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Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II Study)

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Aims Atrial fibrillation (AF) is a common arrhythmia frequently associated with hypertension. This study was designed to test the hypothesis that lowering blood pressure by angiotensin II-receptor blockers (ARB) has more beneficial effects than by conventional calcium channel blockers (CCB) on the frequency of paroxysmal AF with hypertension.

Methods and results The Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan) and a CCB (amlodipine) in the treatment of paroxysmal AF associated with hypertension. Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal AF episodes during a maximum 1 year treatment. The primary endpoint was the difference in AF frequency between the pre-treatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent AF, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of AF episodes (days/month) was 3.8 ± 5.0 in the ARB group vs. 4.8 ± 6.3 in the CCB group (not significant). During the follow-up, blood pressure was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The AF frequency decreased similarly in both groups, and there was no significant difference in the primary endpoint between the two groups. There were no significant differences between the two groups in the development of persistent AF, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

Conclusions In patients with paroxysmal AF and hypertension, treatment of hypertension by candesartan did not have an advantage over amlodipine in the reduction in the frequency of paroxysmal AF (umin CTR C000000427).

Keywords Atrial fibrillation • Hypertension • Renin–angiotensin system • Candesartan • Amlodipine • Secondary prevention • Upstream therapy

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Introduction

Atrial fibrillation (AF) is a common arrhythmia associated with increased mortality and morbidity.[1–3] Antiarrhythmic drugs currently available have limited efficacy in the prevention of AF recurrence, and provide no substantial benefits in the prognosis of AF patients.[4,5] An approach emerging from the experimental evidence is the pharmacological modification of electrical and structural remodelling of atria. Certain neurohumoral elements, including the rennin–angiotensin system (RAS), have attracted the increased attention of cardiologists as the therapeutic target.[6–12] However, a recent large randomized trial, the GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation) study,[13] has demonstrated that treatment with valsartan was not associated with a reduction in the time to AF recurrence, making the issue more controversial.

More than half of AF patients are known to have hypertension as a co-morbid condition,[14,15] and we frequently encounter a clinical question: Which anti-hypertensive drug should be selected for lowering blood pressure (BP) in patients with AF and hypertension? This question proves to be particularly annoying in the treatment of hypertension with frequent paroxysmal AF. We conducted the J-RHYTHM II study[16] to assess the potential benefit of BP control by RAS inhibition with candesartan in patients with both hypertension and paroxysmal AF when compared with that by the conventional calcium channel blocker (CCB), amlodipine.

Methods

Study design

The rationale and the design of this study have been described previously.[16] The J-RHYTHM II study was a prospective, multicentre, randomized, and open-label trial. It was designed and supervised by the Japanese Society of Electrocardiology, and financially supported by the Japanese Heart Foundation. The study protocol was approved by the ethics committee at each participating hospital.

Patients

Patients entering this study needed to meet both of the following criteria: (i) a history of paroxysmal AF within 6 months, and (ii) hypertension, defined as a systolic BP $\geq$140 mmHg and/or a diastolic BP $\geq$90 mmHg, or requiring any hypertension treatment at enrolment. Paroxysmal AF should be an episode with spontaneous termination within 7 days, which was demonstrated on electrocardiograms (ECG) taken within 6 months before enrolment. The exclusion criteria were (i) a history of angina pectoris, (ii) persistent AF with a duration longer than 1 week and permanent AF, (iii) AF that has occurred within 1 month from the onset of myocardial infarction, (iv) transient AF associated with cardiac surgery, (v) contraindication for anticoagulation therapy, (vi) pregnancy or the possibility of pregnancy, and breast feeding, (vii) patient age of 18 or under, and (viii) a judgment by the attending physician that patient participation would be inappropriate. All patients had to have been on a stable regimen of treatment for paroxysmal AF and for any underlying cardiovascular disorders for at least 1 month prior to enrolment. Patients were allowed to continue all previously prescribed treatments and had to provide written informed consent before enrolment.

Observation period, randomization, and treatment

During the first month (4 weeks) after enrolment, the treatment of AF and hypertension was continued without any changes from that prior to entering the study in order to evaluate the baseline data of the patient, including echocardiography and quality-of-life (QOL) assessment by AF-specific QOL questionnaires (AFQLQ).[17] Each patient was provided with a transtelephonic monitoring (TTM) device and was requested to transmit ECG records (for 30 s at least once a day at a predetermined time) and any arrhythmia-related symptoms every day to a central service under contract for the study (Nihon Kohden, Tokyo).

