Lenient Rate Control in Heart Failure

Abstract
Aims
It is unknown whether lenient rate control is an acceptable strategy in patients with atrial fibrillation (AF) and heart failure. We evaluated differences in outcome in patients with AF and heart failure treated with lenient or strict rate control.

Methods and results
This post-hoc analysis of the RACE II trial included patients with a left ventricular ejection fraction (LVEF) ≤ 40% at baseline or a previous hospitalization for heart failure or signs and symptoms of heart failure. Primary outcome was a composite of cardiovascular morbidity and mortality. Secondary endpoints were AF related symptoms and quality of life. Two hundred eighty-seven (46.7%) of the 614 patients had heart failure. Patients with heart failure had significantly higher NT-proBNP plasma levels, a lower LVEF, and more often use of angiotensin converting enzyme, angiotensin receptor blockers and diuretics. At 3 years follow up the primary outcome occurred more frequently in patients with heart failure (16.7% versus 11.5%, p=0.04). In heart failure patients the estimated cumulative incidence of the primary outcome was 15.0% (n=20) in the lenient and 18.2% (n=26) in the strict group (p=0.53). No differences were found in any of the primary outcome components, neither in heart failure hospitalizations (8 [6.1%] versus 9 [6.8%] patients in the lenient versus strict group, respectively), nor in symptoms, nor quality of life.

Conclusion
In patients with AF and heart failure with a predominantly preserved ejection fraction stringency of rate control seems to have no effect on cardiovascular morbidity and mortality, symptoms, and quality of life.
Introduction

Atrial fibrillation (AF) and heart failure have been named the two epidemics in cardiovascular disease of the 21st century and often coexist. (1-3) Previously, every effort was made to maintain sinus rhythm but long term success was poor. (4-6) Recent studies have shown that rate control is not inferior to pharmacological rhythm control with regard to cardiovascular morbidity and mortality. (7,8) Similar findings have been observed in patients with chronic heart failure. (9,10) Therefore, rate control may now be adopted as first choice treatment in patients with and without heart failure without severe symptoms. (11) The optimal level of heart rate control with respect to morbidity, mortality, quality of life and symptoms was never investigated. The recently published RAte Control Efficacy in permanent AF II (RACE II) trial showed that lenient rate control was not inferior to strict rate control therapy. (12) Whether this is also applicable for patients with AF and heart failure is unknown.

Therefore we undertook the present post-hoc analysis of RACE II in patients with left ventricular ejection fraction (LVEF) ≤ 40% or a previous hospitalization for heart failure or signs and symptoms of heart failure, to test the hypothesis that lenient rate control is comparable to strict rate control in patients with AF and heart failure in terms of cardiovascular outcome, symptoms and quality of life.

Methods

Study population

This analysis includes patients randomized into the RACE II trial stratified by the presence of heart failure. For the present study, patients were classified as having heart failure in the presence of a LVEF ≤ 40% at baseline or LVEF > 40% with symptoms associated with heart failure (New York Heart Association [NYHA] functional class II or III), or previous hospitalization for heart failure. The study design, patient characteristics, and results of the RACE II study have been published previously. (12,13) In short, the RACE II study was a Dutch randomized multicenter study comparing long-term effects of lenient versus strict rate control on morbidity and mortality in 614 patients with permanent AF. Patients randomized to lenient rate control had a resting heart rate target < 110 beats per minute. Patients randomized to strict rate control had two heart rate targets: a resting heart rate target < 80 beats per minute and a heart rate target during moderate exercise < 110 beats per minute. Patients were administered one or more negative dromotropic drugs until the heart rate target(s) were achieved. After achievement of the rest and activity heart rate targets in the strict group, 24-hour Holter monitoring was performed to check for bradycardia. Follow-up outpatient visits occurred every two weeks until the heart rate target(s) were achieved (dose-adjustment phase), and in all patients after 1, 2, and 3 years. Follow-up was terminated after a follow-up period of 3 years or on June 30, 2009, whichever came first.

