Rate control in atrial fibrillation, insight into the RACE II study

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Introduction

Currently, in Europe, more than 6 million patients have atrial fibrillation (AF) [1]. It is expected that this number will double in the next 30–50 years [1–3]. With AF, the risk of death, stroke and heart failure is increased [4–6], and exercise capacity and quality of life are reduced [7, 8]. Thus, AF is not a benign disease. Despite efforts to maintain sinus rhythm, AF is a progressive arrhythmia [9–11] and many patients eventually develop permanent AF. Until recently, the treatment of this specific patient group was not evidence based. An evidence-based treatment strategy is indispensable considering the large patient population.

It was not until the beginning of this decade that it became apparent that it was not the rhythm that determined the prognosis, i.e. there was no difference in outcome between rate (treatment aimed at heart rate reduction) and rhythm control (treatment aimed at restoration and maintenance of sinus rhythm) [12–18]. However, different definitions of adequate rate control were used in the rate versus rhythm control studies (Table 1). The guidelines at that time advocated a strict rate-control strategy, but this was based on small, short-term studies which did not investigate prognosis [19]. Thus, an evidence-based rate-control strategy was lacking. Studies which investigated different rate-control strategies showed no difference in outcome between patients with a high and low heart rate [20, 21]. However, these were all retrospective analyses.

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Rationale to initiate the RACE II study

Drugs frequently used to institute rate control consist of beta-blockers, non-dihydropyridine calcium-channel blockers and digoxin. From the 1970s until now, several studies have been performed evaluating the effect of negative dromotropic drugs (beta-blockers, non-dihydropyridine calcium-channel blockers, digoxin, amiodarone, and dronedarone) on heart rate during AF. At first, the focus was on heart rate at rest and during exercise [22–26]. It was expected that exercise capacity would improve due to a reduction in heart rate. Surprisingly, however, later studies showed no improvement of exercise capacity with a more physiological rate response during exercise [27–33].

The previous guidelines recommended the use of strict rate control [19] to reduce symptoms, improve the quality of life and exercise tolerance, reduce heart failure, and improve survival. On the other hand, strict rate control could cause drug-related adverse effects, including bradycardia,

syncope, and a need for pacemaker implantation. Thus, the balance between benefit and risk in terms of cardiovascular morbidity and mortality, quality of life, exercise tolerance, and disease burden remained unknown.

One of the first studies on heart rate during AF and prognosis was a large retrospective analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) [20]. All patients randomised to rate control in AFFIRM who were in AF at baseline and at 2 months follow-up were included in this analysis. The patients were stratified according to the quartiles of resting heart rate at 2 months. There was no difference in cardiovascular hospitalisation or death between the quartiles of achieved heart rate at rest at 2-month follow-up. Resting heart rate was not a predictor for all-cause mortality or cardiovascular hospitalisation. Importantly, in AFFIRM a strict rate-control approach was used, as the guidelines advocated at that time (Table 1). To achieve the strict rate-control targets frequent drug changes were needed; eventually, the rate-control criteria were achieved in two-thirds of the patients [34]. In the RAtE Control versus Electrical cardioversion (RACE) study the rate-control criterion was a resting heart rate below 100 beats per minute [14]. This criterion was solely established on the basis of the clinical experience of the principal investigators that 100 beats per minute would be most feasible as well as clinically relevant in terms of maintaining. A pooled analysis of AFFIRM and RACE evaluated differences in outcome between the studies [35]. In that study patients were included if they met a combination of overlapping inclusion and exclusion criteria of AFFIRM and RACE. The primary endpoint was a composite of all-cause mortality, cardiovascular hospitalisation, and myocardial infarction. In total, 1091 patients were included, 874 from AFFIRM and 217 from RACE. The mean

heart rate in the AFFIRM patients was lower compared with the patients from RACE due to different rate-control definitions (76.1 versus 83.4 beats per minute). There was no difference in outcome between the patients included in AFFIRM or RACE, though a heart rate >100 beats per minute was associated with a worse outcome. Lenient control was associated with far fewer pacemaker implantations than strict control. Thus, all available data showed no clear benefit of strict rate control as compared with lenient rate control; however, only retrospective data were available.

