REVIEW

Implication from Randomized Trials of Rate and Rhythm Controls on Management of Patients with Persistent Atrial Fibrillation

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Recently, several randomized trials were published on the issue of rate or rhythm control for patients with atrial fibrillation (AF). Patients were typically minor symptomatic, relatively old, with age above 70, presenting with a recurrence of AF and suffering from only mild to moderate underlying heart disease. The main outcome of these trials is that rate control is not inferior to rhythm control for the management of patients with AF concerning morbidity and mortality. Also patients' quality of life did not differ significantly in follow-up in these trials. However, rhythm control is not redundant in the treatment of AF. Focus is now on subgroups of patients who could still have benefit being in sinus rhythm. For severely symptomatic patients, patients presenting with the first episode of AF and probably those with severe congestive heart failure, to restore and maintain sinus rhythm should still be the goal. With the failure of antiarrhythmic therapy, nonpharmacological approaches such as pulmonary vein isolation can be performed.

Another finding of the randomized trials is that being in sinus rhythm does not prevent from the occurrence of thromboembolic complications. This means that for patients with AF, with risk factors for thromboembolic events, adequate anticoagulant therapy is indicated irrespective of the current heart rhythm. As with antiarrhythmic therapy, the search for new and safer anticoagulant therapy is underway.

This review will focus on the key aspects we have learned from the randomized trials on rate and rhythm controls for patients with AF.

A.N.E. 2006;11(2):170-186

atrial fibrillation; rate control; rhythm control; oral anticoagulation

Atrial fibrillation (AF) is the most common sustained arrhythmia.¹ It is estimated that around 0.5–1% of the total population suffers from AF. The prevalence of AF rises with increasing age, with approximately 6% affected in those older than 65 years, reaching 10% in individuals above 80 years.^{2,3} With an expanding elderly population in the near future, the incidence and prevalence of AF will increase. Currently, 2.2 million people have AF in the United States, which is expected to increase to nearly 5.6 million in the year 2050.⁴

A wide range of cardiovascular and noncardiovascular diseases have been shown to increase the risk of developing AF or were identified as predisposing factors. The most frequently observed underlying condition is hypertension. Data from the Framingham Study and other studies indicate that hypertension is present in nearly 50% of the subjects who develop AF.^{4–7} Also heart failure predisposes to AF. With more advanced heart failure, as assessed by the New York Heart Association (NYHA) class, the prevalence of AF increases.⁸

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Drs. Van Gelder and Crijns received lecture fees from 3M Pharma. Dr. Crijns is a consultant to Sanofi-Synthelabo, Aventis, and AstraZeneca.

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The prevalence of AF in NYHA class I patients with heart failure is lower than 10%.⁹ In subjects in NYHA class IV, the prevalence of AF is nearly 50%.¹⁰

When a patient with persistent AF is presented, there are basically two treatment options: to restore sinus rhythm (i.e., rhythm control) or to accept the arrhythmia by controlling the ventricular heart rate with negative chronotropic medication (i.e., rate control) and preventing thromboembolic complications with oral anticoagulation. Until recently, the rhythm control approach using electrical cardioversion and antiarrhythmic drugs was the treatment of choice for patients with AF. Restoration of sinus rhythm by cardioversion is highly effective, with success rates in over 90% of the procedures.^{11,12} The problem, however, is to maintain sinus rhythm. After successful cardioversion, only around 40% will remain free of AF after 1 year.¹² With longer follow-up, this percentage is declining further.

To prevent recurrence of AF, antiarrhythmic drugs generally are instituted. Drugs of all four Vaughan-Williams classes have been evaluated for its efficacy of maintaining sinus rhythm after successful cardioversion. Class I, II, and III drugs, except for amiodarone, are about equally effective.^{13–15} Amiodarone was found to be most effective in maintaining sinus rhythm.^{15–19} Despite amiodarone, recurrences frequently occur. In addition, class I and III antiarrhythmic drugs may have significant adverse effects such as the risk of life-threatening proarrhythmia and negative inotropic effects.^{20–23}

The alternative approach of AF is to accept the arrhythmia and to control the ventricular rate in order to reduce symptoms and prevent a tachycardia-induced cardiomyopathy.^{24–26}

Recently, several studies were conducted to evaluate whether rate control could be an alternative to rhythm control for preventing morbidity and mortality in patients with persistent AF.^{27–31} The generally accepted pros and cons of both strategies were taken into account in the design of these studies (Table 1).

This review will describe the results and the implication of the randomized trials concerning rate or rhythm control in AF. A brief summary of these trials is shown in Table 2.

RANDOMIZED TRIALS OF RATE AND RHYTHM CONTROLS IN AF

AF Follow-Up Investigation of Rhythm Management (AFFIRM)

The North American AFFIRM study is the largest randomized trial of rate versus rhythm control. AFFIRM included a high-risk cohort for stroke or death (Table 3).^{28,32} Patients were at least 65 years old or had one or more risk factors for stroke or death including hypertension, diabetes mellitus, congestive heart failure, prior transient ischemic attack, and left ventricular dysfunction. The presence of AF was defined as an episode of AF lasting at least 6 hours over the previous 6 months. Excluded were those with AF of more than 6 months duration. Therefore, of the 4060 patients, many

