Impact of Drug Alteration to Maintain Rhythm Control in Paroxysmal Atrial Fibrillation

– Subanalysis From J-RHYTHM Study –

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Background: The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) study showed rhythm control was associated with fewer changes in the assigned treatment strategy compared to rate control in atrial fibrillation (AF). The aim was to describe how antiarrhythmics (AAs) were altered in the rhythm control arm and whether altering AAs would impact long-term outcomes.

Methods and Results: Of 390 enrolled patients, 23.5% altered their AAs (drug alteration [DA] group). The hard endpoint (HE) was defined as a composite of death, stroke, embolism, major bleeding or heart failure hospitalization; soft endpoint (SE) was defined physical/psychological disability requiring alteration of treatment strategy. The patients were followed for 1.7 years. No significant difference was noted in the occurrence of HE (4.0% vs 6.5%, $P=0.31$), but DA-group patients had higher rates of SE (9.3% vs 18.4%, $P=0.017$) compared to single AA patients. The DA group was also associated with the occurrence of SE after adjustment (HR 1.90, $P=0.042$). When the DA group was subdivided according to the use of class III drugs or change of drugs between classes, there were no differences in outcomes.

Conclusions: The need to change AA was associated with physical/psychological disabilities that seemed not to be relieved simply by changing AAs, and this should be considered as a marker for refractory paroxysmal AF requiring other strategies. (*Circ J* 2010; **74**: 870–875)

Key Words: Antiarrhythmic drug; Atrial fibrillation; Outcome; Rhythm control

Clinical studies have been performed to compare efficacy of initial antiarrhythmic (AA) in order to maintain rhythm control.^{1–5} The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) study, the first randomized comparison conducted in Japan, showed that a rhythm control strategy was associated with fewer primary endpoints when they included patients' tolerability and quality of life (QOL), compared to a rate control strategy.⁶

However, detailed application of actual AAs or their association with clinical outcomes has not been clearly defined. Further, as commonly experienced in the clinical practice, a proportion of paroxysmal atrial fibrillation (PAF) patients remain refractory to rhythm control therapy despite trial of multiple AAs. It is unknown whether maintenance of (or attempt to maintain) sinus rhythm with multiple AAs in these refractory patients would lead to better outcomes.

The prescription pattern of AAs in the J-RHYTHM study was protocol-mandated and reflects the contemporary AA prescription pattern in Japan. Because few studies have been performed to explore drug alternation patterns in refractory PAF patients, we sought to describe how AA prescriptions were altered in this cohort, and investigated whether multiple changes in AAs were related to outcomes.

Methods

The J-RHYTHM study was a randomized multicenter comparative study of patients with PAF treated using either rate or rhythm control. Details of the study design have been published elsewhere.^{6,7} Among the cohort of the J-RHYTHM study, a total of 419 patients who underwent rhythm control treatment for PAF were included in this analysis. PAF was

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defined as atrial fibrillation (AF) expected to convert spontaneously to sinus rhythm within 48 h of onset. Twenty-nine patients who dropped out during the study (6.9% of total cohort whose follow-up information was unavailable) were discarded from this analysis.

The AAs in this rhythm control arm were selected according to the attending physicians' decision based on the "The Japanese Circulation Society [JCS] Guideline for Atrial Fibrillation Management 2001".⁸ Based on this guideline, class I drugs were the drug of choice for PAF. The type of AA and dosages were determined by the treating physician with consideration of the patient's history, including age, baseline left ventricular function, renal and hepatic function, and underlying heart diseases. If pharmacological cardioversion was successful, the same drugs were continued thereafter, but if the follow-up examination showed that the selected drugs were ineffective or adverse, the drug was changed by the treating physician. For the present study, those who stayed on single AA were classified as the control group and those who required changes in their AA regimen were classified as the drug alternating (DA) group.

