*Atrial fibrillation is a serious condition affecting millions of people worldwide. In fact, atrial fibrillation is the most common chronic tachyarrhythmia, accounting for 10% of patients who are admitted with circulatory problems. Furthermore, this arrhythmia is a very 'expensive proposition' both in terms of increased frequency and duration of hospitalisations as well as in the personal cost to patients in reduced quality of life.*

*Drs Hagens and Van Gelder tackled a clinically important question, whether repeated electrical cardioversion, in conjunction with antiarrhythmic drugs, to maintain sinus rhythm is mandatory. In other words, is rate control not inferior to rhythm control in patients with persistent, i.e. non-self-limiting atrial fibrillation.*

*Their study, comprising thirty-one centres in the Netherlands, demonstrated that rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes. Hence, rate control is appropriate in patients with recurrence of persistent atrial fibrillation following electrical cardioversions.*

*W. van Gilst and C.A. Visser,*
*Directors of ICIN.*

## Rate or rhythm control for persistent atrial fibrillation

Atrial fibrillation (AF) affects 0.5 to 1.0% of the general population.[1] The prevalence increases with age, reaching nearly 10% of individuals over the age of 80 years. Despite this enormous population with AF the optimal treatment strategy remains uncertain. The first choice of therapy is the rhythm-control strategy with restoration of sinus rhythm.[2] A severe drawback to this approach is the low success rate for maintenance of sinus rhythm. Outcome will improve with the use of antiarrhythmic drugs after electrical cardioversion, but this unfortunately exposes the patient to the risks of life-threatening proarrhythmia. The second alternative, a rate-control strategy, is easy to achieve but it is not known whether this treatment strategy results in higher morbidity and mortality rates. Recently, several randomised trials were published in which the issue of rate or rhythm control for atrial fibrillation was studied: the Dutch RACE study (RAte Control versus Electrical cardioversion for persistent atrial fibrillation), the North American AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the smaller German PIAF (Pharmacological Intervention in Atrial Fibrillation) and STAF (Strategies of Treatment of Atrial Fibrillation) studies.[3-6]

**Table 1.** Randomised studies of rate- and rhythm-control strategies in atrial fibrillation.

| Study | Patients (n) | Follow-up (year) | Patients in SR* Rate vs rhythm | Primary endpoint incidence Rate vs rhythm |
|---|---|---|---|---|
| RACE | 522 | 2.3 | 10% vs 39% | Composite endpoint (cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker implantation, severe adverse effects of drugs) 17.2% versus 22.6% |
| AFFIRM | 4060 | 3.5 | 35% vs 63% | All-cause mortality 25.9% versus 26.7% (p=0.08) |
| PIAF | 252 | 1 | 10% vs 56% | Improvement of AF-related symptoms 61% versus 55% (p=0.317) |
| STAF | 200 | 2 | 11% vs 26% | Composite endpoint (all-cause mortality, cerebrovascular events, thromboembolism, cardiopulmonary resuscitation) 5% versus 4.5% (p=0.99) |

* Sinus rhythm at the end of follow-up

The designs of these studies were essentially the same (table 1) and have been described elsewhere.[3-6] Rate control was performed with digoxin, verapamil or diltiazem and a β-blocker, alone or in combination. The target heart rate varied per study or was not specified. In the rhythm-control arms patients received prophylactic antiarrhythmic drugs and electrical cardioversion if necessary. Antithrombotic treatment consisted of oral anticoagulation or aspirin, depending on the patient's risk factors for stroke. Patients were allowed to stop anticoagulation when chronic sinus rhythm was obtained. Endpoints varied between studies (table 1). The main goal of each strategy is to reduce the risks associated with atrial fibrillation, i.e. stroke, heart failure and syncope; at the same time side effects of the intervention should be avoided as much as possible. Important side effects include intracranial bleeding and drug proarrhythmia. Considering the above, it is clear that a morbidity and mortality endpoint was chosen rather than an arrhythmia endpoint.


### *Results of the RACE study*

The study design and results have been published previously.[3,7] The 522 patients included in RACE study represented a typical population with persistent AF.[8] Mean age was 69 years, and most patients had an underlying disease of which hypertension (49%) and coronary artery disease (27%) were most common. At baseline, there was a slight over-representation of hypertension in the rhythm-control group: 55% against 43% of the patients (p=0.007). Only 21% of the patients had AF without underlying heart disease.