After this 1 month observation period, the patients were randomly assigned to either a candesartan or an amlodipine group by means of a computerized randomization system based on stratification according to age, sex, BP during the observation period, existence of structural heart diseases and regular use of any antiarrhythmic drugs. After randomization, the assigned therapy was initiated in an open-label fashion and continued throughout the whole follow-up period for a maximum of 12 months.

In the candesartan group, candesartan was prescribed with an initial dose of 4–8 mg/day (maximal dose 12 mg/day), and the use of any dihydropiridine CCB or RAS inhibitors other than candesartan was prohibited during the study. In the amlodipine group, amlodipine was prescribed with an initial dose of 2.5 mg/day (maximal dose 5 mg/day), and the use of any RAS inhibitors or CCB other than amlodipine was prohibited. The target BP was set at 130/85 mmHg in both groups. When the BP did not reach the target level irrespective of the maximal dose of the assigned drug, other anti-hypertensive drugs including diuretics, β-blockers and α-blockers could be used. Antithrombotic therapy was to be continued during the study according to the Japanese Guidelines. Antiarrhythmic drugs available were limited to several class I drugs (disopyramide, procainamide, quinidine, aprindine, pilsicainide, propafenone, and cibenzoline), and the attending physicians could select or change according to their clinical judgment for each patient.

During follow-up, the attending physicians were also to record BP every month, and the patients were requested to send daily and symptom-driven TTM. The dosages and kinds of all the anti-hypertensive drugs and antiarrhythmic drugs used during this period were recorded for each patient. Echocardiography and AFQLQ assessment were performed at the end of the follow-up period.

Endpoints

The primary endpoint was the difference in the frequency (days/month) of AF (symptomatic and asymptomatic) recorded on TTM between the observation period and the final month of the follow-up. The secondary endpoints were (i) cardiovascular events, which included cardiac death, myocardial infarction, cerebral infarction, and congestive heart failure or major bleeding requiring hospitalization, (ii) the progression of paroxysmal AF into persistent AF lasting for longer than 7 days, and/or requiring electrical conversion, (iii) left atrial dimension in echocardiography, and (iv) QOL assessed by the AFQLQ.

Statistical analysis

The estimated sample size was based on our estimate of the primary endpoint difference that the frequency of paroxysmal AF is to be lower by 25% in the candesartan group than in the amlodipine group. For a study to have 80% power to detect this difference, there would have to be 240 cases (120 per group) analysed. Our

target sample size of 376 patients (188 per group) was drawn by adjusting for our estimates of losses through the follow-up being 20% and data loss due to technical errors in sending TTM being 20%.

The primary analysis was the difference between the two groups in the number of days with TTM-recorded AF, which was an unadjusted intention-to-treat comparison using the unpaired Student's *t*-test. Transtelephonic monitoring was overviewed and diagnosed in a blind manner by a TTM diagnosis committee. For each month, patients with uninterpretable ECG on TTM due to artefacts were excluded from the analysis. Inter-group differences in the occurrence of cardiovascular events and development of persistent AF were analysed by the χ^2 test. Inter-group differences in left atrial dimension were assayed by the unpaired Student's *t*-test. Differences between groups and over time in the absolute values of BP were investigated by repeated ANOVA. Secondary endpoint questionnaire results were collected for each group, and any changes from the baseline value were compared between groups by the unpaired Student's *t*-test. Patient background factors and other observation items were aggregated by group, and any inter-group differences were analysed by methods corresponding to the nature of the data. Data were expressed as mean $\pm$ SD, and statistical significance was set at $P < 0.05$.

Role of the funding source

The funding source had no role in the study design, data collection, analysis and interpretation, or the writing of the report.

Results

Patients and follow-up

From September 2006 through August 2008, 326 patients were enrolled at 48 centres throughout Japan; 8 patients withdrew their consent during the observation period. Subsequently, 318 patients were randomized; 158 were assigned to a candesartan group, and 160 to an amlodipine group. This sample size was more than that necessary for the prespecified statistical analysis ($n = 240$). Baseline clinical characteristics of the patients are shown in *Table 1*. The mean age was 69 years old and 69% of the patients were male. A total of 76.7% of the patients had received anti-hypertensive drugs, and 70.4% antiarrhythmic drugs. History of prior embolism, heart failure, and diabetes mellitus was observed in 7.6, 2.5, and 9.1%, respectively. The mean left ventricular ejection fraction was 67.6%, and slightly but significantly greater in the candesartan than in the amlodipine group. Mean left atrial dimension was 39.1 mm and was not significantly different between the groups.

