythm control strategy is employed.

- alleviation of AF symptoms (palpitations, chest discomfort, fatigue or light-headedness, fainting or shortness of breath);
- prevention of thromboembolic complications; and
- control of the ventricular rate to prevent tachycardia-induced cardiomyopathy.

Waldo has suggested that 'rhythm control' would result in fewer symptoms, lower stroke risk, eventual discontinuation of anticoagulation (with its attendant bleeding risk), better exercise tolerance, better quality of life, and lower mortality.[1] However, more recent studies have meant that these concepts must be reappraised.

Treatment Strategy Clinical Trials

The Pharmacological Intervention in Atrial Fibrillation (PIAF) study randomly assigned 252 patients to rate control with diltiazem, or rhythm control with amiodarone, with the primary end-point of improvement in symptoms related to AF.[2] During an observation period of one year, the number of patients reporting improvement in AF-related symptoms in both groups was similar. Patients in the rhythm control group showed better exercise tolerance, walking approximately 50 meters further than their rate control counterparts in six minutes (p=0.008 by fourth follow-up visit). However, maintenance of this sinus rhythm required greater effort – 69% of patients in the rhythm control group were hospitalized at least once, compared with only 24% of patients in the rate control group. Most hospitalizations were for cardioversion (67%) or for amiodarone-related side-effects (27%). Despite this effort, only 56% of patients in the rhythm control arm were in sinus rhythm at the end of the one-year observation period.

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, 4,060 patients were randomized to a strategy of rate control or rhythm control with a primary end-point of overall mortality.[3] To be enrolled, patients were required to be over the age of 65, or to have at least another stroke risk factor, so that the mean age of participants was 69.9 ± 9 years. Only a minority of patients had a history of congestive heart failure (23%) or depressed ventricular function (<25%). The mainstay of rate control therapy was digoxin (used in 70.6% of patients at any time in the study), beta-blocker (68.1%), and diltiazem (46.1%). Rhythm control patients received amiodarone (62.8%), sotalol (41.4%), propafenone (14.5%), and, less commonly, a variety of other medications. As in the Pharmacological Intervention in Atrial Fibrillation (PIAF) study, sinus rhythm was difficult to maintain, with a prevalence of sinus rhythm of 62.5% at five years despite a relatively less 'resistant' population as suggested by the sinus rhythm prevalence of 34.6% in the rate control arm. Additionally, more patients crossed over from rhythm control to rate

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1. *Waldo A L, "Management of atrial fibrillation: the need for AFFIRMative action. AFFIRM investigators. Atrial Fibrillation Follow-up Investigation of Rhythm Management",* Am. J. Cardiol. *(1999), 84: pp. 698–700.*
2. *Hohnloser S H, Kuck K H and Lilienthal J, "Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial",* Lancet *(2000), p. 356.*
3. *AFFIRM Investigators, "A comparison of rate control and rhythm control in patients with atrial fibrillation",* N. Engl. J. Med. *(2002), 347: pp. 1,825–1,833.*

control than the reverse (37.5% versus 14.9%, p<0.001). Also, as in the PIAF study, patients treated with a strategy of rhythm control were more likely to be hospitalized during follow-up. After a mean follow-up of 3.5 years, there was a late developing trend toward more deaths in the rhythm control group than the rate control group, although statistical significance was not achieved (p=0.08). While analysis of death according to specific cause is on-going, ischemic strokes occurred most commonly in patients whose warfarin therapy had been stopped, or the international normalized ratio (INR) was subtherapeutic. The AFFIRM protocol permitted warfarin discontinuation after sinus rhythm had been maintained for four weeks, and the prevalence of warfarin use was greater in the rate control group (85% versus 70%).

The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study group enrolled 522 patients with persistent AF after a previous electrical cardioversion to a strategy of rate control or rhythm control.[4] Rate control was achieved using the same medications as in the AFFIRM trial. To maintain sinus rhythm, sequential trials of sotalol, flecanide, or propafenone, and amiodarone were employed, with cardioversion utilized following each medication change. Anticoagulation in the rhythm control consisted of warfarin (international normalized ratio (INR) 2.5 to 3.5) four weeks before and after cardioversion, after which anticoagulation could be stopped or replaced with aspirin (80mg to 100mg daily). The primary end-point was the composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for an implantable pacemaker, or severe medication side-effects. As with the AFFIRM trial, patients were older (mean age 68 years old) and were at risk of stroke (90% or more in each group had at least one stroke risk factor), and few patients had heart failure (97% New York Heart Association (NYHA) class I or II). As with the other studies, pharmacological maintenance of sinus rhythm was difficult. After a mean follow-up of 2.3 ± 0.6 years, only 39% of patients in the rhythm control arm were actually in sinus rhythm. The primary outcome occurred in 17.2% of the rate control group and 22.6% of the rhythm control group (p=NS). Thomboembolism was more frequent in the rhythm control group. Six patients in the rhythm control group had thromboembolism following cessation of warfarin, and five had sinus rhythm. Interestingly, a pacemaker was implanted in only three patients in the rate control arm (after AV nodal ablation), but in eight patients in the rhythm control arm (most commonly for sinus node dysfunction on medication unmasked following cardioversion). Like AFFIRM, this European trial confirmed the non-inferiority of rate control and raised the possibility of its superiority in an elderly population at risk for stroke.