After a mean follow-up of 2.3 years sinus rhythm was present in 39% (n=103) of the patients in the rhythm-control group after a median of two electrical cardioversions (figure 1). The number of patients on sotalol, class IC antiarrhythmic drugs and amiodarone was 39, 27 and 31, respectively. The other six patients withdrew before the end of the study while they were in sinus rhythm.

Ten percent (n= 26) of the patients in the rate-control group were in sinus rhythm at the end of the follow-up. Spontaneous conversion to sinus rhythm occurred in 13 patients, and 13 patients were in sinus rhythm after electrical cardioversion which was indicated for AF-related symptoms.

The primary endpoint occurred in 44 of the 256 rate-control patients (17.2%) and in 60 of the 266 rhythm-control patients (22.6%) (table 2), which indicated that rate control is not inferior to rhythm control. The components of the primary endpoint were well balanced between the two groups, except for adverse effects of antiarrhythmic drugs and pacemaker implantation, which were more frequently observed under rhythm control. Post-hoc analysis revealed that hypertension and female sex was associated with more (nonfatal) endpoints in the rhythm-control group.

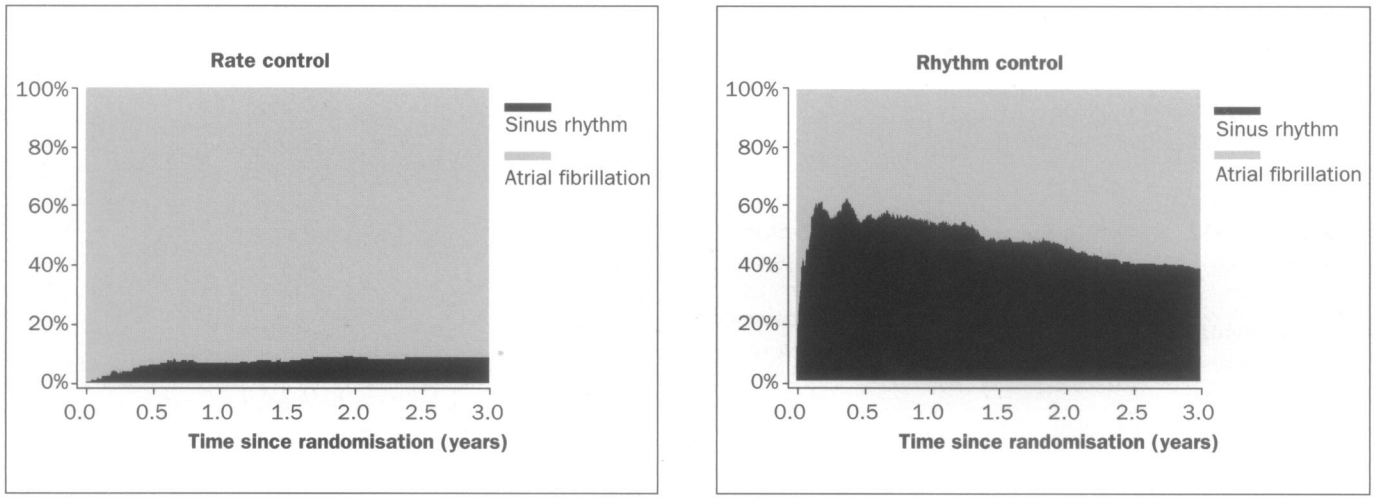
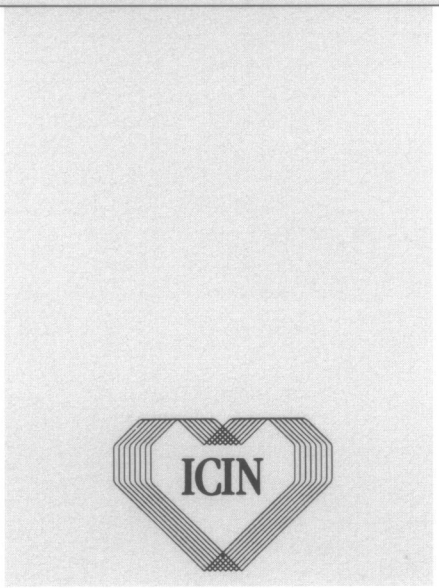



