

## Treatment of Atrial Fibrillation: Evidence Favoring Rate Control

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### Summary

*Atrial fibrillation is the most common tachyarrhythmia affecting millions of patients. Large-scale clinical trials have been conducted on the antithrombotic treatment in patients with atrial fibrillation, but the questions related to strategies of therapy are unanswered. Now large, randomised clinical trials are addressing the "rate versus rhythm" issue. The ongoing trials (AFFIRM, PIAF, STAF) will provide information about the benefit of attempting to maintain the sinus rhythm, or to control the heart rate. Beside the fundamental question these trials are focusing on the costs, adverse effects, efficacy of the two strategies. The only study which has been published so far is the PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) trial. In this trial there was no difference in symptoms between the rate vs. rhythm control group, but the rate control therapy was associated with significant cost-savings. The largest prospective trial, the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) is ongoing. 4060 patients are enrolled. The primary objective is to compare survival between the rate control and rhythm control groups. A pilot trial of the STAF study showed no difference in the treatment strategies. The results of ongoing trials will give us evidence, whether rhythm control or rate control is the superior treatment for AF.*

### Key Words

Atrial fibrillation, antiarrhythmic drug therapy, pacemaker therapy, rate control, rhythm control

### Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia in clinical practice. The incidence of the disease is increasing with age, affecting 5 % of the population older than 65 years. According to the Framingham Study, over the last four decades there has been a permanent increase in the prevalence of AF. By itself, AF is not a lethal condition, but there are multiple, clinical consequences resulting in a decrease in life expectancy. The mortality of patients with AF is twofold that of people without it. Atrial fibrillation is associated with significant morbidity and an increased cost to the health care system [1-2].

The goals in the management of AF are rate control, rhythm control, and stroke prevention. Controlled trials have demonstrated the beneficial effect of anticoagulation with warfarin, which reduces the risk of systemic embolization by 44 – 88 %. The details of anti-coagulant therapy are beyond the scope of this review.

In contrast to anticoagulation therapy, there is no general agreement on which strategy, rate control or rhythm control, is more effective in reducing mortality, disabling consequences, and the cost of therapy, while improving the quality of life.

### Rhythm Control

Rhythm control restores and maintains sinus rhythm in paroxysmal and persistent AF. In permanent AF, the only therapeutic modality is rate control. In about 50 % of patients with recent onset of AF (within 24 – 48 hours), spontaneous cardioversion has been observed. The success rate in restoration of sinus rhythm with external cardioversion ranges from 65 % to 90 %, and with internal cardioversion it is even higher. Pharmacological therapy is also effective in the restoration of sinus rhythm, especially within the first

Advantages	Disadvantages
Improvement of hemodynamics	Ventricular proarrhythmia (increased mortality?)
No electrical/anatomical remodelling	Drug toxicity (amiodarone)
Better exercise capacity	Repeated cardioversion
Decreased symptoms	More hospitalisation
Reduced thrombo-embolic events (?)	Costs
Prevention of tachycardiomyopathy	Medication two or three times a day (except amiodarone)

Table 1. Advantages and disadvantages of rhythm control strategy.

48 hours. In 70 – 80 % of patients with recent onset of AF, oral propafenone or flecainide has proven useful in terminating the condition. At the end of one year, recurrence of AF after successful cardioversion is likely (44 – 85 %), without prophylactic antiarrhythmic therapy. The recurrence rates with treatment are lower, but are still too high. Class IA, IC, and III (amiodarone, sotalol) agents can be used to prevent recurrences of AF. At one year, the relapse rates with different antiarrhythmic agents are about 50 %, and no one drug – except amiodarone – seems to be superior to the others. Low doses of amiodarone proved to be effective (with a relapse rate of 35 % at 16 months) and well-tolerated [3]. Table 1 summarizes the advantages and disadvantages of rhythm control.

### Rate Control

The only therapeutic option in patients with permanent AF is to control the heart rate using either drugs or a non-pharmacological treatment. In other forms of AF (paroxysmal, persistent), sinus rhythm cannot be maintained in the long run despite repeated cardioversions and antiarrhythmic trials. By using a very aggressive approach, sinus rhythm can be maintained over a two-year period in about 60 % of patients [4]. It is a difficult decision when to restore the sinus rhythm and when to simply control the ventricular rate. Since data from controlled prospective clinical trials is lacking, the decisions, until now, have been based on clinical experience. Rate control is preferred in patients with AF of long duration (> 1 year), with a markedly dilated left atrium, severe CHF, drug refrac-

toriness or intolerance of class I or III antiarrhythmic agents, and the risk of proarrhythmia. Rate control may also be preferred in patients who are asymptomatic, lead a sedentary life, and are older.