Oral antithrombotic therapy was applied in rhythm control arms according to the protocol modified from the AFFIRM study.^{7,9} Briefly, in patients with one or more risk factors for stroke, warfarin was prescribed to maintain a prothrombin time-international normalized ratio (PT-INR) between 1.6 and 3.0. Anticoagulant therapy was continued throughout the study, even if sinus rhythm appeared to be maintained by AA.^{6,7}

The hard endpoint (HE) was defined as a composite of death, non-fatal stroke, systemic embolism, major bleeding or heart failure hospitalization. Heart failure hospitalization was defined as requiring intravenous administration of diuretics. A soft endpoint (SE) was as a defined physical or psychological disability requiring alteration of treatment strategy; that is, abandoning pharmacological rhythm control. The examples of physical or psychological disability included 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 one assigned strategy to the other. This is the first study in which patients' reluctance to continue the assigned strategy accompanied by their spontaneous desire to move to the other strategy was also included as an endpoint represented as a patients' disability under an assigned strategy. All the clinical endpoints, including 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 treatment strategy, were confirmed in the core data center. Maintenance of sinus rhythm was assessed via data from snapshot ECGs assessed at 1, 3 and 6 months after initiation of treatment and every 6 months thereafter.

Statistical Analysis

Baseline clinical characteristics of patients were compared with chi-square tests or one-way ANOVA for categorical variables and Student's t-test for continuous variables. Logistic regression analysis was preformed to assess clinical predictors for requirement of multiple AAs. The occurrence of clinical outcomes between control and DA group were assessed via Kaplan-Meier survival curve and Cox-regression hazard model to adjust for known clinical predictors such as age, sex, presence or absence of congestive heart failure, coronary artery disease, valvular disease, cardio-

Table 1. Baseline Characteristics of Patients

	Control (n=298)	DA group (n=92)	P value
Age (years)	65±10	64±9.2	0.72
Male (%)	68.4	75	0.23
Heart failure (%)	3.3	3.2	0.96
Coronary artery disease (%)	8	5.4	0.4
Valvular disease (%)	5.3	4.3	0.69
Cardiomyopathy (%)	0.33	5.4	<0.001
Duration after onset from PAF (days)	2,831±463	2,267±587	0.52
Past history of PAF treatment (%)	33.2	41.3	0.15

Data are mean±SD or n (%).

DA, drug alteration; PAF, paroxysmal atrial fibrillation.

myopathy (CMP), and history of previous medication to AF. A two-tailed P value of <0.05 was considered statistically significant.

Results

In 390 patients with PAF assigned to rhythm control, the median follow-up period was 1.7 years (interquartile range 0.8–2.4 years). The mean age of the cohort was 65.1±10.2 years and 70.0% were men. The mean duration after onset from PAF was 7.4±21 years; and 33.3% had received prior treatment to PAF for rhythm controls.

Baseline Characteristics

The control group consisted of 298 patients (76.4%) and 92 patients (23.5%) required more than one AAs for maintenance of sinus rhythm (DA group). Baseline clinical data of the patients in the control and DA group are summarized in **Table 1**. More patients with CMP were in the DA group compared to the control group (0.3% vs 5.4%, $P<0.001$). In addition, relatively more patients had attempted rhythm control treatment prior to enrollment (33.2% vs 41.3%, $P=0.15$), but otherwise no differences in baseline characteristics were noted.

Pattern of AA Prescription

In the DA group, 71 patients (77.1%) changed their AAs once, 13 patients (14.1%) twice, and 9 patients (9.7%) changed their AAs more than three times. The prescription pattern of AAs at the beginning and the end of the study is demonstrated in **Table 2**. As treating physicians were advised to prescribe AAs according to the JCS Guideline for AF Management, about 90% of patients were started on class I drugs. Bepridil was preferred among class III drugs, and 9.7% of patients were on the agent at the end of the study, whereas, amiodarone was prescribed in 0.5% of the patients. One patient was tried on sotalol during the study, but was switched back to flecainide at the end of study.

