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Rate control efficacy in permanent atrial fibrillation

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RAte Control Efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control in patients with and without heart failure. Background, aims, and design of RACE II

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Background   Recent studies demonstrated that rate control is an acceptable alternative for rhythm control in patients with persistent atrial fibrillation (AF). However, optimal heart rate during AF is still unknown.

Objective   To show that in patients with permanent AF, lenient rate control is not inferior to strict rate control in terms of cardiovascular mortality, morbidity, neurohormonal activation, New York Heart Association class for heart failure, left ventricular function, left atrial size, quality of life, and costs.

Methods   The RACE II study is a prospective multicenter trial in The Netherlands that will randomize 500 patients with permanent AF (≤12 months) to strict or lenient rate control. Strict rate control is defined as a mean resting heart rate <80 beats per minute (bpm) and heart rate during minor exercise <110 bpm. After reaching the target, a 24-hour Holter monitoring will be performed. If necessary, drug dose reduction and/or pacemaker implantation will be performed. Lenient rate control is defined as a resting heart rate <110 bpm. Patients will be seen after 1, 2, and 3 months (for titration of rate control drugs) and yearly thereafter. We anticipate a 25% 2.5-year cardiovascular morbidity and mortality in both groups.

Results   Enrollment started in January 2005 in 29 centers in The Netherlands and is expected to be concluded in June 2006. Follow-up will be at least 2 years with a maximum of 3 years.

Conclusion   This study should provide data how to treat patients with permanent AF. (Am Heart J 2006;152:420-6.)

Background and rationale

Rate control may be adopted as first choice therapy in atrial fibrillation

Permanent atrial fibrillation (AF) is not a benign disease.[1] It may cause symptoms and is associated with thromboembolic complications. Some patients with longer-lasting AF may develop left ventricular dysfunction, even those without underlying heart disease (tachycardiomyopathy). The AFFIRM, RACE, PIAF, and STAF studies and others (HOT CAFÉ) established that morbidity and mortality was comparable between rate and rhythm control therapy.[2-6] As a result, rate control may now be adopted as first choice therapy in a variety of patients, especially those with minor symptoms and a high chance on AF recurrences or adverse effects related to antiarrhythmic drugs. However, the optimal level of heart rate control with respect to morbidity and mortality remains unknown.

Strict or lenient rate control

The question remains whether strict rate control is associated with an improved prognosis compared with a more lenient approach.[7] Intuitively, strict rate control is associated with fewer symptoms, better quality of life (QoL), a lower incidence of heart failure, and a better survival. Strict rate control with higher drug doses, on the other hand, could lead to drug-related adverse effects, causing symptomatic bradycardia, leading to falls, syncope, trauma, and preventable pacemaker implantation. Furthermore, strict rate control does not necessarily lead to fewer symptoms because symptoms may be due to the underlying cardiovascular disease rather than the heart rate. Therefore, the balance between benefit and harm in terms of the combined end point of morbidity, mortality, QoL, and costs remains unknown. In AFFIRM, in accordance with the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society Cardiology (ESC) guidelines,[1] a strict rate control approach was applied that includes a resting heart rate <80 beats per minute (bpm) and either a 6-minute walk test heart rate ≤110 bpm or a mean heart rate on a 24-hour Holter recording ≤100 bpm, in combination with a maximum heart rate ≤110% of predicted maximum heart rate. It was demonstrated that this (strict) rate control approach could be successfully achieved in two thirds of the patients and that, in line with previous data, β-blockers were commonly used to accomplish this goal.[8] Serious adverse effects were uncommon. However, strict rate control was difficult to achieve. To obtain adequate rate control, atrioventricular node ablation and pacemaker implantation were performed in 108 (5.3%) of the 2027 patients and an additional 147 (7.3%) patients had a pacemaker implanted for symptomatic bradycardia due to the rate control medication. In a subanalysis of AFFIRM data, higher resting heart rates were not associated with a worse outcome.[9] In contrast, in the RACE study, a more lenient rate control approach was followed (resting heart rate <100 bpm).[3] In that study, 46% of the patients were treated with a β-blocker. Severe drug adverse effects were also rare (0.8%). In contrast to AFFIRM, however, a pacemaker was implanted in only 3 (1.2%) of the 256 patients (all after atrioventricular node ablation). The data of the post hoc analysis comparing patients in RACE versus patients in AFFIRM randomized to rate control suggest that the stringency of rate control does not influence mortality and cardiovascular morbidity. Stringent rate control, as performed in AFFIRM, was associated with similar rates of a composite end point of major clinical events and with similar overall survival rates but with more pacemaker implantations.[10] In a pooled analysis of both study groups, however, we observed a significant increased probability of a composite event in the highest heart rate group (ie, heart rate above RACE criteria, which means a resting heart rate >100 bpm) on outcome.[10] However, this non-randomized analysis is plagued by a number of methodology issues. In the case of pacemaker implantations, it cannot be determined how much of the association was due to stringent heart rate control and how much was due to continental differences in the threshold for pacemaker implantation. Furthermore, the lack of randomization means there were inherent baseline differences in the two studies. In another post hoc analysis of patients with AF in the setting of advanced heart failure, we observed that higher heart rates at baseline were not associated with a worse survival.[11] In contrast to the latter findings, Khand et al[12] observed that in patients with an impaired left ventricular function and AF, a more strict rate control approach may be beneficial. They randomized patients with heart failure (left ventricular ejection fraction averaging 24%) and AF to carvedilol plus digoxin or to digoxin alone. After a follow-up of 4 months, heart rate was significantly lower in the patients treated with the combination of drugs, compared with the patients who were treated with digoxin alone (65 ± 15 vs 75 ± 11, $P <$ .0001). Compared with placebo, the addition of carvedilol to digoxin significantly improved left ventricular ejection fraction (24% ± 7% to 31% ± 10%, $P < .05$). Whether this observation is due to heart rate control itself or a salutary effect of β-blockade in patients with congestive heart failure cannot be determined. Furthermore, whether such more stringent heart rate control translates into a survival benefit and a reduced morbidity remains to be seen. A strategy producing a higher ejection fraction does not necessarily guarantee improved overall morbidity and mortality, especially if the eventual ejection fraction is still low. Uncertainty about the role of β-blockers under these circumstances remains because the Cardiac Insufficiency BIsoprolol Studies (CIBIS) did not show a survival benefit with β-blockade in the subgroup of heart failure patients who also had AF.[13]