Once the ventricular rate control was already established, the PAF2 investigators evaluated the role of maintenance of sinus rhythm with antiarrhythmic drug therapy.[5] After all patients had undergone successful atrioventricular junction ablation, 68 were then randomized to antiarrhythmic drug therapy (with amiodarone, propafenone, flecainide or sotalol) and 69 were randomized to no antiarrhythmic drug therapy. As in AFFIRM and RACE, the average age of patients was nearly 70, and few patients had left ventricular dysfunction. Fewer patients receiving antiarrhythmic drugs developed permanent AF (21% versus 37%, p=0.02). After 12 months, groups had similar quality-of-life scores and echocardiographic parameters, but more patients in the drug arm had episodes of heart failure and hospitalizations (p=0.05).

There are several important messages that emerge from the trials of rate control versus rhythm control, the main one being that, despite long-held prejudice to the contrary, pharmacologic rate control is not inferior to pharmacologic rhythm control. In fact, it may be preferable for the older AF patients with stroke risk factors, such as those enrolled in the comparative studies. No improvement in quality of life in any study with adoption of a strategy of rhythm control was recorded.[2–5] Second, despite the restoration of sinus rhythm with antiarrhythmic drugs, anticoagulation should be continued in patients with AF and one or more stroke risk factor. The attempted maintenance of sinus rhythm did not reduce the ischemic stroke rate in these patients in the AFFIRM or RACE studies. There are several explanations for this outcome. At the time of their event, the majority of stroke patients in both trials were not receiving, or had subtherapeutic levels of, anticoagulation – one must presume that, since their physicians had observed normal rhythm anticoagulation, it was not thought to be necessary. However, it is well documented that in patients who present with symptomatic arrhythmia often experience asymptomatic episodes of AF.[6] These episodes may not be perceived due to their brevity, or due to a slowed ventricular response

4. *Van Gelder I C, Hagens V E, Bosker H A, et al., "A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation",* N. Engl. J. Med. *(2002), 347: pp. 1,834–1,840.*
5. *Brignole M, Menozzi C, Gasparini M, et al., "An evaluation of the strategy of maintenance of sinus rhythm by antiarrhythmic drug therapy after ablation and pacing therapy in patients with paroxysmal atrial fibrillation",* Eur. Heart J. *(2002), 23: pp. 892–900.*
6. *Page R, Wilkinson W E, Clair W, McCarthy E A and Pritchett E L, "Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia",* Circulation *(1994), p. 89.*

consequent to medications. Furthermore, stroke mechanism is often difficult to confirm, and it is conceivable that, at least for some patients, the presence of AF serves as a marker for stroke risk as opposed to the mechanism of stroke. Thus, in predominantly older patients with stroke risk factors, it has become clear that anticoagulation should be continued, despite attempts at maintenance of sinus rhythm with medications.

It must be questioned whether there is still a role for rhythm control in the treatment of AF. However, there are clearly limitations with these strategy comparison trials that must be acknowledged. Firstly, none of the patients in the RACE study, and only one-third of the patients in AFFIRM presented with an initial episode of AF, and it is not known whether such patients should be subject to life-long anticoagulation and abandonment of sinus rhythm. A trial of cardiovesion in the absence of antiarrhythmic medications seems reasonable, and can be expected to result in the maintenance of sinus rhythm in a fourth of patients after one year follow-up.[7] However, for those patients with stroke risk factors with recurrence, the evidence is in – anticoagulation is warranted.

The group most frequently referred for pulmonary vein isolation therapy are 'younger' patients with symptomatic AF. However, few of this group were included in the comparative studies. The average age in the AFFIRM, RACE, and PAF2 studies was 69. The PIAF study found that exercise tolerance was improved with rhythm control and, interestingly, this was the only study to enroll 'younger' patients. Also, 'young' patients showed reduced mortality with rhythm control compared with rate control, in the AFFIRM study, although statistical significance was not achieved. While confirmation is absent, circumstantial observations suggest that patients with paroxysmal (as opposed to persistent or chronic) AF may have different arrhythmia mechanisms (a predominance of triggers, as opposed to abnormal substrate), and may be more susceptible to symptoms despite rate control.[8] Patients with paroxysmal AF are generally younger.