Heart rate and quality of life can also be assumed to be related. A higher heart rate could cause more or more severe symptoms than a lower heart rate. However, instituting a stricter rate-control strategy requires more negative dromotropic drugs. Prospective data on quality of life and different rate-control studies were also lacking.

Design and methods of the RACE II study

The first, and as yet the only, study to prospectively investigate the effect of different rate-control strategies on outcome is the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II) study. The study was initiated and coordinated by the Interuniversity Cardiology Institute Netherlands, the University Medical Center Groningen, and the Working Group Cardiology Netherlands. The study was funded by a major grant obtained from the Netherlands Heart Foundation and by unrestricted educational grants from the pharmaceutical and device companies listed under Funding. The steering committee was responsible for the design, conduct, analysis and reporting of the study. Study monitoring, data management and validation were

Table 1 Heart rate criteria used in the rate- versus rhythm-control trials

	Primary outcome	Heart rate criteria
AFFIRM [13]	All-cause mortality	≤80 beats/min, and ≤110 beats/min during moderate exercise. On Holter mean HR ≤100 beats/min, and not >110 % of the maximum predicted heart rate
RACE [14]	Composite endpoint ^a	<100 beats/min
PIAF [12]	Symptoms related to AF	Diltiazem 90 mg, 2–3 times per day, additional rate-control therapy at discretion of physician
STAF [15]	Composite endpoint ^b	–
HOT CAFE [16]	Composite endpoint ^c	70–90 beats/min, <140 beats/min during moderate exercise
AF-CHF [18]	Cardiovascular death	≤80 beats/min, and ≤110 beats/min during 6-minute walk test
J Rhythm [17]	Composite endpoint ^d	60–80 beats/min

^a Cardiovascular death, hospitalisation for heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe adverse effects or antiarrhythmic drugs

^b All-cause mortality, stroke or transient ischaemic attack, systemic embolism, and cardiopulmonary resuscitation

^c All-cause mortality, thromboembolic complications and intracranial or other major haemorrhage

^d All-cause mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalisation for heart failure, physical/psychological disability requiring alteration of assigned strategy

independently performed at the Trial Coordination Center (University Medical Center Groningen, the Netherlands). The study was approved by the institutional review boards of all the participating centres.

The hypothesis was that there was no difference in outcome between lenient and strict rate control [36]. Patients were eligible if they met the following criteria: permanent atrial fibrillation for up to 12 months, age of 80 years or younger, mean resting heart rate above 80 beats per minute, and current use of oral anticoagulation therapy (or aspirin, if no risk factors for thromboembolic complications were present). Patients were randomised to lenient (resting heart rate <110 beats per minute) or strict rate control (resting heart rate <80 beats per minute, and during moderate exercise <110 beats per minute). Follow-up outpatient visits occurred every 2 weeks until the heart-rate target or targets were achieved and in all patients after 1, 2, and 3 years. Follow-up was between 2 and 3 years. The primary outcome was a composite of cardiovascular death, hospitalisation for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate-control drugs, and pacemaker or cardioverter-defibrillator implantation. Heart rate was lowered with beta-blockers, non-dihydropyridine calcium-channel blockers, and digoxin, alone or in combination [37].