Heart failure and neurohormonal activation

Heart failure is characterized by neurohormonal activation, including activation of the sympathetic nervous system and the renin-angiotensin system, and an increase in natriuretic peptides (atrial and brain natriuretic peptides [ANP and BNP]). ANP is produced mainly in the atria and BNP mainly in the ventricles, the main stimulus for secretion of both hormones is thought to be stretch of the myocytes. Both ANP and BNP correlate with hemodynamic status and carry prognostic information in patients with heart failure. More recently, N-terminal proBNP (NT-proBNP) has been shown to be of value, in particular given its stable plasma levels as compared with BNP. Atrial fibrillation causes additional neurohormonal activation, including increased ANP and BNP.[14,15] However, longstanding AF can cause irreversible damage to

the atria, thereby reducing ANP production capacity.[16] If anything, this phenomenon suggests ANP is less suitable for monitoring hemodynamic status in patients with AF. In contrast, (NT-pro)BNP, which is not produced by atrial myocytes, would appear more suitable for monitoring hemodynamic status in patients with AF. The aim of the neurohormonal substudy in the present protocol is to buttress the hypothesis that lenient rate control is not inferior to strict rate control.

Study design and methods

The RACE II study (Figure 1) is being conducted in 29 centers in The Netherlands. The institutional review board of each institution approved the study, and all patients gave written informed consent. Recruitment began in January 2005, randomization is expected to be concluded in June 2006, and follow-up will be terminated in June 2008. At present, 375 patients have been included. The trial is funded by grants from the Netherlands Heart Foundation and the Interuniversity Cardiology Institute, The Netherlands.