The frequency of all paroxysmal AF (both symptomatic and asymptomatic) recorded on TTM during the observation period was 3.8 $\pm$ 5.0 days/month in the candesartan group and 4.8 $\pm$ 6.3 days/month in the amlodipine group ($P = 0.116$). Less than half of the AF episodes were symptomatic; the frequency of symptomatic AF was 1.4 $\pm$ 3.0 in the candesartan group and 1.4 $\pm$ 2.9 in the amlodipine group ($P = 0.903$).

Test drug dosage and concomitant cardiovascular therapies in the initial treatment period are shown in *Table 1*. The mean dose of the test drug was 8.0 $\pm$ 2.7 mg/day in the candesartan group and 4.3 $\pm$ 1.7 mg/day in the amlodipine group. Beta-blockers, antiplatelet agents, and anticoagulant agents were used in 30.8, 29.6, and 52.8% of the patients, respectively, and there were no significant differences between the two groups. Diuretics were more frequently used in the candesartan group than in the amlodipine group (12.7% vs. 5.6%, $P = 0.029$). Angiotensin-converting enzyme (ACE)-inhibitors were not used throughout the study in the both groups. The rate of antiarrhythmic drug usage tended to be higher in the amlodipine group than the candesartan group not only in the baseline (*Table 1*), but also throughout the follow-up period (final month: 72.5 vs. 68.2%, $P = 0.447$), although the difference did not reach a statistical significance.

Systolic BP during the observation period was 140.7 $\pm$ 15.5 mmHg in the candesartan group and 139.4 $\pm$ 15.4 mmHg in the amlodipine group ($P = 0.486$). *Figure 1* shows the time-course of BP during the follow-up period. Systolic and diastolic BPs decreased gradually during the study in both groups, but the extent of BP reduction with amlodipine was significantly greater than that with candesartan ($P < 0.0001$ by repeated ANOVA).

Primary endpoint

At the last month of the follow-up, the frequency of total AF was 2.1 $\pm$ 3.8 days/month in the candesartan group ($n = 149$) and 2.4 $\pm$ 4.4 days/month in the amlodipine group ($n = 155$, $P = 0.512$). The frequency of symptomatic AF was 1.0 $\pm$ 3.1 days/month in the candesartan and 0.8 $\pm$ 2.6 days/month in the amlodipine group ($P = 0.544$). *Figure 2A* shows the primary endpoint (the difference in the frequency of AF between the observation period and the final month of the follow-up); there was no significant difference between the two groups ($P = 0.351$). The two groups showed similar gradual decreases in the frequencies of both total and symptomatic AF during the whole follow-up period (*Figure 2B*). In the both candesartan and amlodipine groups, there was a significant decrease in the total AF days from the baseline to the final follow-up month (candesartan $P = 0.002$, amlodipine $P = 0.0002$); a tendency of reduction was also observed in the symptomatic AF days from the baseline to the final follow-up month, although the reduction did not reach a statistical significance (candesartan $P = 0.15$, amlodipine $P = 0.07$).

Secondary endpoints and *post hoc* analyses

Table 2 summarizes the secondary endpoints in this study. There were no significant differences in these endpoints between the two groups. Cardiovascular events tended to occur more frequently in the amlodipine than in the candesartan group, but the difference did not reach statistical significance. The development of persistent AF (lasting >7 days or requiring electrical cardioversion) tended to be more frequent in the amlodipine group (15%) than in the candesartan group (8.2%), but the difference was not statistically significant. The differences in QOL represented by AFQLQ between the observation period and the final follow-up were similar in the two groups in all of the AFQLQ subsets.