Table 1. Presumed Pros and Cons of Rate and Rhythm Control Strategies

	Rate Control	Rhythm Control
Pros	Easy approach Lower costs of treatment	Short-term use of anticoagulants Less AF-related complaints in sinus rhythm Improvement of left ventricular function and functional capacity
Cons	Risk of excessive ventricular heart rate (heart failure and symptoms) Risks of permanent anticoagulation (bleeding) Persistence of an irregular heart beat (heart failure and symptoms)	High recurrence rate of AF Adverse effects of antiarrhythmic drugs Demanding approach for doctor and patient, time-consuming No proved benefit in terms of morbidity and mortality Continuing symptoms despite sinus rhythm due to sick sinus syndrome with syncope or presyncope, and iatrogenic pacemaker implantations, AV block and palpitations due to frequent atrial premature beats

Table 2. Summary of Randomized Studies of Rate and Rhythm Control Strategies in Atrial Fibrillation

Study (n)	Study Characteristic	Follow-Up (years)	Treatment Protocol, Rate vs Rhythm	Patients in SR, ^a Rate vs Rhythm	Primary Endpoint, Incidence in Rate vs Rhythm Control
AFFIRM (4060)	Paroxysmal and persistent AF High risk for stroke and death	3.5 (mean)	Rate: BBL, CCB, digoxin; alone or in combination Rhythm: AAD and ECV, if necessary	35% vs 63%	All-cause mortality, 25.9% vs 26.7% (P = 0.08)
RACE (522)	Persistent AF 1 or 2 previous ECVs	2.3 (mean)	Rate: BBL, CCB, digoxin; alone or in combination Rhythm: serial ECV and AAD	10% vs 39%	Composite (cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker implantation, severe adverse effects of drugs), 17.2% vs 22.6%
PIAF (252)	Persistent AF Symptoms of AF	1	Rate: primarily diltiazem Rhythm: amiodarone and, if necessary, ECV	10% vs 56%	Patients with improvement of AF-related symptoms, 61% vs 55% (P = 0.317)
STAF (200)	Persistent AF Moderate to high risk of recurrent arrhythmia	1.6	Rate: BBL, CCB, digoxin; alone or in combination Rhythm: serial ECV and AAD	9% vs 38%	Composite (all-cause mortality, cerebrovascular events, thromboembolism, and cardiopulmonary resuscitation), 5% vs 4.5% (P = 0.99)
HOT-CAFE (205)	Persistent AF Age: 50–75 years	1.7 (mean)	Rate: BBL, CCB, digoxin; alone or in combination Rhythm: serial ECV and AAD	No data vs 64%	Composite endpoint (all-cause mortality, number of thromboembolic, and major bleeding complications) 5.9% vs 5.8% (p=NS)

^aSinus rhythm at the end of follow-up.

AAD = antiarrhythmic drug; AF = atrial fibrillation; BBL = beta-blocker; CCB = calcium-channel blocker; ECV = electrical cardioversion.

suffered from paroxysmal AF. Rate control tended to be more effective in preventing all-cause mortality than rhythm control.

Causes of death were divided into cardiac, vascular, and noncardiovascular.³⁵ In the rate and rhythm control groups, 130 and 129 patients died of a cardiac cause, respectively. More patients in the rhythm control group died of a noncardiovascular cause. So, after adjusting for other significant covariates, the risk of noncardiovascular death was increased 1.5-fold if the assignment in AFFIRM was to rhythm control. This observation is intriguing. This difference was a result of significant differences in the number of patients who died of a pulmonary cause (23 vs 39, for rate and rhythm controls, $P = 0.04$) or cancer (52 vs 81, for rate and rhythm controls, $P = 0.01$). The authors suppose that there might be a role for amiodarone in this case. Two large amiodarone trials also showed increased noncardiac mortality rate, including cancer and pulmonary death, among those assigned to amiodarone.^{47,48} However, in other studies, this association was not observed.^{49,50} Also the role of warfarin, which was less often used under rhythm control, may be interesting. Warfarin was shown to have a beneficial antineoplastic effect, particularly on the extent of metastatic spread of cancer.⁵¹ So, warfarin may have increased cancer-related outcome in particular in the rate control arm. Still these findings are remarkable and careful evaluation of noncardiovascular deaths remains important.

Sinus rhythm at study end was present in 65% of the patients assigned to rhythm control. Also in the rate control strategy, 35% were in sinus rhythm at the end of follow-up. These rates of sinus rhythm are higher than in other randomized trials. However, around 25% of the patients converted back to sinus rhythm before randomization after their qualifying episode of AF.⁵²

As expected, amiodarone was most effective in maintaining sinus rhythm.⁴⁰ Beta-blockers were most effective in achieving target heart rates under rate control.³⁷

Rate Control or Electrical Cardioversion for Persistent AF (RACE)

In the Rate Control versus Electrical cardioversion for persistent AF (RACE) study, the rate and rhythm controls were compared (Table 4).²⁹ The 522 patients included in RACE represented a typical population with persistent AF.⁶ Mean age was

69 years, and most patients had an underlying disease of which hypertension (49%) and coronary artery disease (27%) were most common. The composite primary endpoint occurred more frequently under rhythm control indicating that rate control is not inferior to rhythm control. A lower mortality rate was observed compared to AFFIRM as in AFFIRM patients with a high risk for stroke and death were included. At the end of the study and after a median of two electrical cardioversions, 39% ($n = 103$) of the patients in the rhythm control group were in sinus rhythm.

Post hoc analysis revealed that hypertension and female sex were associated with more endpoints in the rhythm control group. Especially thromboembolic complications and side effects of antiarrhythmic drugs occurred more frequently.^{29,56} Therefore, for females and patients with hypertension, rate control seems an attractive treatment option.