Hypothesis, patient selection, and randomization

The primary hypothesis of the RACE II study is that lenient rate control is not inferior to strict rate control in patients with permanent atrial fibrillation, with or without heart failure, in terms of cardiovascular mortality and morbidity, neurohormonal activation, New York Heart Association (NYHA) class for heart failure, left ventricular function, left atrial size, QoL, and costs. Cardiovascular morbidity in this trial is defined as a composite of hospitalization for left or right ventricular heart failure, stroke, systemic emboli, bleeding, arrhythmic or potential arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, pacemaker or internal cardioverter defibrillation implantation. Stroke is defined as a disabling hemorrhagic, ischemic, or undetermined stroke confirmed by a neurologist on the basis of computerized tomography or magnetic resonance imaging and necessitating hospitalization. Systemic emboli have to be confirmed by a physician, typically with some type of imaging, and require hospitalization. Bleeding is defined as a bleeding episode where the hemoglobin value decreased by >2 g/L or required blood transfusion or hospitalization or was fatal. Syncope is defined as sudden temporary loss of consciousness associated with a loss of postural tone with spontaneous recovery not requiring electrical or chemical cardioversion. Sustained ventricular tachycardia must be documented on electrocardiogram (ECG) and requires hospitalization. Cardiac arrest is defined as a circulatory arrest requiring resuscitation and hospital admission. Life-threatening adverse effects of rate control drugs include digitalis

Figure 1
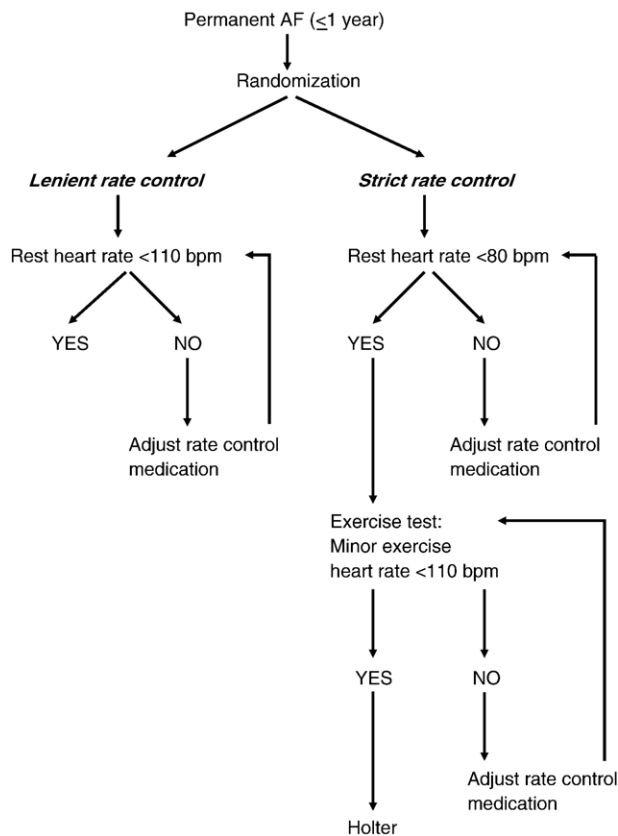
Flow chart of lenient and strict rate control.

intoxication, drug-induced heart failure, and conduction disturbances necessitating hospital admission. A committee of experts who are unaware of the treatment assignments will adjudicate all possible end points. Each component of the primary composite end point will also be a secondary end point.

To be eligible, patients must meet all of the following criteria: (1) a current episode of permanent AF ≤12 months documented on two consecutive ECGs (without known spontaneous conversion), (2) age ≤80 years, (3) mean resting heart rate >80 bpm with or without rate control medication, and (4) oral anticoagulation (or aspirin if no risk factors for thromboembolic complications are present).

The exclusion criteria are as follows: (1) paroxysmal AF, (2) known contraindications for either strict or lenient rate control (eg, previous adverse effects on negative chronotropic drugs), (3) unstable heart failure defined as NYHA IV heart failure or heart failure necessitating hospital admission <3 months before inclusion, (4) cardiac surgery <3 months, (5) any stroke,

(6) current or foreseen pacemaker, internal cardioverter defibrillator, and/or cardiac resynchronization therapy, (7) signs of sick sinus syndrome or AV conduction disturbances (ie, symptomatic bradycardia or asystole >3 seconds or escape rate <40 bpm in awake symptom-free patients), (8) untreated hyperthyroidism or <3 months euthyroidism, (9) inability to walk or bike.

Discontinuation of rate control drugs before inclusion to meet the inclusion criteria is not allowed. Patients are randomized in an open-label fashion to the strict or lenient rate control arm. Randomization is accomplished at the Trial Coordination Center by an automated randomization accessible electronically. To randomize a patient, the clinical site must have available the completed eligibility forms, the signed consent form, the sequential patient number, the center number, and the authorization code. Randomization is stratified according to study center. Random permuted blocks are used and the block sizes are varied randomly at the various sites.

After informed consent, patients will be randomized to (*a*) strict or (*b*) lenient rate control therapy.

