As the Japanese population ages and the number of patients with atrial fibrillation (AF) increases, the management of this arrhythmia gains importance; however, it is unclear what is the most effective therapeutic strategy. For the present study, we selected for investigation 2 strategies that are based on totally distinct concepts: (1) rhythm control that pursues the maintenance of sinus rhythm and (2) rate control that accepts the AF, but controls the ventricular response. Two previous multicenter studies, the AFFIRM study in the United States and Canada1–4 and the RACE study in the Netherlands5,6 investigated these strategies with patient mortality as the primary end-point and neither found a significant difference in mortality between the 2 strategies; both studies recommended the use of anticoagulation with any treatment strategy. Although these important trials produced the first clinical evidence concerning treatment for AF, the results cannot be applied directly to AF patients in Japan for several reasons;7,8 the studies did not differentiate between paroxysmal and persistent AF,1–4 a distinction that should inform any treatment decision; the studies did not assess AF-specific quality of life (QOL).1,4–6

The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM study) is a randomized comparative evaluation of rate control and rhythm control, both combined with antithrombotic therapy, as therapeutic strategies for the treatment of atrial fibrillation (AF). This study differs from the earlier AFFIRM and RACE studies in that it has a composite primary end-point representing mortality and also physical/psychological disablement (total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics, and patient disablement). Patients’ will to change the therapeutic strategy to the other is also considered as an end-point representing disablement under the assigned strategy. The secondary end-point includes quality of life scores and the efficacy and safety of drugs used in treating AF. The J-RHYTHM study emphasizes patient-reported experience and perception of AF-specific disablement, and the safety of antiarrhythmics available in Japan; it will follow 2,600 patients treated at more than 150 sites in Japan for a 3-year period. (Circ J 2003; 67: 738–741)

Key Words: Antiarrhythmic drugs; Atrial fibrillation; Quality of life

Objectives, Implementation, and Design of the J-RHYTHM Study

Primary Objectives

The J-RHYTHM study will investigate and compare the usefulness of rhythm control therapy and rate control therapy in patients with paroxysmal or persistent AF with a composite primary end-point of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics, or physical/psychological disablement requiring discontinuation of the assigned therapu-
tic strategy. In the present study, for the first time, patients’ will to move to the other strategy is also included as an end-point representing patients’ disablement under the assigned strategy, because it should be an important factor in clinical decision making and because, as the earlier studies reported, there is no significant difference in mortality between the 2 treatment options. The most likely causes of patient disablement are uncontrollable symptoms, hesitation in repeating cardioversion, or anxiety about the adverse effects of drugs without any life-threatening consequences, and could not be avoided without movement from one assigned strategy to the other.

The composite secondary end-point of this study is patient QOL scores and the efficacy and safety of drugs required in the AF treatment. In contrast with the AFFIRM and RACE studies, our study will analyze AF-specific QOL as assessed by an original questionnaire and general health-related QOL (vide infra).

Secondary Objective

The secondary objective of the present study is to verify the usefulness of ‘The Japanese Guideline for Atrial Fibrillation Management’ produced by the Japanese Circulation Society.10

Study Design

J-RHYTHM is a randomized multicenter comparative study of paroxysmal and persistent AF under treatment by the rhythm control strategy and by the rate control strategy. Paroxysmal AF is defined as AF in which spontaneous conversion to sinus rhythm is expected within less than 48 h of onset, and persistent AF is defined as AF that persists for 48 h or more, and less than 1 year after onset.

After giving informed consent, the patients will be separated and randomly assigned to one of 2 treatment groups: the rate control group, to be treated by heart rate control in combination with antithrombotic therapy, and the rhythm control group, to be treated by rhythm control with antiarrhythmic drugs in combination with antithrombotic therapy. At the time of randomization, investigators will confirm the presence of sinus rhythm in patients with paroxysmal AF (sinus rhythm check start), so that electrical or pharmacological cardioversion can be performed before treatment if necessary, and the presence of AF will be confirmed in patients with persistent AF (AF check start). If they are assigned to the rhythm control group, electrical cardioversion will be performed to recover sinus rhythm and in the event of unsuccessful cardioversion, the patients will be treated by the rate control strategy (Fig 1).

The exclusion criteria are as follows.

1. Persistent AF lasting 1 year or longer, and permanent AF.
2. Initial episode of paroxysmal AF.
3. AF that has occurred within 1 month of the onset of myocardial infarction.
4. Transient AF associated with cardiac surgery.
5. Requirement of continuous treatment with \( \beta \)-blockers and \( Ca \) antagonists, excluding dihydropyridines, that affect the heart rate.
6. AF with a history of 2 or more electrical cardioversions.
7. Contraindication for anticoagulation therapy.
8. Pregnancy or possibility of pregnancy, and breast feeding.
9. Judgment by attending physician that patient participation would be inappropriate.

Each patient will read and sign the informed consent form approved by the institution where he or she will be participating in the study.

Baseline Tests

Before randomization, the patients will undergo clinical assessment, which will include patient history with quantification of AF duration, frequency, and predisposing factors, and a physical examination. Specified cardiac tests including electrocardiography, chest X-ray, and echocardiography will be also performed.