For patients with NYHA class II–III for heart failure, event rate was comparable between rate and rhythm controls.⁵⁹ However, more severe endpoints occurred under rate control. The number of events in patients with lone AF, i.e., AF without demonstrable underlying heart disease, was low.⁵⁵

Pharmacological Intervention in AF (PIAF)

The German PIAF study was the first randomized comparison of rate and rhythm controls in patients with AF.²⁷ Included were patients with symptomatic persistent AF, with palpitations and dyspnea as the leading symptoms. Over the entire observation period, symptoms improved equally for both the rate and the rhythm control strategy. However, exercise tolerance turned out to be better with rhythm control.

Strategies of Treatment of AF (STAF)

The second German AF trial, STAF, included 200 patients (100 per strategy) with a moderate to high risk of AF recurrence. A total of 56% of the patients were in NYHA class II or III for heart failure. The composite primary endpoint occurred in 10 and 9 patients assigned to rate control and rhythm control, respectively. Comparable to other randomized trials, rhythm control resulted in significantly more hospitalizations: 54 for the rhythm control group compared to 26 for the rate control group.

Table 3. Overview of the Published AFFIRM Substudies

Issue	Main Outcome	Implication
Secondary endpoints Quality of life ³³	Quality of life scores were similar in the rate and rhythm control groups at all time points in follow-up. Also no differences stratified to the actual heart rhythm, AF, or sinus rhythm	In order to improve quality of life in AF, restoring sinus rhythm seems not necessary.
Cost-effectiveness ³⁴	After a mean of 3.5 years of follow-up, rate control costs were \$5.077 less per person than rhythm control.	Rate control is a cost-effective approach.
Survival and mortality		
Modes of death under rate control (310 of 2027) and rhythm control (356 of 2033) ³⁵	Arrhythmic: 79 (4%) vs 77 (4%), $P = 0.88$	Cardiovascular mortality is comparable for both arms.
	Nonarrhythmic: 43 (2%) vs 46 (2%), $P = 0.75$	
	Stroke/cerebral hemorrhage: 17/11 (1%) vs 15/13 (1%), $P = 0.99$	Noncardiovascular death needs to be evaluated.
	Noncardiovascular: 113 (6%) vs 169 (8%), $P = 0.0008$	
Relation of rhythm, drugs, and survival ³⁶	Sinus rhythm is associated with decreased risk of death, $P < 0.0001$	Current antiarrhythmic drugs are neither highly efficacious nor completely safe.
	Rhythm control drugs increased, whereas warfarin decreased mortality rate, $P < 0.0001$. In general, survival was predominantly determined by the presence of underlying heart disease.	
Feasibility of rate control treatment		
Effectiveness of rate control (at rest ≤ 80 bpm and moderate increase on exercise) ³⁷	Beta-blockers were most effective: 70% achieve effective rate control on beta-blockade (with or without digoxin). 37% required a change in or the addition of another in rate-controlling drug; most changes to beta-blockers.	Rate control is not as easy as previously assumed. Beta-blockers are most effective.
Relation between heart rate under rate control and survival ³⁸	Rigid rate control did not improve event-free survival ($P = 0.81$), overall survival ($P = 0.13$), and quality of life for patients with AF.	Lenient rate control may not be inferior to a rigid approach.
Benefit of subgroups from rate or rhythm control ³⁹	Survival of patients was worse for those older than 65 years of age and with underlying disease, including left ventricular dysfunction. Patients > 65 years of age and those without heart failure seemed to have benefited from rate control above rhythm control ($P < 0.01$).	It is important to identify subgroups of patients with AF who will specifically benefit from rate or rhythm control.

Table 3. Overview of the Published AFFIRM Substudies (continued)

Issue	Main Outcome	Implication
Feasibility of rhythm control treatment	Amiodarone was superior to class I drugs ($P = 0.011$) and sotalol ($P < 0.001$) in maintaining sinus rhythm. Class I drugs and sotalol were equally effective ($P = 0.867$).	Amiodarone is most effective in maintaining sinus rhythm.
Effectiveness of antiarrhythmic drugs for rhythm control ⁴⁰	At 5 years of follow-up, in 85% of the patients in the rate control group and 62% of the patients in the rhythm control group ($P < 0.001$), the original treatment strategy was maintained. Long standing AF and previous failure of antiarrhythmics was associated with abandonment of the rhythm control approach.	Patients with a long duration of AF at presentation or previous failure of antiarrhythmic drugs, rate control seems preferable.
Abandonment of rhythm and rate control strategies ⁴¹	Patients in the highest quartile of initial resting ventricular rate while in AF (range 132–300 beats per minute) were more likely to achieve and maintain sinus rhythm compared to those in the lowest quartile (range 37–81 beats per minute) ($P < 0.0002$).	In patients with an initial higher resting ventricular rate, rhythm control should be considered.
Relation between resting ventricular heart rate in AF and efficacy of rhythm control ⁴²	A total of 2033 patients received 3030 exposures to antiarrhythmic drugs, with 96 arrhythmic events in 6 years of follow-up. A total of 12 torsade de pointes were recorded.	Strict criteria for the safe use of antiarrhythmic drugs were successful in minimizing proarrhythmic events.
Proarrhythmic events ⁴³	A total of 15% of AFFIRM patients suffered from pulmonary disease at inclusion. Amiodarone had no effect on pulmonary death rates in these subjects ($P = 0.43$).	Use of amiodarone in patients with AF and preexisting pulmonary disease is acceptable.
Amiodarone and pulmonary disease ⁴⁴	The annual incidence of major bleeding was 2%. Besides warfarin or aspirin use, this was associated with older age, heart failure, renal and hepatic disease, and diabetes.	In patients at low or moderate risk for thromboembolic events, bleeding risk factors should be considered once anticoagulant therapy is initiated.
Miscellaneous	At inclusion, 12% of the patients had asymptomatic AF. These patients had less severe heart disease but more frequently a history of cerebrovascular accidents. During follow-up, mortality was comparable to patients with symptomatic AF.	Asymptomatic AF is not a marker of more favorable prognosis.
Bleeding risk during anticoagulant therapy ⁴⁵		
Asymptomatic AF ⁴⁶		