Therapy for strict rate control

Therapy for strict rate control is defined as a mean resting heart rate (12-lead resting ECG) <80 bpm and heart rate during minor exercise (at 25% of the maximal achieved exercise time during bicycle exercise test) <110 bpm. Exercise test to determine activity heart rates will only be performed after reaching the resting target heart rate. After achievement of the rest and activity rate control targets as defined for this group, a 24-hour Holter monitoring will be done to check for bradycardia (Figure 1). If the patient remains symptomatic due to AF after achieving rate control as defined above, 24-hour Holter monitoring or exercise tests may be deemed necessary by the attending physician. These investigations may lead to adjustment of rate control drugs or atrioventricular node ablation and even electrical cardioversion or arrhythmia surgery (attending physician's choice). Nevertheless, analysis is based on an intention-to-treat basis, although such crossovers will be noted.

Therapy for lenient rate control

Lenient heart rate control is defined as a heart rate <110 bpm on a 12-lead resting ECG (Figure 1). If the patient remains symptomatic due to AF after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the attending physician. These evaluations may be followed by adjustment of rate control drugs or atrioventricular node ablation and even electrical cardioversion or arrhythmia surgery (attending physician's choice). If the heart rate target <110 bpm cannot be achieved, Holter monitoring or exercise tests may be deemed necessary by the attending physician. These evaluations may be followed

by atrioventricular node ablation and even electrical cardioversion or arrhythmia surgery (attending physician's choice). As noted above, however, primary analysis is by intention-to-treat.

Rate control medication

Primary therapy is pharmacological using β-blockers, calcium-channel blockers, and digoxin, alone or in combination. It is encouraged that maximal dosages of individual rate control drugs are instituted before adding/switching to an alternative choice rate control medication. Secondary pharmacological therapies include sotalol or amiodarone, but use of these drugs for heart rate control is strongly discouraged, although not strictly (alone or in combination with one or more of the primary pharmacological therapies) when rate control cannot be achieved with first choice drugs. Pacing therapies, alone or with atrioventricular node ablation, are utilized as indicated in the view of the treating physician.

Follow-up and outcome events

Patients will be seen after 1, 2, and 3 months (until adequate titration of rate control therapy is as required), whenever study end points are detected, and after 1 and 2 years at the outpatient department in the absence of end points (Figure 2). The last study visit (end of study) is planned 3 years after start of the study so individual duration of follow-up will vary between 2 and 3 years.

The primary end point is defined above. In addition to individual components of the primary end point, secondary end points include (*a*) all-cause mortality; (*b*) cardiovascular hospitalizations; (*c*) NYHA class for exercise tolerance, left ventricular function, and left atrial size determined by echocardiography; (*d*) QoL, using a variety of general and AF-specific instruments; (*e*) neurohormonal activation, measured by NT-proBNP; (*f*) hospitalization for new or worsened heart failure; (*g*) hospital admission for unstable angina pectoris or myocardial infarction; (*h*) renal function; and (*i*) costs.

Quality of life

Quality of life will be studied using the Short Form–36 health survey questionnaire, the Minnesota Living with Heart Failure questionnaire, and the Toronto Atrial Fibrillation Severity Scale at inclusion, after 1 and 2 years of follow-up, and at the end of study visit.

Economic evaluation

Costs will be calculated from a societal perspective. All relevant costs inside and outside the health care system are taken into account. Direct medical costs, direct nonmedical costs, and indirect nonmedical costs are calculated. The time horizon of the economic evaluation will be equal to that of the clinical study.

Figure 2

	0 (1)(2)(3)	12	24	months	36
NYHA	x	x	x		x
RR	x	x	x		x
ECG	x (x)(x)(x)	x	x		x
exercise	**X**	**X**	**X**		**X**
HM	**X**	**X***	**X***		**X***
Echo	x				x
Creatine	x	x	x		x
QoL	x	x	x		x
Costs		x	x		x
BNP	x	x	x		x

— **Only strict group**   (x): only if necessary   *: only after dosage change

Follow-up. *HM*, Holter monitoring; *RR*, hypertension.

