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Original article

# Relationships between maintenance of sinus rhythm and clinical outcomes in patients with heart failure with preserved ejection fraction and atrial fibrillation☆

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ABSTRACT

*Background:* Although atrial fibrillation (AF) is associated with exacerbation of heart failure with preserved ejection fraction (HFpEF), the relationships between maintenance of sinus rhythm (SR) and clinical outcomes in HFpEF is unknown. We investigated whether maintenance of SR was associated with better prognosis compared with rate control in patients with concomitant HFpEF and AF.

*Methods:* We conducted a retrospective, observational study of 283 patients with HFpEF and AF. Of these, 107 patients achieved maintenance of SR by catheter ablation and/or antiarrhythmic drugs (rhythm control) and 176 were treated with rate control. The propensity score (PS) for each patient in both treatment groups was estimated, resulting in selectively matched subgroups of 79 patients each. All-cause death and a composite of cardiovascular death or hospitalization for heart failure (HF) were analyzed.

*Results:* During a median follow-up period of 24 months, all-cause mortality was comparable between groups; however, maintenance of SR was significantly associated with a lower incidence of the composite endpoint [adjusted hazard ratio (HR), 0.30; 95% confidence interval, 0.18–0.98; $p = 0.04$] in the PS-matched cohort. The PS-adjusted multivariable analysis based on 283 pre-matched patients also revealed that rhythm control was associated with a lower rate of the composite endpoint (adjusted HR, 0.27; 95% CI, 0.12–0.61; $p = 0.002$). Subgroup analyses suggested that rhythm control was consistently related to the composite endpoint across a wide spectrum of HFpEF patients.

*Conclusions:* Maintenance of SR was associated with a lower risk of composite of cardiovascular death or hospitalization for HF in patients with HFpEF and AF. A randomized trial is necessary to confirm this result.



## Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) has been progressively increasing due to global aging [1,2]. Although the prognosis of HFpEF is poor [3,4], no effective therapeutic strategy to reduce adverse cardiac events has yet been developed. Since the increased stiffness of the left ventricle (LV) causes left atrial (LA) remodeling, patients with HFpEF are predisposed to atrial fibrillation (AF), with a prevalence ranging from 20% to 65% [2–6]. The already vulnerable hemodynamic state in patients with HFpEF resulting from LV diastolic dysfunction can be significantly affected by AF leading to loss of atrial contraction, insufficient ventricular filling, and reduction in cardiac output. Indeed, it has been suggested that concurrent AF and HFpEF carry a worse prognosis than either condition alone [2,5–7]. In patients with heart failure (HF), maintenance of sinus rhythm (SR) has been reported to improve LV function, functional capacity, and HF symptoms [8–13]; however, there is a general lack of evidence

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indicating a survival advantage to rhythm control in HFpEF patients. Accordingly, the present study aimed to investigate whether maintenance of SR was associated with better clinical outcomes compared with rate control in patients with HFpEF and AF through a retrospective chart analysis of a multicenter registry of HF patients.

## Methods

### *Study protocol*

We conducted a retrospective, observational, multicenter study utilizing data from 11 participating institutions. Between June 2012 and December 2015, there were 643 hospitalized patients who had AF and presented with HF symptoms (pulmonary edema, ankle swelling, fatigue, or dyspnea on exertion). All patients were screened for noncardiac causes of symptoms. Of these, 360 patients were excluded according to the following criteria: reduced LV ejection fraction (LVEF) <50%, age <20 years, history of pacemaker implantation, valvular heart disease requiring surgical intervention, active ischemic heart disease, severe pulmonary disease or liver failure, and lack of informed consent. The final analysis was composed of 283 patients who met the criteria for diagnosis of HFpEF [14,15] and had concurrent AF. These included 106 patients with paroxysmal AF, 56 with persistent AF, and 121 with long-standing persistent AF [16]. Data on demographics, medical comorbidities, medication usage, and New York Heart Association (NYHA) functional class were collected. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 $m^2$ (Cockcroft-Gault formula) or need for dialysis therapy. Coronary artery disease was defined as a prior history of coronary revascularization or confirmed myocardial infarction. Ethical approval for the study was obtained from the local review committee and all patients provided their informed consent.