N-terminal prohormone of brain natriuretic peptide

After inclusion at the outpatient clinic 10 cc blood was collected by vein puncture into an EDTA-tube. Within 1 hour, the tube was centrifuged for 10 minutes, and the plasma was removed and stored at −80°C at the local hospital. After completion of the study, all samples were transported (on dry ice) to the core laboratory of the University Medical Center Groningen, the Netherlands for analysis. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) measurements were performed in plasma on a Roche Modular E170 analyzer, a commercially available electrochemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany). Overall machine day-to-day variation was 2.2% (at level of 126 pg/ml) and 2.0% (at level of 4230 pg/ml), with an analytical range of 5-35000 pg/ml. NT-proBNP was determined at baseline and end of study.

Outcome

The primary outcome was a composite of cardiovascular death, hospitalization 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. (12)

Quality of life

The Dutch version of The Medical Outcome Study Short Form-36 (SF-36) was used to assess quality of life. It contains items to assess physical and mental health. Severity of AF-related symptoms was assessed with the University of Toronto AF Severity Scale. (14)
Questionnaire is a patient self-assessment measure being developed to evaluate the therapeutic response to interventions for heart failure. (15)

Statistical Analysis
Baseline descriptive statistics are presented as mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Differences between patients treated with lenient or strict rate control were evaluated by the Student-t-test, Mann-Whitney-U test, Chi-square test, and Fisher’s exact test depending on normality and type of the data. The first occurrence of the composite primary outcome was assessed by Kaplan-Meier curves. All tests of significance were two-tailed, with p-values of <0.05 assumed to indicate significance. All analyses were generated using STATA 11.0 for Windows.

Results
Baseline characteristics
Of 614 patients randomized into RACE II, 287 (47%) had heart failure. Heart failure was present in 93 of 287 patients (32.4%) because of a LVEF ≤ 40% at baseline, in 149/287 (51.9%) because of LVEF > 40% with symptoms and in 45/287 (15.7%) because of previous hospitalizations for heart failure. Patients with heart failure differed significantly from those without heart failure (n=327, 53%): they had significantly higher levels of NT-proBNP (1189 pg/ml vs. 877 pg/ml, p<0.001), a lower LVEF (47 vs. 56, p<0.001), and used more often angiotensin converting enzyme inhibitors or angiotensin receptor blockers (55.1% vs. 45.3% p=0.015), and diuretics (47.7% vs. 29.7% p<0.001) at baseline. Table 1 shows baseline characteristics of the present population of 287 patients with heart failure randomized to lenient or strict rate control.

Dose-adjustment phase
Table 2 shows data recorded at the end of the dose-adjustment phase. Lenient rate control was easier to achieve. Patients were instituted on fewer rate control drugs and lower dosages. Fewer hospital visits were necessary. The mean resting heart rate was 94±11 beats per minute in the lenient versus 76±12 in the strict group (p<0.001). After 1 and 2 years and at the end of follow-up, the resting heart rates in the lenient group were 84±13, 83±13, and 85±14.
beats per minute, respectively, as compared with 76±12, 75±12, and 76±15 beats per minute, respectively, in the strict group (p<0.001 for comparisons between the two groups).

### Table 2. Rate Control Target and Drug Therapy at the End of the Dose-Adjustment Phase, According to Treatment Group.*