Lastly, these randomized trials compared rate with rhythm control strategies using only pharmacologic therapies. Thus, it is impossible to extend these results to non-pharmacologic therapies. Fewer than 5% of AFFIRM patients underwent atrioventricular junctional ablation, and even fewer underwent ablation of atrial flutter or pulmonary vein isolation ablation for AF. Typically, non-pharmacologic approaches do not burden the patient with long-term side-effects, and they do not rely on compliance with pill-taking. Moreover, the efficacy rates are substantially higher with non-pharmacologic than with drug treatments at least for atrial flutter. The lack of benefit seen with a rhythm control strategy may stem partly from the fact that with antiarrhythmic medications, rhythm control was, in fact, often not achieved – the prevalence of sinus rhythm was only 39% to 64% during follow-up in the pharmacologic trials.[2–5] Whether non-pharmacologic can surpass these limited efficacies over the long-term remains to be proven, but short-term success rates in selected AF patients are promising.[9–11]

Atrial flutter non-pharmacologic therapies are more established than those for AF. One small study that compared ablation with medication for rhythm control in atrial flutter found ablation superior. Natale *et al.*[12] randomized 61 patients with typical atrial flutter to first- line therapy with radiofrequency catheter ablation or to antiarrhythmic drugs. After a mean follow-up of 21 ± 11 months, 80% of patients ablated were in sinus rhythm, versus 36% of patients treated with drugs ($p<0.01$). Compared with the ablation group, patients treated with drugs were more likely to be hospitalized (63% versus 22%, $p<0.01$), required more cardioversions in follow-up (4.4 ± 1.7 versus 0.5 ± 1.2, $p<0.01$), and had more arrhythmia episodes (5.1 ± 2.0 versus 0.7 ± 1.4). Long-term follow-up is often absent despite the promise of non-pharmacologic therapies and the procedures are performed at specialized centers, currently limiting their wide-scale availability. Despite this, the on-going efforts to refine minimally invasive procedures to maintain sinus rhythm seem warranted.

7. *Singh S, Zoble RG, Yellen L, et al., "Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study",* Circulation *(2000), 102: pp. 2,385–2,390.*
8. *Oral H, Knight B P, Ozaydin M, et al., "Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: feasibility and mechanistic insights",* Circulation *(2002), 106: pp. 1,256–1,262*
9. *Haissaguerre M, Jais P, Shah D C, et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins",* N. Engl. J. Med. *(1998), 339: pp. 659–666.*
10. *Chen S A, Tai C T, Tsai C F, et al., "Radiofrequency catheter ablation of atrial fibrillation initiated by spontaneous ectopic beats ", [In Process Citation],* Curr. Cardiol. Rep. *(2000), 2: pp. 322-328.*
11. *Haissaguerre M, Shah D C, Jais P, et al., "Electrophysiological breakthroughs from the left atrium to the pulmonary veins", [In Process Citation],* Circulation *(2000), 102: pp. 2,463–2,465.*
12. *Natale A, Newby K H, Pisano E, et al., "Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter,"* J. Am. Coll. Cardiol. *(2000), p. 35.*

Finally, only a small number of patients in the randomized comparative studies of AF treatment strategies had heart failure. Patients with heart failure who develop AF are at an increased risk of death compared with those with normal rhythm.[13] The Veterans Affairs Congestive Heart Failure Trial of Antiarrhythmic Therapy (CHF-Stat) enrolled patients with dilated cardiomyopathy and Class II to Class IV heart failure. Patients receiving amiodarone who converted to sinus rhythm had a lower mortality than those who did not.[14] Similarly, in a post hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD), Dries *et al*. found increased mortality in patients with AF at baseline compared with those with sinus rhythm, with excess mortality due to pump failure.[15] This clinical observation is supported by acute hemodynamic studies in patients at the time of atrioventricular node (AVN) ablation demonstrating significant deterioration in cardiac output in association with irregular ventricular contraction, compared with regular ventricular contraction at the same average heart-rate.[16] Discovery of whether heart failure patients derive benefit from pharmacologic rhythm control, warrants on-going study.

Conclusions

It had long been agreed that a rhythm control strategy of AF treatment would result in fewer symptoms, lower stroke risk, eventual discontinuation of anticoagulation (with its attendant bleeding risk), better exercise tolerance, better quality of life, and lower mortality.[17] However, following the completion of randomized studies, it is now clear that for most patients with AF, a strategy of rate control is at least as effective as rhythm control. Uncertainty still remains over the optimal approach for younger patients, and for patients with heart failure, the undertaking of on-going studies will better clarify management strategies for these subgroups. Furthermore, it is essential to develop novel therapies, and in particular, non-pharmacologic therapies to advance and change in the management of this ancient arrhythmia.

13. *Pedersen O D, Bagger H, Keller N, Marchant B, Kober L and Torp-Pedersen C, "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 *(2001), 104: pp. 292–296.*
14. *Deedwania P C, Singh B N, Ellenbogen K, Fisher S, Fletcher R and Singh S N, "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)", The Department of Veterans Affairs CHF-STAT Investigators,* Circulation *(1998), 98: pp. 2,574–2,579.*
15. *Dries D L, Exner D V, Gersh B J, Domanski M J, Waclawiw M A and Stevenson L W. "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, Studies of Left Ventricular Dysfunction,"* J. Am. Coll. Cardiol. *(1998), 32: pp. 695–703.*
16. *Daoud EG, Weiss R, Bahu M, et al., "Effect of an irregular ventricular rhythm on cardiac output",* Am. J. Cardiol. *(1996), 78: pp. 1,433–1,436.*
17. *Waldo A L, "Management of atrial fibrillation: the need for AFFIRMative action. AFFIRM investigators. Atrial Fibrillation Follow-up Investigation of Rhythm Management",* Am. J. Cardiol. *(1999), 84: pp. 698–700.*