### *Transthoracic echocardiography*

At the baseline examination, all patients underwent transthoracic echocardiography. Two-dimensional, pulsed-wave, continuous-wave, and color Doppler images were recorded and analyzed using an offline analysis workstation at a dedicated core laboratory blinded to clinical information. Each parameter was determined based on the current recommendations [17]. LV mass was calculated according to the Cube formula and was indexed by body surface area. LV hypertrophy was defined according to LV mass index thresholds of 116 g/$m^2$ for males and 96 g/$m^2$ for females [17]. LA volume was measured from the apical view with the biplane method of disks and was indexed by body surface area. Severe LA enlargement was defined as an LA volume index >48 ml/$m^2$ and mild-moderate LA enlargement was defined as LA volume index within 35–48 ml/$m^2$ [17]. The peak pressure gradient derived from the tricuspid regurgitation signal was measured. Longitudinal LV global strain (GLS) was measured using a B-mode speckle-tracking vendor independent software with algorithms specifically designed for the LV (TomTec Imaging System, Munich, Germany). For patients in SR during examination, analyses were performed on a single cardiac cycle. For patients in AF rhythm, an index beat, the beat after the nearly equal preceding (RR1) and pre-preceding (RR2) intervals, was used for each measurement as previously described [18]. Echocardiography was assessed again 12 months after the initial assessment. We defined patients with improvement of echocardiographic parameters as those who showed improvement of more than 3 of 5 major parameters (LVEF, GLS, LA volume, $E/E'$ ratio, and peak tricuspid regurgitant pressure gradient) at follow-up.

### *Treatment*

The treatment strategy for AF (rhythm control or rate control) in each patient was determined according to the attending physician's

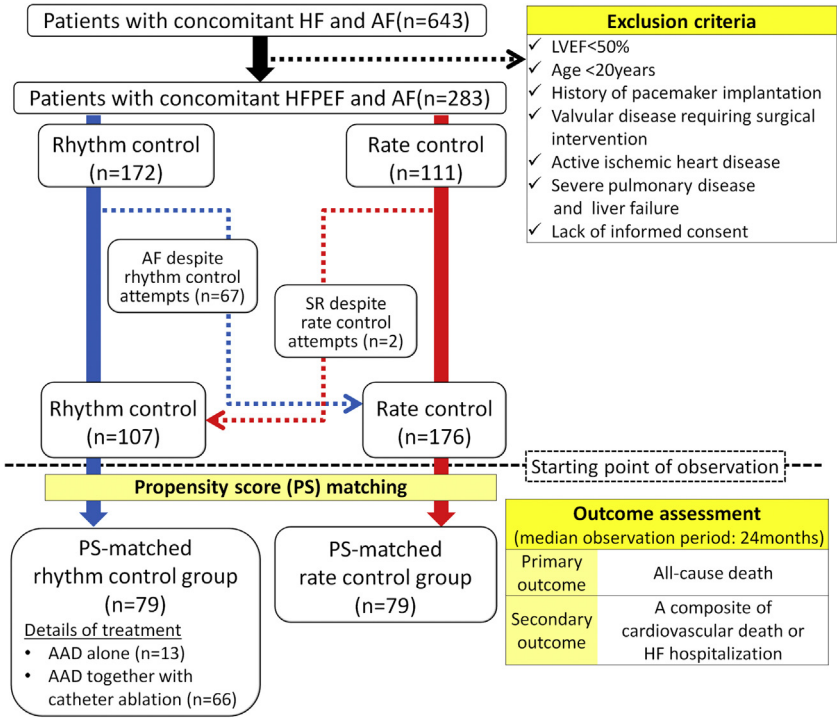



**Fig. 1.** Flow chart illustrating the study population. A total of 283 patients with concomitant heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) were enrolled. Of these, the outcomes of 158 propensity score (PS)-matched patients, including 79 on rhythm control and 79 on rate control, were assessed. The propensity score-matched rhythm control group included 66 cases with maintained sinus rhythm (SR) after catheter ablation and antiarrhythmic drugs (AADs) while 13 received AADs therapy alone.
HF, heart failure; LVEF, left ventricular ejection fraction.

preference. Initially, 172 patients underwent attempts to restore sinus rhythm and 111 were treated with heart rate control. If the attending physician did not perform electrical cardioversion or prescribe any antiarrhythmic drugs (AADs) to terminate or prevent AF after the inclusion to the study, such cases were included in the rate control group even if they had paroxysmal AF as in the previous study [19]. Patients who experienced a recurrence of their AF despite antiarrhythmic therapy ($n = 67$) were included in the rate control group and patients who maintained SR despite rate control therapy ($n = 2$) were included in the rhythm control group. The final rhythm control and rate control groups consisted of 107 and 176 patients, respectively. A flow chart illustrating the study design is shown in Fig. 1.