Because the two groups showed significant differences in BP reduction during the follow-up period (*Figure 1*), *post hoc* analyses were performed to examine the influence of systolic BP on the primary endpoint. The patients were divided into three groups according to their systolic BP at the final follow-up: a lower group ($\leq$126 mmHg, $n = 108$), a middle group (126–139 mmHg,

Table 1 Baseline characteristics

Characteristics	Candesartan ($n = 158$)	Amlodipine ($n = 160$)	*P*-value
Age (years)	66.0 ± 9.7	65.1 ± 9.3	0.429
Male (%)	109 (69.0)	110 (68.8)	0.905
SBP (mmHg)	139.5 ± 15.4	140.7 ± 15.5	0.486
DBP (mmHg)	81.0 ± 11.3	82.5 ± 11.2	0.256
Heart rate (bpm)	70.9 ± 14.4	69.5 ± 13.9	0.379
Duration of AF			0.818
<1 year	41 (25.9)	37 (23.1)	
≤1, <5 years	57 (36.1)	66 (41.3)	
>5 years	43 (27.2)	41 (25.6)	
Unknown	17 (10.8)	16 (10)	
Coexisting conditions			
Prior embolism (%)	12 (7.6)	12 (7.5)	1.000
Heart failure (%)	4 (2.5)	4 (2.5)	1.000
Myocardial infarction (%)	3 (1.9)	1 (0.6)	0.370
Angina pectoris (%)	3 (1.9)	4 (2.5)	1.000
Cardiomyopathy (%)	4 (2.5)	3 (1.9)	0.690
Valvular disease (%)	9 (5.7)	14 (8.8)	0.387
Diabetes (%)	15 (9.5)	14 (8.8)	0.848
Hyperlipidaemia (%)	47 (29.7)	47 (29.4)	1.000
Echocardiograms			
LVDd	47.5 ± 4.9	47.87 ± 4.9	0.549
LVEF	69.1 ± 8.1	66.2 ± 8.2	0.003
LAD	38.9 ± 6.7	39.3 ± 6.8	0.618
Treatment at baseline			
Anti-hypertensive therapy (%)	120 (75.9)	124 (77.5)	0.791
AAD (%)	105 (66.5)	119 (74.4)	0.141
PAF frequency during observation period			
Total PAF (days/month)	3.8 ± 5.0	4.8 ± 6.3	0.116
Symptomatic PAF	1.4 ± 3.0	1.4 ± 2.9	0.903
Treatment at initial follow-up			
Candesartan	8.0 ± 2.7 mg/day	—	—
Amlodipine	—	4.3 ± 1.7 mg/day	—
Diuretics (%)	20 (12.7)	9 (5.6)	0.029
β-Blockers (%)	48 (30.4)	50 (31.3)	0.867
Antiplatelet therapy (%)	46 (29.1)	48 (30.0)	0.863
Anticoagulant therapy (%)	80 (50.6)	88 (55.0)	0.435
Statins (%)	26 (16.5)	24 (15.0)	0.721

Data represent mean ± SD or frequency. SBP, systolic blood pressure; DBP, diastolic blood pressure; PAF, paroxysmal atrial fibrillation; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AAD, antiarrhythmic drug; bpm, beat per minute. Anti-hypertensive therapy includes ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, β-blockers, α-blockers, and diuretics.

$n = 95$), and a higher group (≥139 mmHg, $n = 105$). There were no significant differences between the two groups in the reduction in AF frequency during the follow-up period in any subset analysis (*Table 3*).

Discussion

In the present J-RHYTHM II study, we tested a hypothesis that, in patients with paroxysmal AF associated with hypertension, candesartan may exert beneficial effect on the frequency of paroxysmal AF when compared with conventional hypertension therapy with amlodipine. In our study population, we could not find any differences between the two therapies in the nature of paroxysmal AF during the maximal follow-up of 1 year. These results were essentially unaffected by subgroup analyses depending on the systolic BP attained by the therapies. Our findings, in concordance with a recent GISSI-AF study,[13] do not support the concept that the blockade of RAS may have a favourable effect on the occurrence of AF beyond the control of BP.

There is considerable experimental evidence suggesting that the administration of angiotensin II-receptor blockers (ARB) may prevent or reverse the progression of atrial fibrosis in association

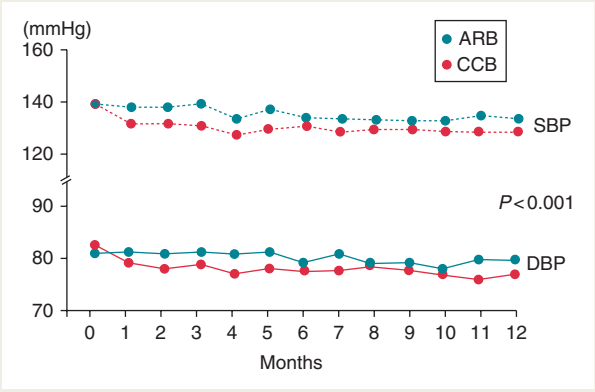

Figure 1 The time-course of systolic blood pressure and diastolic blood pressure in the candesartan (angiotensin II-receptor blocker) and amlodipine (calcium channel blocker) group. There were significant differences both in systolic and diastolic blood pressure between the groups ($P < 0.0001$ by ANOVA).