The QOL of the patients will be evaluated by a questionnaire comprising general health-related and also AF-specific QOL as assessed by an original questionnaire and general health-related QOL (vide infra).
Interventions

Rhythm Control Group  The antiarrhythmic drugs will be selected on the basis of ‘The Japanese Guidelines for Atrial Fibrillation Management’ according to the attending physician’s assessment of the patient’s cardiac function. Patients with persistent AF who are assigned to the rhythm control group will receive electrical cardioversion with prior administration of antiarrhythmic drugs. If pharmacological cardioversion is successful, the same drugs will be continued thereafter, but if the follow-up examination shows that the selected drugs are ineffective or adverse, either pharmacological or electrical cardioversion will be performed as required before changing the drug regimen. The drug dosages will be determined by the attending physician with consideration of the patient’s history including age, renal and hepatic function, and underlying heart diseases.

Heart Rate Control Group  As in the AFFIRM study, the therapeutic purpose in this group is the control of the heart rate itself rather than of the doses of drugs administered. The target heart rate is 60–80 beats/min at rest. Patients will receive digitalis, Ca antagonists (excluding bepridil), or β-blockers as required, selected on the basis of the patient’s clinical background. The selection of drugs and their dosages will be adjusted as necessary.

Antithrombotic Therapy In Patients with Nonvalvular Atrial Fibrillation

Risk Assessment

Age ≥65 years old, Hypertension, Diabetes mellitus, Congestive heart failure, Stroke/TIA/systemic embolism, Left atrial diameter >50 mm, %EF ≤25%, LVEF <40%

One or more risks

No risk

Warfarin PT-INR 1.6 – 3.0 (TT: 10–20%)  No antithrombotic drug is required or aspirin (80 – 200 mg)

Fig 3. The antithrombotic strategy employed in the J-RHYTHM study is a modification of that used in the AFFIRM study.1,4

Antithrombotic Therapy  In the present study, different antithrombotic treatment strategies will be used for patients with nonvalvular AF and those with valvular AF. Patients with nonvalvular AF will receive a modified form of the treatment used in the AFFIRM study1,4 (Fig 3), and patients with valvular AF will be treated according to the published guidelines. Patients with nonvalvular AF will be assessed for the risk of stroke using the following factors: 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%, or ejection fraction <40%. In patients with one or more of these factors, warfarin will be administered to maintain a PT-INR (prothrombin time-international normalized ratio) between 1.6 and 3.0. In patients without risk factors, either no antithrombotic treatment or aspirin at a dose of 80–200 mg/day will be administered. The antithrombotic treatment in the J-RHYTHM study differs substantially from that in the AFFIRM study, and patients with valvular AF will be treated according to the published guidelines.

Another difference from the AFFIRM study is maintenance of low intensity (PT-INR 1.6–2.0) anticoagulation therapy possible because of the bleeding tendency in Japanese patients undergoing warfarin treatment. Anticoagulation therapy for 3 weeks before defibrillation of persistent AF that has continued for 48 h or more, will be mandatory in this study if transeosophageal echocardiography is unavailable.

Patient Follow-up  After randomization, every effort will be made to maintain the patients’ original group assignments. Heart rhythm...
(presence or absence of AF, duration and frequency of AF episodes, classification as paroxysmal or persistent AF), electrocardiographic findings, blood pressure, heart rate, cardiac function, and QOL will be assessed at 1, 3, and 6 months after initiation of treatment and every 6 months thereafter. In selected institutions, transtelephonic electrocardiograms will be recorded daily and if any symptoms occur during the first 1 month after the initiation of treatment. All cardiac and extracardiac events, including the primary end-point and any drug-induced adverse events, will be investigated during the 3-year follow-up period.

Data Analyses and Sample Size

The primary analysis will be an unadjusted intention-to-treat comparison between groups of time to any part of the composite primary end-point using the Kaplan-Meier method and log-rank test. Secondary end-point questionnaire results will be collected for each group, and absolute values for each question will be used to calculate the mean value, SD, number of cases, and median value (as required) per question per group. The inter-group difference will be assayed at each measurement point question by unpaired Student's t-test or Mann-Whitney's U test. Differences between groups and over time in the absolute values of measurement points will be investigated by repeated ANOVA. Items that cannot be appropriately assessed and analyzed by absolute values will be subjected to separate analysis by the most appropriate method. Patient background factors and other observation items will be aggregated by group, and any inter-group differences will be analyzed by methods corresponding to the nature of the data.

The target number of cases (2,600) has been established on the basis of our estimate of the primary end-point incidence (the projected incidence of rate control-related events during the study period is estimated as 15% and the expected event decrease rate in the rhythm control group as 30%) and with reference to the measurement method established by Freedman et al.4,15

Expected Implications

The J-RHYTHM study will emphasize both mortality and physical/psychological disableness of all types of AF. The study design makes the best use of the AFFIRM and RACE results4,5 and focuses on the safety of antiarrhythmics in response to the anxiety about drug-induced adverse effects that is frequently seen in Japanese patients. Attention to these points of emphasis is expected to improve patient mortality. Moreover, the J-RHYTHM study moves beyond the previous trials to improve the QOL of AF patients, and thus will support optimal medical care for AF patients in the clinical settings. Simultaneously, the study will generate the first large database of Japanese AF patients, which can be used for subgroup analyses that could provide further information to improve AF therapy.

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