Table 4. Overview of the Published RACE Substudies

Issue	Main Outcome	Implication
Secondary endpoints Quality of life ⁵³	Quality of life largely unchanged in follow-up for both rate and rhythm controls. Complaints of AF, short duration of AF, and presence of sinus rhythm, but not randomized strategy, were associated with improvement of quality of life.	Treatment strategy does not affect quality of life. Those with complaints of AF may benefit from sinus rhythm.
Cost-effectiveness ⁵⁴	Mean costs per patient under rate control were € 7386 and € 8284 under rhythm control due to higher costs for electrical cardioversions, hospital admissions, and antiarrhythmic medication. Costs were higher in older patients, patients with underlying heart disease, those who reached a primary endpoint, and women.	Rate control is cost-effective for the treatment of AF.
Rate and rhythm control in subgroups Patients with mild to moderate heart failure ³³	The primary endpoint occurred in 29/130 (22.3%) under rate control and in 32/131 (24.4%) under rhythm control. More cardiovascular deaths, hospitalization for heart failure, and bleeding occurred under rate control. Thromboembolic complications, drug side effects, and pacemaker implantation were more frequent under rhythm control.	In patients with mild to moderate heart failure, rate control seems not inferior to rhythm control.
Patients with lone AF ⁵⁵	The primary endpoint occurred in 9 (10%) patients with lone AF, 7 under rate control, and 2 under rhythm control, and in 95 (22%) patients with underlying heart disease. Quality of life is higher in patients with lone AF.	Patients with lone AF have a better outcome than those with underlying heart disease. Lone AF seems a benign disease.
Influence of female gender ⁵⁶	Females randomized to rhythm control developed more endpoints (adjusted hazard ratio was 3.1 [1.5–6.3], $P = 0.002$), mainly heart failure, thromboembolic complications, and adverse effects of antiarrhythmic drugs.	Rate control seems preferable in females with persistent AF.
Patients with hypertension ⁵⁷	In patients with hypertension, more endpoints occurred under rhythm control (45 of 146, 31%) than under rate control (19 of 110, 17%). Especially thromboembolic complications and adverse effects of antiarrhythmic drugs were more frequently observed.	Rhythm control in hypertensives enhances cardiovascular morbidity and mortality. Rate control seems preferable in these patients.
Data on echocardiography Ventricular and atrial remodeling ⁵⁸	Fractional shortening significantly improved under rhythm control after 2 years of follow-up. In the rate control group, left and right atrial size increased. Sinus rhythm at study end was associated with improvement of fractional shortening.	Rate control prevents impairment of left ventricular function. Sinus rhythm leads to improvement of cardiac function and smaller atria.

How To Treat Chronic AF (HOT CAFE)?

In the Polish HOT CAFE study, patients with AF lasting from 7 days to 2 years were included.³¹ Treatment protocols were comparable to RACE and STAF. The primary endpoint, a composite of all-cause mortality, and number of thromboembolic and major bleeding complications, occurred evenly in both groups. As in PIAF, exercise tolerance improved with rhythm control. Hospital admissions were more frequent for rhythm control, mainly due to electrical cardioversions.

INFLUENCE OF RATE AND RHYTHM CONTROLS ON QUALITY OF LIFE, COSTS OF THERAPY, AND CARDIAC PERFORMANCE

Although morbidity and mortality are the frequently used endpoints in randomized trials on AF therapy, assessment of quality of life (QoL), general well-being, and costs of treatment are important indicators of treatment effectiveness and feasibility.⁶⁰ In RACE, AFFIRM, and PIAF, these aspects of AF treatment were also taken into account and are discussed below.

Quality of Life

The first randomized comparison of QoL in patients treated with rate or rhythm control was performed by the PIAF investigators.^{27,61} In fact, improvement of symptoms was their primary endpoint. After 1 year of follow-up, symptom improvement was comparable for both the rate and the rhythm control strategies. Of note, around 60% of the patients reported an improvement of symptoms in PIAF. This high success rate of treatment may be related to the fact that all 252 patients had symptomatic AF at inclusion and that any intervention, slowing the heart rate or restoring normal rhythm, is likely to improve the well-being.

An important RACE predetermined secondary endpoint was the evaluation of QoL.⁵³ In 352 analyzed patients, QoL did not significantly differ between those treated according to the rate control strategy and those treated under rhythm control. Complaints of AF were present in 72% of the patients at inclusion, with fatigue (56%) and dyspnea (50%) most frequently observed. Remarkably, only 37% complained of palpitations, a typical arrhythmia-related symptom. The first year after inclusion, the QoL increased significantly for both

groups, probably due to adjustments of rate control treatment and restoration of sinus rhythm for the rhythm control group. However, at the end of the study, QoL was largely comparable to baseline levels. So, in the moderately symptomatic RACE patient, QoL may improve shortly after influencing heart rate and heart rhythm, but this effect vanishes with long-term follow-up. Subanalysis revealed that QoL improvement could be expected for those with complaints of AF at inclusion and in sinus rhythm at study end. Unfortunately, the number of patients for whom QoL improved significantly was small ($n = 35$, 10%).