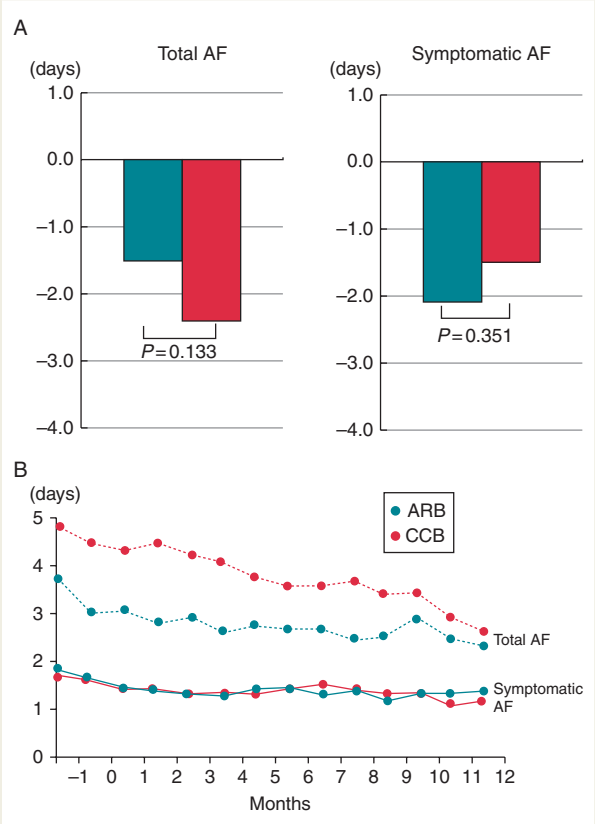

Figure 2 (*A*) Difference in the frequency of atrial fibrillation (days/month) between the observation period and the final month of the follow-up (Left: Total atrial fibrillation, Right: Symptomatic atrial fibrillation). Both in the candesartan (angiotensin II-receptor blocker) and amlodipine (calcium channel blocker) groups, the atrial fibrillation days decreased, but there were no significant differences between the two groups. (*B*) The time-course of the frequency (days/month) of total atrial fibrillation (dotted lines) and symptomatic atrial fibrillation (solid lines).

Table 2 Secondary endpoints

	Candesartan (n = 158)	Amlodipine (n = 160)	P-value
Cardiovascular events (%)			
Cardiovascular death	0 (0.0)	0 (0.0)	—
Acute myocardial infarction	0 (0.0)	0 (0.0)	—
Stroke	0 (0.0)	3 (1.8)	0.084
Major bleeding	0 (0.0)	1 (0.6)	0.320
Heart failure	0 (0.0)	0 (0.0)	—
Development of persistent AF	13 (8.2)	24 (15.0)	0.080
Changes in LAD	+0.34 ± 5.8	+0.25 ± 4.9	0.895
Changes in QOL assessment			
AFQLQ1	+0.9 ± 5.6	+1.8 ± 6.0	0.246
AFQLQ2	+1.5 ± 3.8	+2.2 ± 4.2	0.189
AFQLQ3	+1.6 ± 7.4	+2.6 ± 10.0	0.412

Data represent mean ± SD or frequency. AFQLQ1, frequency of symptoms; AFQLQ2, severity of symptoms; AFQLQ3, limitations of daily activities and mental anxiety (higher is better in these components).

Table 3 Frequency of paroxysmal atrial fibrillation in three tertiles of systolic blood pressure

	Candesartan	Amlodipine	P-value
Lower group			
Baseline (day/month)	3.5 ± 3.6 (49)	5.4 ± 6.8 (59)	0.081
Final follow-up	1.7 ± 2.7 (48)	3.1 ± 4.9 (58)	0.089
Difference	−1.6 ± 4.4 (48)	−2.4 ± 7.5 (58)	0.493
Middle group			
Baseline	3.5 ± 5.7 (42)	4.8 ± 6.5 (52)	0.306
Final follow-up	2.6 ± 5.4 (41)	2.7 ± 5.3 (51)	0.928
Difference	−1.0 ± 4.8 (41)	−2.2 ± 5.5 (51)	0.260
Higher group			
Baseline	3.9 ± 4.6 (61)	3.9 ± 5.2 (43)	0.936
Final follow-up	2.1 ± 3.3 (57)	1.3 ± 2.4 (44)	0.164
Difference	−1.7 ± 3.8 (57)	−2.6 ± 4.2 (43)	0.265

