Optimal Treatment Strategy for Patients With Paroxysmal Atrial Fibrillation
—— J-RHYTHM Study ——

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Background  Although previous clinical trials demonstrated the non-inferiority of a rate control to rhythm control strategy for management of atrial fibrillation (AF), the optimal treatment strategy for paroxysmal AF (PAF) remains unclear.

Methods and Results  A randomized, multicenter comparison of rate control vs rhythm control in Japanese patients with PAF (the Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) study) was conducted. The primary endpoint was a composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/psychological disability requiring alteration of treatment strategy. In the study, 823 patients with PAF were followed for a mean period of 578 days. The primary endpoint occurred in 64 patients (15.3%) assigned to rhythm control and in 89 patients (22.0%) to rate control (P=0.0128). No significant differences between the treatment strategies were observed in the incidences of death, stroke, bleeding and heart failure. Meanwhile, significantly fewer patients requested changes of assigned treatment strategy in the rhythm control vs the rate control group, which was accompanied by improvement in AF-specific quality of life scores.

Conclusion  The J-RHYTHM study showed that rhythm control was associated with fewer primary endpoints than rate control. However, mortality and cardiovascular morbidity were not affected by the treatment strategy (umin-CTR No. C000000106).  (Circ J 2009; 73: 242–248)

Key Words:  Antiarrhythmic agents; Atrial fibrillation (AF); Mortality; Morbidity

Atrial fibrillation (AF), which is associated with increased mortality and morbidity,1-3 is a growing public health problem that has reached epidemic proportions.4,5 There has long been controversy concerning the basic question of whether reestablishment and maintenance of sinus rhythm or control of heart rate alone is better in the management of AF.6-9 Many randomized clinical trials have been conducted to answer this question, including the Pharmacological Intervention in Atrial Fibrillation (PIAF), Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), Rate Control vs Electrical Cardioversion (RACE) and Strategies of Treatment of Atrial Fibrillation (STAF) trials,10-13 but none has shown superiority of rhythm control to rate control with respect to the mortality and morbidity of AF patients.10-14

Nevertheless, in certain patients, there is an actual need to maintain sinus rhythm, not to reduce mortality and morbidity but to improve quality of life (QOL), which is quite important from the AF patient’s viewpoint.15 Moreover, previous clinical trials, focusing on AF patients with expected high mortality, under-represented certain patient groups: younger patients without risk factors for stroke, patients with severe symptoms, and, particularly, those with paroxysmal AF (PAF).10-13 Therefore, efforts should be continued to determine the optimal management of AF for various endpoints and in a variety of patients.

The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM study) was designed to determine the optimal strategic approach for AF patients, including those usually under-represented in previous trials.17 The study emphasized patient-reported experience and perception of AF-specific disability, in addition to mortality and

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Author’s institution are listed in Appendix 1.

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We herein present new data concerning rate and rhythm control strategies in patients with PAF.

Methods

Study Design

The J-RHYTHM study was a randomized multicenter comparative study of patients with PAF treated by either rate or rhythm control. Study design details are published elsewhere. PAF was defined as AF expected to convert spontaneously to sinus rhythm within 48 h of onset. Exclusion criteria included initial AF episodes, contraindication for anticoagulation, and AF occurring during the acute phase of myocardial infarction or cardiac surgery. Patients were randomly assigned to either the rate control or rhythm control treatment group. In the rate control group, control of heart rate itself was by β-blockers, calcium-channel blockers, and digitalis. In the rhythm control group, antiarrhythmic drugs were selected according to “The Japanese Guideline for Atrial Fibrillation Management.”

Oral antithrombotic therapy was used in both rate and rhythm control arms according to a protocol modified from that used in the AFFIRM study. Factors for assessment of stroke risk included age >65 years, hypertension, diabetes mellitus, congestive heart failure, history of stroke/transient ischemic attack/systemic embolism, left atrial diameter >50 mm, fractional shortening <25%, and ejection fraction <40%. In patients with 1 or more factors, warfarin was prescribed to maintain the prothrombin time – international normalized ratio between 1.6 and 3.0. Anticoagulant therapy was continued throughout the study, even if sinus rhythm appeared to be maintained by rhythm control therapy. Institutional review boards in each participating clinical site approved the study protocol, and all patients gave written informed consent for the study.