The AFFIRM investigators recently published their QoL analysis.³³ For 716 patients, around 21% of the total AFFIRM population, a variety of QoL instruments showed that QoL was comparable between the rate and the rhythm control strategies. Interestingly, QoL scores were similar whether the actual heart rhythm was sinus rhythm or AF. In terms of QoL improvement, the AFFIRM conclusion is that restoring sinus rhythm for this purpose is unsuccessful.

It should be kept in mind, however, that nearly 25% of AFFIRM patients were in sinus rhythm at inclusion. Furthermore, severely symptomatic AF patients were also excluded from AFFIRM, as was also for RACE. This is illustrated by the finding that more than 20% of the patients studied reported their health as "excellent" or "very good." So, patients were already in good QoL, limiting the effect of the rhythm intervention. It is likely that the underlying conditions are important for a decrease or an improvement in QoL.

There is still some debate on the question that if sinus rhythm can be restored, AF will still be as good as sinus rhythm regarding QoL. The RACE data indicate that if sinus rhythm can be achieved, QoL will improve. In selected patients, effective rhythm control can be achieved by circumferential pulmonary vein isolation for AF.⁶² In a nonrandomized study, Pappone and coworkers showed that patients were more likely to remain in sinus rhythm after the procedure compared to patients treated using conventional rhythm control strategies.⁶³ While in sinus rhythm, QoL improved.

Costs of Therapy

With increasing numbers of patients in the (near) future and increasing number of hospital admissions for AF, it is important to examine the

cost-effectiveness of AF treatment.^{4,64-66} Recent data showed that in the United Kingdom, AF was estimated to account for nearly 1% of the National Health Service expenditures in the year 2000, largely due to hospital admissions and drug prescriptions.⁶⁷ These data are in accordance with the results from France showing that hospital admissions and costs of drugs are the major cost drivers in the treatment of AF.⁶⁸

To date, the economic consequences of applying rate or rhythm control in patients with AF are only explored by the AFFIRM and RACE investigators.^{34,54} Both studies showed that a rate control patient used fewer resources than a rhythm control patient (Tables 3 and 4). The difference is largely explained by more days hospitalized, more short-term visits to the emergency department, and more costs for the electrical cardioversion procedure under rhythm control.

Given the main message from both trials, rate control is not inferior to rhythm control, data of the cost analysis show that rate control is more cost-effective than rhythm control for patients with persistent AF. However, it is important to realize that most patients in both studies were relatively old and did not suffer from severely symptomatic AF. It remains to be seen whether these results can be extrapolated to other subgroups of patients with AF. For instance, younger patients with symptomatic episodes of AF who still work. In these patients, AF may be of more economic importance, as they have to stay at home or at least are less productive at work while in symptomatic AF.

In the near future, rhythm control is likely to become more expensive with the increasing use and indications for radiofrequency catheter ablation procedures, and possibly, the application of pacemaker techniques. These techniques will be preferably used in severely symptomatic patients, or patients for whom sinus rhythm is preferred, after failure of antiarrhythmic drug treatment. Despite being expensive, these approaches may produce better QoL and general well-being. It remains to be seen how the overall costs balance QoL and probably morbidity and mortality. Future research is needed to clarify this issue.

Ventricular and Atrial Remodeling in AF

An important reason for restoring and maintaining sinus rhythm is the assumed improvement of left ventricular function. Indeed, many stud-

ies were performed to show that left ventricular function improved once the patient was in sinus rhythm. The majority of these trials were performed in those with rapid AF, in the setting of tachycardiomyopathy. Not surprisingly, data of the RACE study showed that left ventricular function (as measured using the fractional shortening) improved under rhythm control, especially if patients kept long-term sinus rhythm.⁵⁸ A remarkable finding was that ventricular function did not deteriorate under rate control aiming at a resting heart rate below 100 beats per minute. So, regarding the prevention of tachycardiomyopathy, rate control is effective.

Preventing tachycardiomyopathy is a matter of rate regularization in addition to rate control. Lowering the heart rate probably is most important, but regularization of the rhythm has been shown to improve cardiac output compared to an irregular heart rhythm, at the same rate.⁶⁹

Therefore, apart from restoring sinus rhythm, treatment of tachycardiomyopathy may also be achieved with AV-nodal ablation and implantation of a pacemaker. Alternatively, lowering heart rate using rate control drugs usually also produces a reasonable regularization of R-R intervals. This may provide sufficient protection from and even restoration of ventricular dysfunction in patients with tachycardiomyopathy due to AF.

It remains to be determined whether the improvement of left ventricular function observed in recent trials also results in the improvement of survival.^{70,71} These data are yet not available.

Data from RACE confirmed previous findings that atrial diameters increase under rate control.⁵⁸ Rhythm control prevents atrial enlargement. Indeed, sinus rhythm was a strong predictor for reduction of atrial diameters. Despite reduction of atrial size, more thromboembolic complications occurred under rhythm control. The effects of discontinuation of oral anticoagulation in sinus rhythm probably outweighed the benefit of sinus rhythm with respect to atrial diameters.

RATE CONTROL FOR ALL?

Despite a wide range of inclusion criteria, AF and patient characteristics and primary and secondary study endpoints, the randomized trials showed a remarkably consistent outcome: rate control is at least as effective as rhythm control in preventing morbidity and mortality. In AFFIRM, there was

even a statistical trend toward superiority of rate control over rhythm control. A recently performed meta-analysis of all the five trials including all the 5239 patients (77% of the included patients were from AFFIRM) concluded that all-cause mortality was comparable for both strategies with a trend toward rate control.⁷² The question is whether rhythm control is now redundant. Should all patients with AF be treated by just controlling the ventricular rate?