Data represent mean ± SD. ( ), number of patients.

with AF.[18–20] Actually, a series of clinical studies also showed that RAS inhibition had beneficial effects on the recurrence and perpetuation of AF.[21–23] On the contrary, however, *post hoc* analyses of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) and CTAF (Canadian Trial of Atrial Fibrillation) studies could not find any beneficial effects of RAS inhibition on AF recurrence,[24,25] making it controversial that the experimental concept can be applied to clinical practice.

Recently, the first prospective randomized control trial, the GISSI-AF study,[13] challenged this issue. The trial enrolled all types of AF, evaluated the antiarrhythmic efficacy of valsartan

when compared with a placebo in a double-blind manner, and has demonstrated that valsartan was not associated with any beneficial effects on AF recurrence. Also, the results were consistent in any subgroups according to age, presence of heart failure, and usage of ACE-inhibitors, beta-blockers and antiarrhythmic drugs.[13]

The present J-RHYTHM II study focused upon a specific proportion of patients in the GISSI-AF study, patients with frequent paroxysmal AF associated with hypertension, in order to answer a question regarding which type of drug, ARB or CCB, is more favourable as an anti-hypertensive therapy for these patients. The primary endpoint was also somewhat different from the GISSI-AF study. We focused on the frequency of paroxysmal AF, while the GISSI-AF trial evaluated the time to a first recurrence of AF. Our study, using every-day TTM recordings, has revealed that anti-hypertensive therapy with candesartan has no significant advantage over amlodipine in the reduction in the frequency of paroxysmal AF. These results would strengthen the evidence from the GISSI-AF study.

In our secondary endpoint analysis, ~12% of the patients showed progression into persistent AF. This figure is consistent with a recent study[26] that revealed the rate of progression of paroxysmal into persistent AF in a variety of paroxysmal AF patients and identified hypertension as one of the potent risk factors for AF perpetuation. In the present study, we ascertained the similar progression rate in hypertensive patients with the use of daily TTM recordings and also found that the rate was not significantly affected by the administration of candesartan in a sample size of >300 patients. The changes in the left atrial dimension were also similar between the groups, which would be consistent with this result on AF perpetuation. The present results of the AF-specific QOL assessment are also plausible, because the frequency and perpetuation of AF was similar between the groups.

In our study, the incidence of thrombo-embolic events tended to be higher in the amlodipine than in the candesartan group. This might be inconsistent with the GISSI-AF study,[13] where strokes were more frequently observed in the valsartan group. However, we believe that our observation may have resulted from a by-chance occurrence due to the small number of patients studied.

Recently, several reports have been made on the relationships between anti-hypertensive drugs and AF primary prevention.[27–29] The effects of antihypertensive drugs on primary AF prevention might differ from drug to drug, but remain a matter of controversy. One of the difficult problems results from BP differences during long anti-hypertensive therapy.[30,31] Similarly, the present results could be influenced by the significant differences in BP between the two groups. However, the AF frequencies were not different between ARB and CCB in any of the subgroups divided according to the attained BP levels at the final follow-up; this *post hoc* analysis would suggest that the BP differences between the two groups were unlikely to play a major role in the results of the present study.

Limitations of our trial should include (i) it is an open-label trial, (ii) lack of a placebo arm, (iii) relatively higher rate of anti-arrhythmic drug usage in the amlodipine group, and (iv) a relatively short follow-up period. Although this was an open-label trial, the primary endpoint was blinded to the attending physicians and patients, and also to the TTM diagnosis committee, in order to minimize information biases. Because there was no placebo control group, we could not know the relationships between BP and the frequency of paroxysmal AF. The slightly higher rates of antiarrhythmic drug usage in the amlodipine group (the difference was statistically insignificant) might have affected the present results. Moreover, our results should be applied to a short-term follow-up of the patients.

In conclusion, under the conditions of the study and with statistical limitations, there were no differences in the frequency or perpetuation of paroxysmal AF with hypertension between anti-hypertensive therapies using candesartan and amlodipine. These data suggest that, for both patients and health-care providers, selection of anti-hypertensive drugs could be individualized from other patient characteristics.

Conflict of interest: none declared.

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Appendix 1

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