<table>
<thead>
<tr>
<th>Rate control target or targets achieved – no. (%)</th>
<th>Lenient rate control (n=138)</th>
<th>Strict rate control (n=149)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate control target or targets achieved – no. (%)</td>
<td>134 (97.1)</td>
<td>108 (72.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 beats per minute</td>
<td>1 (0.7)</td>
<td>33 (22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70 to 80 beats per minute</td>
<td>3 (2.2)</td>
<td>87 (58.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80 to 90 beats per minute</td>
<td>47 (34.1)</td>
<td>13 (8.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90 to 100 beats per minute</td>
<td>51 (37.0)</td>
<td>9 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;100 beats per minute</td>
<td>36 (26.1)</td>
<td>7 (4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at 1 year</td>
<td>84±13</td>
<td>76±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at 2 years</td>
<td>83±13</td>
<td>75±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at end study</td>
<td>85±14</td>
<td>76±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate target achieved – no. (%)</td>
<td>134 (97.1)</td>
<td>120 (80.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise heart rate target achieved – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean heart rate – beats per minute</td>
<td>117 (78.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holter monitoring†</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean heart rate – beats per minute</td>
<td>78±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to achieve rate control target or targets – total no.</td>
<td>41</td>
<td>347</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>0 (0-0)</td>
<td>2 (1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reasons for failure to achieve rate control target or targets – no./ total no. (%)</td>
<td>5/5 (100.0)</td>
<td>17/41 (41.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No rate control drugs</td>
<td>7 (5.1)</td>
<td>1 (0.7)</td>
<td>0.024</td>
</tr>
<tr>
<td>Beta-blocker alone</td>
<td>62 (44.9)</td>
<td>30 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verapamil or Diltiazem alone</td>
<td>8 (5.8)</td>
<td>8 (5.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Digoxin alone</td>
<td>8 (5.8)</td>
<td>1 (0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Beta-blocker and either verapamil or diltiazem</td>
<td>8 (5.8)</td>
<td>18 (12.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Beta-blocker and digoxin</td>
<td>25 (18.1)</td>
<td>49 (33.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Digoxin and either verapamil or diltiazem</td>
<td>12 (8.7)</td>
<td>19 (12.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Beta-blocker, digoxin, and either verapamil or diltiazem</td>
<td>1 (0.7)</td>
<td>17 (11.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>82 (59.4)</td>
<td>80 (53.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diuretics</td>
<td>74 (53.6)</td>
<td>82 (55.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>Dose – mg. (no. of patients)</td>
<td>129±82 (98)</td>
<td>167±91 (116)</td>
<td>0.001</td>
</tr>
<tr>
<td>Beta-blocker (normalized to metoprolol-equivalent doses)</td>
<td>171±62 (25)</td>
<td>219±106 (63)</td>
<td>0.036</td>
</tr>
<tr>
<td>Verapamil</td>
<td>215±75 (4)</td>
<td>200 (1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.2±0.1 (49)</td>
<td>0.2±0.1 (90)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Plus–minus values are means±SD. ACE = angiotensin converting enzyme; ARB = Angiotensin receptor blockers. The strict-control group had two heart-rate targets (resting and exercise), whereas the lenient-control group had only one (resting). According to the protocol, exercise tests and 24-hour Holter monitors were only performed in the strict group.

Figure 1. Kaplan-Meier estimates of the cumulative incidence of the primary outcome, according to treatment group in patients with heart failure. The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

**Lenient versus strict rate control in patients with heart failure**

Kaplan-Meier curves for the primary outcome are shown in Figure 1. Among patients with heart failure the 3-year estimated cumulative incidence was 15.0% in the lenient and 18.2% in the strict group (Hazard Ratio [HR] 0.83; 95% Confidence interval [CI] 0.46-1.49, Table 3). There were no differences in the components of the primary outcome, including heart failure hospitalizations. None and only 1 death were due to progression of heart failure in the lenient and strict group, respectively. All cause mortality occurred in 10 in the lenient (7.7%) versus 10 patients in the strict group (7.5%).

**Quality of life**

No differences in the SF-36, AF severity scale and the Minnesota living with heart failure questionnaires were observed at baseline as well as at end of study (Figure 2).
no significant changes occurred in both groups: from a median of 1197 pg/ml at baseline to 1029 pg/ml (IQR, 633-1544) at end of follow-up (p=0.01) in the lenient, and from 1162 pg/ml to 976 pg/ml (IQR, 684-1696, p=0.26) in the strict group, respectively.