Costs and effects in year 2 and 3 of the study will be discounted at a discount rate of 4%. In addition, sensitivity analysis will be performed in which the influence of the major cost categories and the discount rate will be varied to estimate the effect on the total costs. Data about costs of hospital stay, outpatient visits, medication, and pacemaker implants are collected throughout the study period using case records forms. Information on costs not made in the hospitals, general practitioner visits, professional and nonprofessional help, and productivity losses is collected through self-administered patient questionnaires. If the study results show no significant difference regarding morbidity, mortality, or QoL, a cost minimization analysis will be performed to determine which treatment option is most cost-effective, otherwise a cost-effectiveness or a cost-utility analysis will be performed.

Neurohormones

NT-proBNP will be measured at baseline and after each year (including the end of study visit). Three to four samples per patient will thus be obtained. Values of NT-proBNP will not be available for the attending physician during the course of the study.

Pacemaker indication

According to The Netherlands guidelines, symptomatic bradycardia or asystole >3 seconds or an escape rate <40 bpm in awake symptom-free patients are indications for permanent pacing. If necessary, drug dose reduction and/or pacemaker implantation will be performed as needed. Pacemaker implantation is part of the primary end point.

Electronic data collection

All data will be recorded electronically and will be transferred to the server holding the central database at the Trial Coordination Center, which is regularly backed up and password protected. The electronic case record forms are monitored at regular times by the study monitor.

End point monitoring

All (possible) end points will be sent (by fax or mail) to the Trial Coordination Center (University Medical Center Groningen, Groningen, The Netherlands) as soon as they are detected. Missing data will be gathered as expediently as possible for review by the end point adjudication committee.

Concomitant medication

Patients will be treated for their underlying heart disease according to established guidelines, including maximal β-blocking therapy and angiotensin-converting enzyme inhibitors for heart failure and lipid-lowering therapy in case of coronary artery disease.

Anticoagulation

All patients must be on oral anticoagulation at inclusion (acenocoumarol or fenprocoumon, INR 2.5-3.5) as directed according to guidelines. Patients without risk factors for thromboembolic complications may be treated with aspirin.

Statistical considerations

Sample size determination and statistical analysis

The primary aim is to show noninferiority of lenient rate control as compared with strict rate control in terms of the primary end point. The expected incidence of the primary end point in both groups is 25%. Noninferiority will be established if it is shown that the absolute difference in the incidence of the primary end point does not exceed 2.5% (relative difference is ≤10%). To achieve a power of at least 80% with a 95% confidence limit (1-sided test with $\alpha = 5\%$), 250 patients in each treatment arm are required. Because all secondary analyses are exploratory, no formal sample size calculations have been done. Repeated measurements analysis will be used to analyze changes over time. Statistical evaluation will be performed according to the intention-to-treat principle. Kaplan-Meier techniques will be used to describe the occurrence of the primary end point over time.

Conclusions

Rate control is now first choice therapy in many patients with AF. However, the optimal heart rate during AF is unknown. The ACC/AHA/ESC guidelines recommend a heart rate between 60 and 80 bpm in rest and 90 and 120 bpm during moderate exercise. Although, these recommendations are arbitrary and are not evidence based. The results of this trial should provide information concerning two widely applicable treatment strat-

egies in typical permanent AF patients. Clinical decision making will be improved regardless of outcome. If a lenient rate control approach is not inferior, it will facilitate therapy of AF for the patient and the physician and probably will lower costs. If not, the therapy proposed by the ACC/AHA/ESC guidelines will after a long wait find their basis in the clinical evidence.

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Appendix A
RACE II Investigators

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Appendix B
Steering committee

The steering committee includes Isabelle C. Van Gelder (chair), MD, Maarten P. Van den Berg, MD, Harry J.G.M. Crijns, MD, Ype S. Tuininga, MD, A. Marco Alings,

MD, Hans A. Bosker, MD, Jan H. Cornel, MD, Otto Kamp, MD, Jan G.P. Tijssen, PhD, Nic J.G.M. Veeger, MSc, Dirk J. Van Veldhuisen, MD.

Appendix C
End point adjudication committee

This committee of experts, masked to the treatment assignments, who will adjudicate all possible end points includes Jan Van der Meer, MD, hematologist (chair), Johan Brügemann, MD, cardiologist, and Gert-Jan Luijckx, MD, neurologist.

Appendix D
Advisory board

The advisory board includes A. John Camm, MD, D. George Wyse, MD, PhD, Albert L. Waldo, MD, John G.F. Cleland, MD.

Appendix E
Data Safety and Monitoring Board

Tha data safety and monitoring board includes Hein J.J. Wellens, MD (chair), Arthur A.W. Wilde, MD, and Richard N. Hauer, MD.