Endpoints

The primary endpoint was a composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics, and physical/psychological disability requiring alteration of the assigned treatment strategy. This is the first study in which patient reluctance to continue the assigned strategy accompanied by their spontaneous desire to move to the other strategy was also included as an endpoint to represent patient disability under an assigned strategy. The cross-over would likely result from uncontrollable symptoms, hesitation to repeat cardioversion, or anxiety about the adverse effects of drugs without any life-threatening consequences, and could not be avoided without movement from 1 assigned strategy to the other. The reasons were reported by patients themselves.

Secondary endpoints were patient QOL scores, and the efficacy and safety of drugs required in AF treatment. Patient QOL was evaluated using the Japanese Society of Electrocardiology’s Atrial Fibrillation Quality of Life Questionnaire (AFQLQ), which comprises 3 subsets that include 26 questions concerning frequency of occurrence of 6 symptoms (palpitations, dizziness, shortness of breath, chest discomfort, irregular pulse, and pulse deficit) (AFQLQ1), the severity of these symptoms (AFQLQ2), and anxiety and limitation of daily activities related to AF and AF treatment (AFQLQ3).

Statistical Analysis

The primary analysis was an intention-to-treat comparison between groups of time to first event of any of those forming the composite primary endpoint. Baseline patient characteristics were compared using chi-square tests and unpaired Student’s t-test. Rates for all time-to-event analyses were estimated by the Kaplan-Meier method and were compared by the log-rank test. Secondary analyses were conducted to evaluate results within subgroups. Unadjusted hazard ratios for primary endpoint with rhythm control vs rate control were estimated in each subgroup. Covariates of age, sex, presence or absence of congestive heart failure, and presence or absence of hypertension were used to construct a multivariate Cox proportional hazards survival model by a stepwise procedure. Covariates significantly associated with primary endpoint were then used to adjust the primary treatment comparison. A 2-tailed P-value of <0.05 was considered statistically significant.

Table 1 Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Overall (n=823)</th>
<th>Rate control group (n=404)</th>
<th>Rhythm control group (n=419)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.7±11.3</td>
<td>64.5±12.3</td>
<td>64.9±10.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>570 (69.3)</td>
<td>281 (69.6)</td>
<td>289 (69.0)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>61 (7.4)</td>
<td>31 (7.7)</td>
<td>30 (7.2)</td>
</tr>
<tr>
<td>Valvular disease (%)</td>
<td>46 (5.6)</td>
<td>26 (6.4)</td>
<td>20 (4.8)</td>
</tr>
<tr>
<td>Cardiomyopathy (%)</td>
<td>13 (1.6)</td>
<td>5 (1.2)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>History of CHF (%)</td>
<td>30 (3.6)</td>
<td>16 (4.0)</td>
<td>14 (3.3)</td>
</tr>
<tr>
<td>History of TIA/thromboembolism (%)</td>
<td>52 (6.3)</td>
<td>23 (5.7)</td>
<td>29 (6.9)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>352 (42.8)</td>
<td>165 (40.8)</td>
<td>187 (44.6)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>96 (11.7)</td>
<td>48 (11.9)</td>
<td>48 (11.5)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66.4±9.9</td>
<td>66.0±10.3</td>
<td>66.7±9.4</td>
</tr>
<tr>
<td>LAd (mm)</td>
<td>38.4±7.0</td>
<td>38.4±7.1</td>
<td>38.4±6.9</td>
</tr>
<tr>
<td>CHADS2 score (%)</td>
<td>0</td>
<td>356 (43.3)</td>
<td>184 (45.5)</td>
</tr>
<tr>
<td>1</td>
<td>286 (34.8)</td>
<td>134 (33.2)</td>
<td>152 (36.3)</td>
</tr>
<tr>
<td>2</td>
<td>121 (14.7)</td>
<td>55 (13.6)</td>
<td>66 (15.8)</td>
</tr>
<tr>
<td>3</td>
<td>36 (4.4)</td>
<td>17 (4.2)</td>
<td>19 (4.5)</td>
</tr>
<tr>
<td>4</td>
<td>18 (2.2)</td>
<td>11 (2.7)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>5</td>
<td>6 (0.7)</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>

Data are mean±SD or n (%). CHF, congestive heart failure; TIA, transient ischemic attack; EF, ejection fraction; LAd, left atrial diameter.
Table 2  Drugs for Initial Therapy in the Rate Control and the Rhythm Control Groups