Discussion
The present post-hoc analysis of the RACE II study shows that in patients with permanent AF and heart failure with many of whom had a preserved ejection fraction the occurrence of cardiovascular morbidity and mortality is comparable between lenient and strict rate control. In addition, no differences in symptoms and quality of life were observed between both groups.

Lenient rate control in patients with heart failure
It is generally believed that a low heart rate is beneficial, both in patients with heart failure (16,17) and coronary artery disease. (18) This assumption, however, is primarily derived from studies in patients in sinus rhythm. In
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observed, and also not in a prior trial in patients with AF and moderate heart failure treated with a more lenient rate control approach.(9) Also in advanced heart failure patients, a higher heart rate was not associated with enhanced morbidity and mortality.(27) Apparently, lenient rate control in the present population led to a heart rate that was low enough to prevent excess heart failure hospitalizations and other cardiovascular morbidity and mortality.

NT-proBNP

NT-proBNP levels were high in RACE II with a median of almost 1200 pg/ml. This is remarkable as in RACE II patients were included during stable conditions at the outpatient clinic, and not during visits to the emergency department for dyspnea.(28) This may be a sign of the presence of diastolic dysfunction. Comparably, elevated median levels of NT-proBNP were observed in post-hoc analysis of Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, 800 pg/ml and 714 pg/ml respectively.(29,30)

Symptomatology

There were no differences in symptoms and quality of life between the lenient and strict group. Dyspnea was the main symptom and was significantly associated with baseline Minnesota Living with Heart Failure Questionnaire, which is associated with prognosis.(31) Thus, well-being of patients with AF seems to be associated with more factors than only heart rate and the physician should be aware that intensifying rate control therapy does not necessarily imply fewer symptoms.(32) It may even do the opposing due to increasing adverse effects associated with rate control drugs. Noteworthy, the quality of life analyses of RACE I and II concluded that underlying heart disease predominantly influences quality of life rather than strictness of rate control itself.(33,34)

Study Limitations

The results may be particularly true for patients with AF and heart failure with preserved left ventricular function since our study did not include patients with a very low LVEF and severe systolic heart failure. The present study
was a post-hoc analysis, thus it was not in essence designed to determine differences in outcome with lenient or strict rate control in patients with permanent AF and heart failure. Additionally, due to small sample size there is low statistical power. Echocardiographic assessment of diastolic function was not performed. NT-proBNP levels have been shown to be well correlated with diastolic dysfunction. (35) Finally, long-term follow up (beyond 3 years) of a lenient rate control strategy was not evaluated in RACE II.

Conclusions
In patients with permanent AF and heart failure with many of whom had a preserved ejection fraction lenient rate control seems to be as effective as strict rate control and easier to achieve. Therefore, a more lenient rate control strategy may be considered as initial treatment approach in this group of patients.

Conflict of interest
RACE II was supported by the Netherlands Heart Foundation (2003B118) and Interuniversity Cardiology Institute the Netherlands and unrestricted educational grants from AstraZeneca, Biotronik, Boehringer Ingelheim, Boston Scientific, Medtronic, Roche, and Sanofi Aventis France (paid to the Interuniversity Cardiology Institute of the Netherlands). Dr. Van Veldhuisen, board membership fees from Amgen, Vifor, BG Medicine, Sorbert, Johnson & Johnson and Biocontrol. Dr. Crijns, consulting fees from Boehringer Ingelheim, Sanofi-Aventis, and AstraZeneca, grant support from St. Jude Medical, Boston Scientific, Boehringer Ingelheim, Sanofi-Aventis, Medapharma, and Merck, and honoraria from Medtronic, Sanofi-Aventis, Medapharma, Merck, Boehringer Ingelheim, and Biosense Webster; Dr. Alings, consulting fees from Boehringer Ingelheim and Sanofi-Aventis and Dr. Van Gelder reports receiving consulting fees from Sanofi-Aventis, Boehringer Ingelheim, and Cardiome, grant support from Medtronic, Biotronik, and St. Jude Medical, and lecture fees from Sanofi-Aventis, Boehringer Ingelheim, and Medtronic.

References