*Figure 1. Heart rhythm in follow-up.*




*The AFFIRM study in short*

Like RACE, AFFIRM was designed to evaluate rate and rhythm control in patients with atrial fibrillation.[4,9] Patient characteristics were comparable with those of the RACE study. After a mean follow-up of 3.5 years, the primary endpoint, which was overall mortality, occurred in 310 of the 2027 assigned to rate control. Even more endpoints were observed in the rhythm-control strategy: 356 of 2033 patients. Mortality at five years amounted to 21.3% versus 23.8%, which resulted in a trend towards superiority of the rate-control strategy (p=0.08). Thromboembolic complications occurred frequently, predominantly after cessation of oral anticoagulation or with the international normalised ratio (INR) at subtherapeutic levels. All AFFIRM patients had one or more risk factors for stroke and therefore the authors also state that all patients with AF and these risk factors should be adequately anticoagulated irrespective of the heart's rhythm. The outcomes of the RACE, AFFIRM, PIAF and STAF are shown in table 1.

*Anticoagulation in the treatment of AF*

More than half of the components of the primary endpoints in RACE were related to thromboembolic complications and bleedings (table 2). Most of these occurred at an INR outside the therapeutic range. The number of patients receiving oral anticoagulation in RACE ranged under rhythm control from 228 (86%) to 263 (99%) against 246 (96%) to 254 (99%) in the rhythm-control group. In the rhythm-control group it was allowed to stop oral anticoagulation if sinus rhythm was present for longer than one month after cardioversion. This may have caused excess strokes in the rhythm-control arm in RACE since thrombosis risk probably persists despite sinus rhythm.[10] Thoracic aortic atherosclerosis is also a well-recognised risk factor for stroke in these patients which may have contributed.[11] In addition, asymptomatic episodes of AF may add to the continued stroke risk.[12] Also the AFFIRM investigators reported more thromboembolic complications under rhythm control.[4] A meta-analysis of the AFFIRM, RACE, PIAF and STAF further substantiated these observations: the incidence of an ischaemic stroke was significantly higher under rhythm control than under rate control: 6.3% versus 4.7% (p=0.04).[13] In this respect, it is important to note that

**Table 2.** Incidence of the primary endpoint and its components.*

| Primary endpoints in the RACE | Number (%) Rate control (n=256) | Rhythm control (n=266) |
|---|---|---|
| **Composite endpoint** | **44 (17.2)** | **60 (22.6)** |
| Total cardiovascular mortality | 18 (7.0) | 18 (6.8) |
| - sudden death/nonsudden cardiovascular | 8/10 | 8/10 |
| Heart failure | 9 (3.5) | 12 (4.5) |
| - fatal/nonfatal | 4/5 | 1/11 |
| Thromboembolic complications | 14 (5.5) | 21 (7.9) |
| - fatal/nonfatal | 0/14 | 6/15 |
| Bleeding | 12 (4.7) | 9 (3.4) |
| - fatal/nonfatal | 6/6 | 3/6 |
| Severe adverse effects of antiarrhythmic drugs | 2 (0.8) | 12 (4.5) |
| - fatal/nonfatal | 0/2 | 0/12 |
| Implantation of a pacemaker | 3 (1.2) | 8 (3.0) |
| - fatal/nonfatal | 0/3 | 0/8 |

* Some patients had more than one endpoint.

all of the 35 patients with a thromboembolic complication in RACE had one or more risk factors for stroke. These risk factors were age above 65 years, hypertension, diabetes, atrial enlargement, left ventricular dysfunction and a previous thromboembolic event. In AFFIRM, patients were included only if they had one or more risk factors for stroke. It must be noted that among the well-known risk factors for stroke the rhythm is not included.[10] Therefore, the main lesson learned from the randomised studies is that anticoagulation must be continued if stroke risk factors are present even if patients maintain sinus rhythm.

### *Clinical implications*

First of all, as mentioned above, the randomised studies show that in the presence of stroke risk factors, anticoagulation cannot be stopped even if chronic sinus rhythm can be maintained. Therefore the bottom line here is that cardiologists can no longer sell the cardioversion to their patients using the argument that anticoagulation can be stopped after a successful shock. Secondly, the RACE, AFFIRM, PIAF and STAF studies demonstrate that a rate-control strategy is an acceptable alternative to rhythm control in patients with recurrent AF.

However, the results of these studies do not make rhythm-control therapy redundant. Patients first presenting with AF should still get a chance to maintain sinus rhythm in the long term. In a significant number, sinus rhythm may appear feasible and beneficial in terms of reducing palpitations or dyspnoea. In addition, in patients who are severely symptomatic with 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. ■

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