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate control group (n=404)</th>
<th>Rhythm control group (n=419)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker</td>
<td>208 (51.5)</td>
<td>136 (32.5)</td>
<td></td>
</tr>
<tr>
<td>CCB*</td>
<td>107 (26.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>77 (19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilsicainide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cibenzoline</td>
<td></td>
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<tr>
<td>Propafenone</td>
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<tr>
<td>Disopyramide</td>
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<td></td>
<td></td>
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<tr>
<td>Flecaïnide</td>
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<td></td>
<td></td>
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<tr>
<td>Aprindine</td>
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<tr>
<td>Pirmenol</td>
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<td></td>
<td></td>
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<tr>
<td>Bepridil</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amiodarone</td>
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<td></td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; CCB: calcium-channel blockers; DM: diabetes mellitus.

*Verapamil, diltiazem.

Fig 1.  (A) Kaplan-Meier estimate of event-free survival (composite endpoints).  (B) Event-free survival curves from mortality, embolism, major bleeding, and heart failure (Left) and from cross-over for physical/mental disability (Right).
Results

Baseline Patient Characteristics
A total of 885 patients with PAF were enrolled in the study; rate control group, n=442; rhythm control group, n=443. The average follow-up period was 578 days, and 62 patients dropped out (7.0%) during the study: rate control group, n=38; rhythm control group, n=24. Mean age was 64.7±11.3 years. Baseline clinical data are summarized in Table 1. The proportion of patients with structural heart diseases was low compared with that in trials in Western countries10–13 Only approximately 20% of the patients were considered at high risk for stroke. Low CHADS2 scores24 of 0 and 1 were observed in 43.3% and 34.8% of the patients, respectively. Patient clinical characteristics were not significantly different between the rate and rhythm control groups.

Treatment
Drugs for initial therapy in the 2 groups are outlined in Table 2. Beta-blockers were used in over 50% of patients in the rate control group. Antiarrhythmic drugs used in the rhythm control group were different from those used in previous clinical trials10–13 More than 85% of patients were started on class I drugs in accordance with the “The Japanese Guideline for Atrial Fibrillation Management”21 Amiodarone was prescribed in only 0.5% of the patients as initial therapy. The prescription rate of warfarin was high and not significantly different between groups.

Sinus Rhythm Maintenance
In the rhythm control group, sinus rhythm was observed in 87.2% of the patients at 6 months, 88.9% at 1 year, 84.3% at 2 years, and 72.7% at 3 years on periodic ECGs. In contrast, the rate control group showed significantly lower proportions of patients with sinus rhythm: 74.0% at 6 months, 69.2% at 1 year, 65.6% at 2 years, and 43.9% at 3 years.

Primary Endpoint
Event-free survival was significantly higher in the rhythm than in the rate control group (hazard ratio 0.664, 95% confidence interval 0.481–0.917; P=0.0128, Fig 1A). Components of the primary endpoint are shown in Table 3. The primary endpoint occurred in 64 (15.3%) of the 419 rhythm control patients and in 89 (22.0%) of the 404 rate control patients. Total mortality, however, was low and was not significantly different between groups (1.0% in the rhythm and 0.7% in
the rate control group). The incidence of symptomatic stroke, systemic embolisms, major bleeding or heart failure was not significantly different between groups. Consequently, there were no significant differences between the groups in the total occurrences of mortality, embolism, major bleeding and heart failure (Fig 1B). Most of the primary endpoints resulted from the patients’ desire to move to the alternate treatment strategy because of physical/psychological disability caused by their current treatment (Fig 1B). In the rhythm control group, 46 patients (11.0%) requested a change to rate control, whereas 67 rate control patients (16.6%) requested a change to rhythm control. Reasons for this endpoint differed between the groups: in the rhythm control group, it was uncontrollable symptoms in 19, anxiety over drug adverse events in 14, hesitation concerning electrical cardioversion in 6 and others in 7 patients; in the rate control group, it was uncontrollable symptoms in 56, anxiety over drug adverse events in 8 and others in 3.

**Secondary Endpoints**

The AFQLQ1 (frequency of symptoms) subset scores were higher (higher = better) in the rhythm control than in the rate control group, whereas the AFQLQ2 (severity of symptoms) and AFQLQ3 (AF-related anxiety and limitation of daily activities) subset scores improved with both treatment strategies and were not significantly different between groups (Fig 2).

Drug-related adverse events occurred very rarely: syncope in 2, ventricular tachycardia in 1, atrial flutter in 9, and symptomatic bradycardia in 4 patients. There were no significant differences in incidences between groups.