In the DA group, those who were on class I drugs were switched within the same class ($n=61$ [76.3%]) and onto class III drugs ($n=19$ [23.7%]). All of the patients who were on class III drugs were switched onto class I drugs ($n=9$, 100%). As a consequence, the number of patients who were on class I drugs decreased (80 [87%] to 72 [78%]) and class III drugs increased (9 [13%] to 19 [21%]). Among the class I drugs, the use of pilsicainide (30 [32%] to 14 [15%]), propafenone (14 [15%] to 6 [6%]), and disopyramide (9 [10%] to 3 [3%]) decreased, the use of cibenzoline (11 [12%] to 24 [26%])

Table 2. The Prescription Pattern of Antiarrhythmics

Initial AA		Total	Final AA									
			Ia			Ib	Ic			III		None
			Disopyramide	Pirmenol	Cibenzoline	Aprindine	Propafenone	Flecainide	Pilsicainide	Bepridil	Amiodarone	
Ia												
Disopyramide	32	23 (23)*	1	2	2	0	2	2	0	0	0	0
Pirmenol	2	0	0 (0)*	0	0	0	0	0	2	0	0	0
Cibenzoline	84	0	0	76 (73)*	1	1	0	3	3	0	0	0
Ib												
Aprindine	30	0	1	0	24 (24)*	0	1	1	3	0	0	0
Ic												
Propafenone	46	0	1	4	1	32 (32)*	2	2	4	0	0	0
Flecainide	32	1	0	1	1	1	25 (24)*	2	1	0	0	0
Pilsicainide	126	1	0	12	1	1	8	97 (96)*	6	0	0	0
III												
Bepridil	28	1	0	0	2	3	1	2	19 (19)*	0	0	0
Amiodarone	2	0	0	0	0	0	0	0	0	2 (2)*	0	0
None	8	0	0	2	0	0	0	1	0	0	5 (5)*	0
Total	390	26	3	97	32	38	39	110	38	2	5	0

AA, antiarrhythmic.

*Some patients alternated their AA more than once and were switched back to their original AA. Number within the parenthesis indicates patients who did not alternate drugs throughout the study.

and flecainide (8 [9%] to 15 [16%]) increased (**Figure 1**).

Sinus Rhythm Maintenance

Rates of preserved sinus rhythm (100% at entry) were 89.3% in the control group and 65.8% in DA group at the first month ($P<0.001$). At the end of the study, the rates were 79.4% in control compared to 42.6% in DA group ($P<0.001$). Event free Kaplan-Meier plot curve is demonstrated in **Figure 2**.

Clinical Endpoints

The HE occurred in 3.3% ($n=10$) of the control patients and in 3.2% ($n=3$) of the patients in the DA group (**Figure 3**; log-rank test $P=0.96$). The SEs occurred in 9.3% ($n=28$) of the control group and 18.4% ($n=28$) of the DA group patients

(log-rank test $P=0.017$). DA group was also associated with the occurrence of SEs after adjustment for known predictors of outcomes (HR 2.01 [SE 0.30], $P=0.023$, adjusted for age and sex; HR 1.97 [SE 0.31], $P=0.031$, adjusted for all clinical variables; HR 1.90 [95%CI: 1.59–2.21], $P=0.042$ adjusted for all clinical variables and AF duration).

Subanalysis Among Drug Alteration Group

Notably, when the DA group was subdivided into those who used class III drugs, and those who did not, there was no difference in any of the predefined outcomes (4.5% vs 7.1% [$P=0.66$] and 9.0% vs 21.4% [$P=0.19$], respectively for HE and SE). A similar result was obtained when this group was subdivided into those who changed classes (eg, change from

class I drugs to class III drugs or vice versa) and those who didn't (3.2% vs 8.1% [$P=0.36$] and 16.1% vs 19.6% [$P=0.67$], respectively). Comparing DA-once ($n=75$) vs DA-more than twice ($n=17$) did not highlight any difference in outcomes (HR for SE 0.95 [95%CI: 0.38–1.52], $P=0.97$). Numerical limitations in the DA cohort prevented us from performing further subanalysis regarding the frequency of drug alteration.