Differences in treatment strategy between lenient and strict rate control

In total 614 patients were randomised to lenient or strict rate control. After the dose-adjustment phase there was a

significant difference in heart rate between the two groups. The mean resting heart rate at the end of the dose-adjustment phase was 93 ± 9 beats per minute in the lenient-control group, as compared with 76 ± 12 beats per minute in the strict-control group. After 1 and 2 years and at the end of the follow-up period, the resting heart rates in the lenient-control group were 86 ± 15 , 84 ± 14 , and 85 ± 14 beats per minute, respectively, as compared with 75 ± 12 , 75 ± 12 , and 76 ± 14 beats per minute, respectively, in the strict-control group. Patients in the lenient-group used less rate-control drugs as compared with the patients in the strict group. In the lenient group 10 % of patients used no rate-control drugs as compared with 1 % in the strict. More than 60 % of patients in the strict group required two or more rate-control drugs to achieve the rate-control targets. Patients in the strict rate-control group also used higher dosages of rate-control drugs and more additional visits were required to achieve the rate-control targets.

Primary outcome of the RACE II study

After a follow-up of 3 years there was no difference in primary outcome between lenient and strict rate control. A total of 81 patients (38 or 311 in the lenient-control group and 43 of 304 in the strict-control group) reached the primary outcome (Fig. 1). The absolute difference between lenient control and strict control was -2.0 percentage points (90 % confidence interval [CI], -7.6 to 3.5) and a hazard ratio of 0.84 (90 % CI, 0.58 to 1.21) [37]. This showed that lenient rate control was non-inferior to strict rate control, which confirmed our hypothesis [37]. However, a few limitations have to be kept in mind when interpreting the results

Fig. 1 Cumulative incidence of the primary outcome in patients randomised to lenient versus strict rate control. The numbers at the end of the Kaplan–Meier curves represent the estimated cumulative incidences of the primary outcome at 3 years. Adapted from Van Gelder et al. with permission from Massachusetts Medical Society

of the RACE II. In the strict rate-control group 33 % of patients did not meet the heart rate targets, this may have affected outcome (see below). In addition, the difference in heart rate between the lenient and strict group was not as large as could have been expected from the design of the study. Finally, follow-up was limited to 3 years. However, the two treatment strategies used were completely different, which is shown in the higher number of drugs, higher dosages and higher number of additional visits that were required to achieve the strict rate-control criteria.

Failure of strict rate control and outcome

Previous studies on rate control in atrial fibrillation have shown that strict rate control is difficult to achieve [34]. In the AFFIRM trial there were frequent medication changes necessary to achieve the strict rate-control criteria as defined (Table 1). Eventually the rate-control criteria were achieved in 68 % of patients [34]. In RACE II we observed the same phenomenon with a comparable figure: 67 % of patients randomised to strict rate control achieved the strict rate-control criteria, as compared with 97 % of patients randomised to lenient rate control [37]. This large difference could have influenced the outcome of RACE II, in favour of lenient rate control. Therefore an additional analysis was performed investigating outcome in patients with failed strict, successful strict and lenient rate control [38]. In this analysis outcome events in the strict rate-control group were analysed from the end of the dose-adjustment phase, i.e. the moment the heart rate targets were either achieved or deemed impossible or unnecessary (due to absence of symptoms) to achieve, until the end of follow-up.

By definition, heart rates were higher in the failed strict and lenient group as compared with the successful strict group. There was no difference in the primary outcome, as described above, between failed strict, successful strict and lenient rate control. A total of 76 patients (27 of 203 in the successful strict and 14 of 98 in the failed strict group, and 35 of 307 in the lenient group) reached the primary outcome [38]. The cumulative difference between successful strict and lenient rate control was 0.2, (90 % CI −7.4 to 3.2). In other words, even in the subgroup of patients with ‘true’ strict rate control, outcome was not superior as compared with patients with lenient rate control. There was also no difference in primary outcome when analysing patients with an ejection fraction <40 %. This showed that failure of strict rate control did not influence the results of RACE II. Thus, patients with permanent atrial fibrillation can be treated according to a lenient rate-control strategy. However, when symptoms persist a more strict approach can be used, as is currently stated in the European guidelines (Fig. 2) [1].