Which Patient Benefits from Rhythm Control?

To answer this question, it is necessary to look back to the patient groups studied. The typical patient treated in the trials was a 70-year-old male with complaints of fatigue, dyspnea, and palpitations from recurrent AF with a history of hypertension. Indeed, for this patient, the rate control strategy is an attractive option. However, several subgroups can be identified likely to gain from restoration of sinus rhythm. Clinical determinants influencing the benefit of either rate control or rhythm control are the type of AF, severity of AF-related complaints, and underlying diseases.

For making the right decision for the patient, it is important first to determine if a patient presenting with AF suffers from a first episode of AF, paroxysmal, persistent or permanent AF. This differentiation is essential for choosing the best possible treatment strategy for the patient. RACE included patients with persistent AF after a recurrence of AF. Other trials also evaluated predominantly patients with persistent AF. Only AFFIRM included a fairly large number of patients with paroxysmal AF. Patients presenting for the first time with AF should undergo at least one electrical cardioversion to restore sinus rhythm. Irrespective of the treatment decision, underlying heart disease should be evaluated and adequately treated.

One of the main drivers for adopting rhythm control is symptoms. Remarkably, the primary endpoint of the PIAF study, improvement of AF-related symptoms, was comparable for both strategies.^{27,61} Rate control does not seem inferior to rhythm control for management of mild to moderate complaints. In RACE, there were only small differences between rate and rhythm controls concerning effects on QoL.⁵³ Subanalysis revealed, however, that for patients with complaints at inclusion and sinus rhythm at study end, the QoL improved

the most. This indicates that in specific subgroups rhythm control is preferable. Furthermore, highly symptomatic patients were never included in the randomized trials. Indeed, severely symptomatic AF was regarded as an absolute indication for rhythm control, excluding these patients from analysis. Therefore, in patients with highly symptomatic AF, sinus rhythm is still the heart rhythm of choice.

Another driver for adopting a rhythm approach might be the presence of severe congestive heart failure (CHF). Further research is needed to clarify the rate-rhythm issue in these patients. AF in the setting of heart failure is discussed below.

The mean age of the included patients was 68 years of age. In general, younger patients tend to have more complaints of AF than the elderly. Especially, palpitations were reported more frequently. This is partly due to more frequent paroxysmal AF in the young. The sudden and unexpected onset of paroxysmal AF accompanied by rapid heart rates, frequently gives rise to severe symptoms with hospitalization as a consequence.⁷³ The body of evidence suggests that in older patients with AF, rate control may be sufficient, but for younger patients outcome in terms of improvement of QoL tends to be better in a rhythm control approach. Table 5 gives an overview for the patients best suited for one of the two approaches.

Patients with Heart Failure

AF is commonly present in the setting of an underlying cardiovascular condition like hypertension, myocardial ischemia, valvular heart disease, and heart failure.

Just as AF, heart failure is an ever increasing condition with severe impact on morbidity and mortality.⁷⁴ The relation between AF and heart failure is clear: patients with heart failure are at increased risk of developing AF and vice versa.^{75,76} Despite a large number of descriptive data on the relation between AF and heart failure, the treatment of patients with AF in the setting of heart failure remains challenging. It seems reasonable to believe that patients with heart failure are better off in sinus rhythm due to improved hemodynamics. Unfortunately, in heart failure, rhythm control usually is not a success due to frequent recurrences and increased risk of proarrhythmia.^{12,77,78} Especially, class IC drugs are contraindicated in patients with

Table 5. The Typical Rate and Rhythm Control Patients^a

Patients eligible for rhythm control
All AF patients presenting for the first time
Patients with (severely) symptomatic AF
Patients without stroke risk factors and risk factors for proarrhythmia
Patients with severe congestive heart failure ^b
Patients eligible for rate control
Patients with asymptomatic AF
Patients in whom ECV, ablation, or arrhythmia surgery failed
Women
Patients with hypertension

^aPatients in NYHA class II and III for heart failure: Currently no benefit of rhythm control was observed. Age per se does not qualify for one of the two treatment strategies. Concerning heart failure status and age: look for other criteria.

^bIf rhythm control strategies could be improved, e.g., pulmonary vein isolation.

heart failure or left ventricular dysfunction as it increases mortality risk.⁷⁹

Furthermore, it is questionable whether sinus rhythm should be restored in all patients with heart failure as the benefit of sinus rhythm seems insignificant for those with severe heart failure.⁸

Analysis of patients in NYHA class II and III at inclusion of the RACE study showed that the primary endpoint of morbidity and mortality occurred at a similar frequency in the rate and rhythm control strategies.⁵⁹ However, there was a striking difference in the components of the primary endpoint with less severe morbidity and less mortality under rhythm control.