Discussion

We compared the outcomes of patients continued on the single AA and those who required multiple AAs to achieve rhythm control in PAF. The need to use alternative AAs for maintenance of sinus rhythm after initiating rhythm control did not affect the HEs, but was related to the occurrence of

SEs. The maintenance of sinus rhythm in these patients was largely associated with their response to the initial AA rather than with the type or class of AAs; further analysis of the DA group indicated that neither alternating AAs, whether intraclass or interclass, nor the use of class III drugs would prevent occurrence of SEs and improve maintenance of sinus rhythm.

Those who were maintained on single drug may represent a specific group of patients that respond favorably to AAs, and may even include a small group of patients that do not require any AAs for sinus maintenance. Although no differences in prespecified demographics were noted between the DA and control groups, unidentified factors such as genetic or pathological components might assist in identifying such subjects, as previous studies have shown in Asians.¹⁰ Significantly lower mortality and morbidity rates could also be due

to decreased drug-related adverse events from selecting class I drugs rather than class III drugs, but further investigation in a larger prospective study is needed.^{11,12}

The high number of these “favorable responders” in Asian population may also explain better outcomes for the rhythm control group compared to rate control group in the J-RHYTHM study. Overall, 67% of patients maintained sinus rhythm at the end of the study and this number was considerably higher compared to previous studies performed in Western countries. This was even higher in our control group (~80%), whereas the rate of sinus maintenance was similar to previous studies in DA group (~40%).

Low sinus maintenance rate in the DA group could be attributed to the fact that these patients may represent repetitive and refractory AF, which is difficult to convert, even with the use of class III agents. Higher rates of previously attempted rhythm control treatment in the DA compared to control group supports this hypothesis. We commonly encounter such cases of AF in the real-world practice. If this necessity to alter AAs represents a limitation of medical therapy in patients with PAF, clinicians may need to consider strategy change in AF management (eg, rate control) or alternative rhythm control methodology (eg, radiofrequency ablation) relatively early during the rhythm control of refractory AF patients, perhaps at the point of switching AAs.

Study Limitations

First, in the rhythm control group of the J-RHYTHM study, selection of therapeutic strategies was not blinded to physicians and patients. Rather, selection of drugs and dosages was dependent primarily on the evaluation of patient symptom reports by attending physicians. Dosages and timings of AAD were not included in our study protocol and warrant further investigation. In addition, it was possible that this study could not prove the effectiveness of AAD alteration because of the small number of subjects, the non-uniform protocol for alteration and lack of objective markers for the evaluating effectiveness of therapy.

Periodical snap shot ECGs were used to assess the maintenance of sinus rhythm in our study. This modality would only allow periodical monitoring of the cardiac rhythm and may potentially overestimate the maintenance rate. Implantable loop recorders were not available at the time of study, but such continuous-monitoring devices may lead to more accurate assessment of AAs.

There was a notable difference in the available AAs compared to previous studies; in the J-RHYTHM study, physicians selected drugs principally according to the JCS Guideline for AF Management.^{6–8} As a result, 82.2% patients were started on class Ia or Ic drugs, and 7.7% at class III drugs (predominantly bepridil).¹³ The other studies have used class III agents predominantly (total 68.7%, amiodarone: 37.5%, sotalol: 31.2%).¹⁴

Lastly, patients with PAF enrolled in the J-RHYTHM study were characterized by younger age, and absence of structural heart diseases or previous history of congestive heart failure, all predictors of better prognosis, and only 20% of patients were at high risk for stroke. Therefore, assessing clinical endpoints, such as death or stroke, was not practical and our focus was on patient QOL, reflected in physical or psychological disability requiring alteration of treatment strategy.⁶

Conclusions

This subanalysis from the J-RHYTHM study showed that pa-

tients who tolerated the same modality of AA drug during the study period experienced fewer SEs than patients who were obliged to change drugs more than once. The requirement to change AA may be considered as a marker for increased physical or psychological disability in patients who undergo rhythm-control strategy for PAF, and early switchover to rate control strategy or mechanical measures of rhythm control (eg, radiofrequency ablation) may be a reasonable option for those who require alteration of AA during rhythm control.

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Appendix

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