Fig. 2 Optimal level of heart rate control. Institution of rate control, adapted from Camm et al. with permission of Oxford University Press

All-cause mortality, hospitalisation and heart failure in RACE II

The ideal outcome parameter in a study on prognosis is mortality. However, this would require a very large patient cohort due to the relative good prognosis in patients with atrial fibrillation. Therefore a composite outcome was used in RACE II. Cardiovascular hospitalisation is an alternative outcome parameter which is associated with mortality [39, 40]. To further investigate differences between lenient and strict rate control we performed an additional analysis on cardiovascular hospitalisation and mortality. There was no difference in cardiovascular hospitalisation and mortality between lenient and strict rate control. It is, however, striking that many patients were hospitalised during the study, showing the vulnerability of patients with permanent atrial fibrillation.

One of the major concerns prior to the RACE II was that lenient rate control might lead to the development of heart failure. However, the incidence of heart failure was similar between the two groups [37]. In addition, there was no deterioration of left ventricular function during a lenient rate-control approach. Apparently, a resting heart rate below 110 beats per minute was low enough to prevent an increased number of hospitalisations for heart failure. This is in line with the notion that beta-blockers do not improve the prognosis of patients with heart failure who have atrial fibrillation [41, 42].

Despite absence of a difference in cardiovascular hospitalisation in RACE II one cannot exclude that excessive rate control can be deleterious. In PALLAS, the immediate rise in both co-primary composite endpoints in the dronedarone group compared with placebo may have been related to excessive rate control. This notion is supported by the fact that the heart rate at 1 month in survivors in the dronedarone arm had decreased by 7.6 ± 14.5 beats per minute (from 77 ± 16 beats per minute at baseline), which may have harmed a significant number of patients. To what extent digoxin toxicity due to interaction with dronedarone may have played a role here is unknown [43].

Quality of life and stringency of rate control

Quality of life is another important outcome parameter in the treatment of patients with permanent atrial fibrillation. A predefined analysis on difference in quality of life between lenient and strict rate control was performed in RACE II [36]. The hypothesis concerning quality of life was that there would be no difference in quality of life between lenient and strict rate control [36]. Strict rate control may reduce symptoms due to a lower heart rate, but, on the other hand, it may also cause more drug-related side effects, resulting in reduced quality of life. A post-hoc analysis of the AFFIRM trial showed no difference in quality of life between the quartiles of resting heart rates [20]. In RACE there was also no difference in quality of life between patients with a lower (rate <80 beats per minute) as compared with patients with a higher (≥ 80 beats per minute) mean resting heart rate [21]. Quality of life was assessed with the SF-36, MFI-20 and AF severity scale. At baseline there were no differences in quality of life between lenient and strict rate control in any of the questionnaires used. Importantly, at one-year follow-up, and at end of study there were also no differences in quality of life between lenient and strict rate control. At the end of the study there was no difference in quality of life measured with the SF-36, MFI-20 and AF severity scale between lenient and strict rate control. There were also no differences in quality of life between failed strict, successful strict and lenient rate control [44]. In addition, heart rate did not influence quality of life. Changes in quality of life were related to age, symptoms at baseline and at the end of study, severity of underlying disease and female sex. This again shows that lenient rate control is the treatment of choice in patients with permanent atrial fibrillation without severe symptoms.

The results of RACE II make treatment of AF more convenient for the patient and the physician. Lenient rate control is easier to achieve than strict rate control, requires fewer drugs, outpatient department visits and additional examinations.

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Conflict of interest Dr. Van Gelder reports receiving consulting fees from Sanofi-Aventis, Boehringer Ingelheim and Cardiome, grant support from Medtronic, Biotronik and St. Jude Medical, lecture fees from Sanofi-Aventis, Boehringer Ingelheim and Medtronic. Dr. Crijns reports receiving consulting fees from Boehringer Ingelheim, Sanofi-Aventis and AstraZeneca, grant support from St. Jude Medical, Boston Scientific, Boehringer-Ingelheim, Sanofi-Aventis, Medapharma and

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