**Primary Endpoint Hazard Ratios in Subgroups**

Hazard ratios for primary endpoints in subgroups are shown in Fig 3. Rhythm control was associated with a better rate of event-free survival than was rate control among patients aged ≥65 years, male patients, hypertensive patients, and those without previous history of congestive heart failure.

**Discussion**

The present study shows that in PAF patients the mortality and cardiovascular morbidity are not affected by treatment strategy, and also that rhythm control is associated with fewer occurrences of the patient’s desire of cross-over than rate control strategy. The study population was quite different from that in past clinical trials completed in the US and Europe, comprising relatively young and symptomatic patients with PAF. The present findings substantiate the importance of individualizing PAF therapy.

**Cardiovascular Mortality and Morbidity in PAF**

For clinicians, AF type (paroxysmal, persistent, or permanent) may be a simple surrogate marker for designing a therapeutic strategy, as reflected in many guidelines published previously. The present study focused on PAF, which is different from previous clinical trials. In the present study, total mortality and cardiovascular morbidity rates were remarkably low compared with those in the previous studies, in which most or all patients had persistent AF. However, low mortality and morbidity rates should be attributed to patient comorbidities rather than AF type. The J-RHYTHM study patients were characterized by PAF, young age, no structural heart diseases, and no previous history of congestive heart failure, all of which may predict good prognosis and only approximately 20% of patients were at high risk for stroke. These low comorbidities would lessen the role of the treatment strategy in the mortality and cardiovascular morbidity of these PAF patients.

**Disability Requiring Alternation of Assigned Strategy**

In these lower risk patients, safe and effective control of symptoms should be the clinician’s primary goal, and thus an important guide when selecting a therapeutic strategy. Although disability requiring cross-over was more frequently observed in the rate control group, more important was that the reasons for the movement between the strategies were different. In rate control patients, the reason was mainly uncontrollable symptoms. In contrast, in rhythm control patients, the reasons were mostly hesitation over drug-related adverse events or electrical cardioversion, indicating the presence of some conservative patients. These diversities in this study population emphasize the importance of individualizing PAF therapy.

We should realize that the endpoint representing patient acceptance in our study may be biased by the impressions of both patients and physicians who were unblinded to treatment strategy. To substantiate this subjective assessment, we used the AF-specific questionnaire, the AFQLQ. Both treatment strategies significantly improved QOL scores in the 3 AFQLQ subsets, with a significant difference only in...
the AFQLQ1 scores between groups. These facts would support the validity for the occurrence of the cross-over in view of AFQLQ1, and at the same time, could imply possible information bias by the physicians in view of AFQLQ2 and AFQLQ3. Therefore, we should not overestimate the beneficial effects of rhythm control strategy on the QOL of the patients, but should focus upon individualizing therapy. Conversely, it is noteworthy that approximately 80% of the PAF patients undergoing rate control were satisfied with the assigned strategy.

Subgroup Analysis

Subgroup analysis, showing a relationship between the occurrence of the primary endpoints and clinical background, indicated that the lower incidence of cross-over in the rhythm control group was not uniformly observed in the present PAF patients. The rhythm control strategy resulted in better composite primary endpoints in elderly and male patients, whereas the 2 strategies were not significantly different in young and female patients. These results suggested that age and gender might affect the psychological perception of AF therapy.

Study Limitations

First, in the present study, therapeutic strategies were not blinded to physicians and patients, which could lead to biases in the occurrence of endpoints. Second, in the assessment of control of PAF, transtelephonic monitoring could not be used to evaluate drug effects on PAF, such as prevention of episodes or heart rate control during episodes. Selection of drugs and dosage was dependent primarily on the evaluation of patient symptom reports by attending physicians. Third, most patients in the present study had no structural heart disease. Although limited, the present study, by clarifying the role of the rhythm or rate control strategy in the mortality, morbidity and QOL of PAF patients, supports the importance of individualizing PAF therapy.

Conclusion

The J-RHYTHM study showed that a rate control strategy of PAF is equivalent to a rhythm control strategy in terms of mortality and morbidity. However, event-free survival of the primary endpoint in this study was significantly higher with the rhythm control than with the rate control strategy, implying the importance of individualizing PAF therapy according to the patient’s background and QOL.

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References


Appendix 1

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Appendix 2

The J-RHYTHM Investigators