The STAF study, in mostly patients with left ventricular dysfunction, showed no benefit of rhythm control. Also, AFFIRM patients with heart failure or reduced left ventricular ejection fraction were not better off with rhythm control.²⁸ In addition, recent data from the PIAF investigators showed no differences between patients with and without heart failure in terms of improvement of symptoms and exercise tolerance.⁸⁰

For most patients rate control does not seem inferior to rhythm control, but for those in whom sinus rhythm can be maintained, the outcome may improve. Interesting in this respect is a retrospective analysis of the DIAMOND study (Danish Investigations of Arrhythmia and Mortality ON Dofetilide).⁸¹ A total of 506 patients with left ventricular dysfunction were in AF or atrial flutter at

inclusion. Conversion to sinus rhythm was associated with a significantly lower mortality rate compared to those remaining in AF. This lower mortality rate was similar in both the dofetilide (class III drug) group and the placebo group. In the CHF-STAT study, patients with AF and congestive heart failure who converted to sinus rhythm on amiodarone showed a significantly lower mortality rate ($P = 0.04$) than those who remained in AF.⁸² Also beta-blockers were shown to be beneficial for patients with AF in the setting of heart failure.⁸³ Compared to placebo, carvedilol resulted in a significant improvement of left ventricular function and QoL. Importantly, there was no benefit on mortality. In a rate control approach in patients with heart failure, carvedilol, in combination with digoxin, improved left ventricular ejection fraction and symptoms.⁷¹

Overall, it is currently not demonstrated whether beta-blockers improve survival in patients with AF in the setting of heart failure.^{83,84} The positive effect on survival of beta-blockers in AF and CHF, in contrast to patients in sinus rhythm with CHF, remains to be determined.

In summary, there are currently no prospective studies comparing rate and rhythm controls concerning morbidity and mortality in patients with heart failure. To fill this gap, a large randomized study (the AF-CHF trial) comparing rate and rhythm controls in patients with heart failure is conducted.⁸⁵ The study protocol encourages the use of new antiarrhythmic agents and nonpharmacological approaches to achieve sinus rhythm. It is possible that especially patients with heart failure have much to gain from nonpharmacological arrhythmia suppression, bypassing the negative effects of current antiarrhythmic drugs. Results of this important trial will become available in the next few years. This will add much needed information on arrhythmia management in heart failure. Nonrandomized data from the group of Hais-saguerre indicate that catheter ablation may be a good option for patients with AF and congestive heart failure.⁷⁰

ANTICOAGULATION FOR RATE AND RHYTHM CONTROLS

A important issue highlighted by RACE and AFFIRM is that rhythm control therapy does not prevent stroke. It was observed from RACE that 21 of the 35 thromboembolic complications occurred under rhythm control, mostly at an International

Normalized Ratio (INR) below the therapeutic range of 2–3. Six patients had the event after cessation of oral anticoagulant therapy, with five of them in sinus rhythm. The majority (23 of 25) of strokes occurred while receiving inadequate anticoagulation therapy. One reason for this was that in the rhythm control group, it was allowed to stop oral anticoagulation if sinus rhythm was present for >1 month after cardioversion. This may have caused the excess strokes in this treatment arm in RACE since thrombosis risk probably persists despite sinus rhythm.⁸⁶ Moreover, the list of accepted stroke risk factors in AF of higher age (above 65 years), hypertension, diabetes, atrial enlargement, left ventricular dysfunction, and a previous thromboembolic event does not contain heart rhythm. Also emboli originating in the thoracic aorta and the carotid artery may contribute to stroke in patients with AF.⁸⁷ So, with the restoration of sinus rhythm in patients with AF, other stroke risk factors will remain. Again, underlying disease accounted for increased risk of thromboembolic events and bleeding. Furthermore, interruption of oral anticoagulation itself, with fluctuating INR levels, is an identifier of increased risk of thromboembolic events and bleeding.⁸⁸

Asymptomatic episodes of AF may add to the continued stroke risk in rhythm control patients who are believed to be in persistent sinus rhythm.⁸⁹ Recent data from patients with an implantable monitoring device showed that nearly 20% of AF recurrences occurred asymptomatic.⁹⁰ This percentage of asymptomatic or “silent” AF was also found in another study using recording of routine transtelephonic electrocardiograms.⁹¹ Obviously, these patients are not likely to seek and receive oral anticoagulation. Also in AFFIRM, with patients with one or more stroke risk factors, more strokes were present under rhythm control. Therefore, one of the main lessons learned from the randomized studies is that anticoagulation must be continued if stroke risk factors are present even if patients maintain sinus rhythm.

The vast majority of patients with AF have stroke risk factors necessitating adjusted-dose oral anticoagulation to reduce the risk of thromboembolic events.⁹² The problem with these vitamin K antagonists is the narrow therapeutic window and the numerous interactions with other drugs and foods and regular coagulation monitoring with dose adjustments are needed to keep the INR at the rec-

ommended target of at least 2.0–3.0.^{93–95} To overcome the risks of inadequate anticoagulation, new drugs were developed for preventing stroke in AF. One promising drug in this regard was the oral direct thrombin-inhibitor ximelagatran. This twice-daily, fixed-dosed drug (i.e., no monitoring and dose adjustments required) was compared in the SPORTIF III and V trials with adjusted-dose warfarin in patients with persistent or paroxysmal AF who do not have impaired renal function.⁹⁶ The open-label SPORTIF III study found that ximelagatran was not inferior to warfarin in preventing stroke in patients with AF.⁹⁷ Importantly, ximelagatran was associated with significantly less major bleeding. However, in 107 (6%) of the 1703 patients randomized to ximelagatran, the serum alanine aminotransferase rose above three times the upper limit of normal. In 59 patients, elevations returned spontaneously to baseline levels without clinical sequelae, and in the remaining 48 subjects, normalization occurred after cessation of treatment. In the SPORTIF V trial, the double-blinded randomized counterpart of the SPORTIF III also established the efficacy of ximelagatran for the prevention of thromboembolism in patients with AF requiring chronic anticoagulant therapy.⁹⁸ Nevertheless, also in SPORTIF V, a 6% incidence of elevation of significant serum alanine aminotransferase level was observed. Accordingly, the principal concern with ximelagatran is that with long-term use, some hepatotoxicity may occur.⁹⁹ These concerns have resulted in the decision by the manufacturer to withdraw ximelegatran from the market.¹⁰⁰ Other drugs are currently under investigation.