Ventricular rate control during AF is poorly defined. Rate control is believed to be adequate when the resting heart rate ranges between 60 and 80 beats/min, and between 90 and 115 beats/min during moderate exercise, or is < 85 % of the maximal predicted heart rate at 4 MET exercise [1]. It is a useful method to control the heart rate trends on Holter recordings; the recommended average daily rate is < 80 beats/min, and the recommended average hourly rate is < 100 beats/min. To control heart rate, drugs that depress the atrioventricular conduction are needed. Commonly used drugs for rate control include digoxin, beta-receptor blockers, and non-dihydropyridine calcium antagonists. The effect of digoxin on acute rate control is not impressive; it requires a long time (9.5 hours) to become efficacious. Other drugs such as intravenous verapamil, diltiazem, metoprolol, or esmolol are suggested. Except for diltiazem, these drugs have a negative inotropic effect. For long-term rate control, digoxin is generally considered to be effective, especially when CHF is present. Digoxin does not control the heart rate during exercise. Ca-antagonists or beta-blockers alone or in combination with digoxin are recommended to control the excessive heart rate during exercise. Ca-antagonists are preferred in patients with chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, and peripheral arterial diseases. Exercise duration increases with the use of verapamil or diltiazem. Chronic beta-blockers are also effective in prevention of exercise-induced tachycardia; they improve exercise duration and make patients less symptomatic. In one study that investigated the effect of digoxin, atenolol, diltiazem, digoxin and diltiazem, and digoxin and atenolol, the best rate control was achieved with the combination of digoxin and atenolol [5]. Amiodarone markedly depresses the atrioventricular conduction, but it should not be used as a first-line agent because of its side effects. Use of the above-mentioned drugs are contraindicated in the treatment of AF in patients with WPW syndrome, since they improve the antegrade conduction via the accessory pathway. Intravenous Class I or class III agents can be used in hemodynamically stable patients. Table 2 summarizes the advantages and disadvantages of rate control.

Advantages	Disadvantages
Reduction of symptoms	Impaired hemodynamics
No risk of proarrhythmia	Long-term anticoagulation
Reduction of tachycardiomyopathy	
Low cost	
Fewer compliance problems	

Table 2. Advantages and disadvantages of rate control strategy.

### Pacing for Rate Control

Radiofrequency (RF) catheter ablation of the AV junction is suggested in patients with AF who are refractory to medical treatment or who cannot tolerate drug treatment. It is estimated that 12 % of patients with AF are refractory to medical therapy [6]. The advantages of RF include effective control of symptoms (especially palpitation), prevention of rate-induced cardiomyopathy, elimination of antiarrhythmic drugs, and better hemodynamics. An additional benefit of this method is a decrease in the number of hospitalizations [1,6]. The rate control achieved by this method is undoubtedly superior to that of medical treatment. The type of pacemaker selected prior to or following ablation is an important issue; in permanent AF, a rate-responsive, ventricular (VVIR) pacemaker is used, while in paroxysmal AF, a dual-chamber pacemaker (with mode switch) is recommended. Rapid heart rate can cause

cardiomyopathy and heart failure, but the ventricular irregularity may have a deleterious effect, which contributes to the development of myocardial damage. AV junctional ablation and pacing seem to be more effective than adequate rate control using pharmacological therapy [7]. There has been some concern about a very slight excess in mortality that is attributable to ablation and pacing therapy. Basic programming of a high pacing rate (80 – 90 beats/min) after ablation for at least 2 months seems to eliminate this complication [8]. To date, there is no evidence whether or not this technique has a beneficial effect on survival.

### Comparison Trials

In the last two decades, we have learned a lot about AF. Large-scale clinical trials assessed the thrombo-embolic prophylaxis in AF. Important studies examined the pathophysiology, genetics, prevention, and epidemiology of AF. Essential questions related to strategies for AF therapy still need to be answered. Five trials have performed comparison of rate control and maintenance in sinus rhythm. Table 3 shows the main features of the two treatment strategies.

It is hoped that a large-scale, prospective, randomized trial, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, will determine whether rate control or rhythm control is a superior treatment in reducing mortality, stroke, and cost of therapy, while improving the quality of life [9,10]. The primary objective of the AFFIRM trial is to compare survival rates between the rate control and rhythm control groups. Secondary objectives include comparing total mortality, rate of stroke, major hemorrhage, embolism and bleeding, ejection fraction, functional capacity, cost, and quality of life. A total of 4060 patients with AF and at least one risk factor were randomized. This is the largest cohort of AF ever collected, and the follow-up will continue through October, 2001.

So far, the only published data is from the Pharmacological Intervention in Atrial Fibrillation Trial (PIAF) study [11]. This trial randomized 252 patients into either the rate control (with diltiazem) or rhythm control (with amiodarone) groups. The observation period was one year. There were no differences in symptoms between patients in the two groups. Exercise tolerance was better in the rhythm control group, although hospital admission was more frequent. Sixty

	Rhythm control	Rate control
Hemodynamics	better	impaired
Risk of proarrhythmia	high	no
Drug toxicity	common	rare
Exercise tolerance	better	limited
Hospitalisation	frequent	infrequent
Cost of therapy	higher	lower
Quality of life	no difference	no difference
Survival	no data	no data
Thromboembolic complications	reduced?	higher?
Rate-induced cardiomyopathy	no	no
Compliance	worse	better

Table 3. Comparison of rhythm vs. rate control therapy.

percent of the amiodarone group remained in sinus rhythm at the end of one year.

The STAF study is a prospective, randomized, multi-center study involving 11 centers in Germany. Primary endpoints are mortality, complications, and quality of life. The estimated sample size is 2000 patients. A pilot trial (200 patients) was performed with a minimum follow-up of one year. The maintenance of sinus rhythm was low; it was 23 % after 3 years with up to 4 cardioversions and up to 4 antiarrhythmic drug therapies. The only difference between the two groups was that patients in the rhythm control group were hospitalized more frequently and their hospital stay was longer. There were no differences in the primary endpoints between the two groups, not because AF and sinus rhythm are equal, but because sinus rhythm could not be maintained for a sufficient time period [12].

The results of the ongoing RACE and CRRRAFT trials have not yet been released.

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