The AMADEUS trial is another trial evaluating a new therapy to prevent stroke in patients with AF: subcutaneous injection with idraparinux sodium.¹⁰¹ This drug, a synthetic anti-Xa pentasaccharide, is suitable for once-weekly administration without the need for monitoring.

In conclusion, anticoagulation has become one of the cornerstones of therapy in AF. The Achilles heel of these drugs are the risks of severe bleeding complications, especially in the elderly patient.¹⁰² Therefore, continuing effort should be taken to develop and evaluate effective and safe drugs for the prevention of thromboembolic events in patients with AF. Side effects of these drugs should be balanced against the benefits of improvements in oral anticoagulation therapy.

PROS AND CONS OF RATE AND RHYTHM CONTROLS AFTER THE RANDOMIZED TRIALS

The randomized trials redefined the pros and cons of rate and rhythm controls for the treatment of AF (Table 6). The most important finding is that rate control does not increase morbidity and mortality compared to rhythm control. Generally, rate control was regarded as an easy approach, but data from the AFFIRM study showed that many drug titrations and changes of medication are needed to obtain predefined rather strict heart rate control.³⁷ Surprisingly, the strict target heart rate which was aimed for in AFFIRM, was only achieved in 70% of the rate control subjects. Rhythm control was known as a demanding therapy for both patient and treating physician due to frequent repeat cardioversions and rotation of antiarrhythmic drugs. Strict rate control can now also be regarded as time-consuming and difficult to achieve. It has to be established whether this also accounts for a more lenient rate control approach.

As expected current antiarrhythmic drugs are associated with considerable risk for severe adverse effects.²⁹ Also AFFIRM showed the hazards of current antiarrhythmic drugs as these drugs, after adjustment for the presence of sinus rhythm, were associated with increased mortality.³⁶ These data reflect the fact that currently available antiarrhythmic drugs are neither highly efficacious nor completely safe. However, if the strict criteria for prescribing antiarrhythmic drugs are taken into account, the risk of proarrhythmic events can be minimized.⁴³

The rate-rhythm issue concerning QoL also needs to be reconsidered. Both rate and rhythm

controls improved QoL, as was shown by the PIAF. Other studies also did not show any difference in QoL between the two treatment options.

FUTURE DIRECTIONS

Management of AF remains an important field of research. In general, continued evaluation of improvements of the rate control and rhythm control strategies should be undertaken. Rate control is adequate for most patients with persistent AF, however, what is meant by "adequate"? It remains undefined what the optimum resting heart rate or heart rate during exercise should be for patients with permanent AF, despite retrospective nonrandomized data of AFFIRM and the AFFIRM-RACE cooperation.^{38,103–105} Obviously, the goal is to minimize complaints, risk of heart failure, and other cardiovascular events with, on the other hand, limitation of side effects and morbidity of rate controlling drugs. Currently, the RACE investigators are conducting a prospective randomized trial, Rate Control Efficacy in permanent AF (RACE II) to evaluate a lenient versus a rigid rate control approach for patients with permanent AF to tackle this issue.¹⁰⁶

For those with severely symptomatic AF, continued rhythm control is unavoidable. For these patients, safer and more effective methods of maintaining sinus rhythm are needed to reduce morbidity related to palpitations and AF-induced heart failure. The current cardioversion protocols may be improved with controlled combining of antiarrhythmic drugs or the use of new antiarrhythmics like dronedarone, azimilide, and tedisamil.^{107–110} However, these drugs are currently not registered for use in daily clinical practice. In addition, non-pharmacologic approaches may result in higher

Table 6. Pros and Cons of Rate and Rhythm Control Strategies: The Era After the Randomized Trials

	Rate Control	Rhythm Control
Pros	Not inferior to rhythm control for the majority of patients with AF Preservation of left ventricular function Lower costs of treatment Less hospitalizations	Improved quality of life with maintenance of sinus rhythm Improvement of left ventricular function and functional capacity
Cons	Target heart rate is unknown Not as easy to achieve as assumed Not attractive in highly symptomatic AF Persistence of an irregular heart beat Need for permanent anticoagulation	No benefit in terms of morbidity and mortality Demanding approach for doctor and patient, time-consuming Adverse effects of antiarrhythmic drugs High recurrence rate of AF Need for permanent anticoagulation even with maintenance of sinus rhythm

rates of maintaining sinus rhythm for these patients.¹¹¹ A promising strategy is radiofrequency ablation or cryoablation for AF.^{63,70,112} Also specific pacemaker protocols may be effective in preventing and terminating AF also when AF occurs outside the setting of sick sinus syndrome.^{113,114}

CONCLUSION

Clinical decision making regarding the treatment for patients with AF is significantly improved by the randomized trials evaluating rate and rhythm controls. For the majority of patients without severely symptomatic AF, rate control is the first choice. However, it remains essential to determine the subgroups of patients who will benefit the most from restoration of sinus rhythm. A summary of these typical patients eligible for rate or rhythm control was presented in Table 5. The pros and cons of both current and new drugs and non-pharmacological techniques should be included in future analysis on optimal treatment. The goal is to perform an individualized approach for patients with AF to select the optimal treatment strategy to reduce morbidity, mortality, and improve QoL for the lowest possible price.

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