In the rhythm control group, aggressive therapy including catheter ablation (CA) and/or AADs was administered to maintain SR. Our protocol for CA and postprocedural follow-up has been extensively described elsewhere [9]. AADs included class Ia (procainamide, disopyramide), class Ic (propafenone, flecainide, pilsicainide), aprindine, amiodarone, and bepridil. All CA was performed for patients with hemodynamically stable condition after enough decongestion therapy. We used amiodarone alone during the acute phase of decompensated HF according to the current guideline [15]. After sufficient decongestion therapy, other AADs were started in some patients to prevent HF worsening due to AF recurrence. No AADs were prescribed after the CA in patients with paroxysmal AF. In patients with non-paroxysmal AF, the continuation and dosing of AADs after CA was determined by the attending physicians. During the follow-up period, all patients were examined every 1–3 months at the outpatient clinic. In patients taking AADs, chest radiography, serum biomarkers of interstitial lung disease, and liver and

**Table 1**
Baseline characteristics by atrial fibrillation (AF) management before and after propensity score (PS) matching.

| | Before PS matching ($n = 283$) | | | After PS matching ($n = 158$) | | | |
|---|---|---|---|---|---|---|---|
| | Rhythm control ($n = 107$) | Rate control ($n = 176$) | $p$-Value[a] | Rhythm control ($n = 79$) | Rate control ($n = 79$) | $p$-Value[a] | Absolute standardized differences, % |
| Propensity score logit | 0.47 ± 0.22 | 0.72 ± 0.21 | <0.001 | 0.45 ± 0.19 | 0.44 ± 0.19 | 0.62 | 5.26 |
| Age[b] | 68 ± 7 | 73 ± 9 | <0.001 | 68 ± 7 | 68 ± 9 | 0.78 | 8.53 |
| Female[b] | 39 (36.4%) | 74 (42.0%) | 0.35 | 32 (40.5%) | 30 (38.0%) | 0.75 | 6.12 |
| Body mass index, kg/m$^2$[b] | 25.5 ± 4.6 | 23.2 ± 4.3 | <0.001 | 24.6 ± 4.2 | 24.3 ± 4.3 | 0.73 | 7.06 |
| Systolic blood pressure, mmHg | 129 ± 23 | 124 ± 22 | 0.06 | 127 ± 23 | 126 ± 22 | 0.55 | 4.44 |
| Diastolic blood pressure, mmHg | 73 ± 17 | 68 ± 15 | 0.03 | 70 ± 14 | 70 ± 14 | 0.74 | 0 |
| Heart rate, bpm | 68 ± 16 | 70 ± 13 | 0.25 | 69 ± 16 | 70 ± 13 | 0.58 | 6.65 |
| $CHADS_2$ score | 2.5 ± 1.0 | 2.7 ± 1.0 | 0.15 | 2.6 ± 1.0 | 2.7 ± 1.1 | 0.44 | 7.12 |
| $CHA_2DS_2$-VASc score | 3.9 ± 1.3 | 4.2 ± 1.4 | 0.10 | 3.9 ± 1.3 | 4.0 ± 1.5 | 0.58 | 9.51 |
| NYHA class III or IV[b] | 27 (25.2%) | 47 (26.7%) | 0.79 | 20 (25.3%) | 23 (29.1%) | 0.59 | 4.25 |
| Comorbid conditions | | | | | | | |
| Hypertension[b] | 86 (80.4%) | 132 (75.0%) | 0.30 | 59 (74.7%) | 62 (78.5%) | 0.57 | 7.05 |
| Diabetes[b] | 37 (34.6%) | 55 (31.3%) | 0.56 | 27 (34.1%) | 30 (38.0%) | 0.62 | 8.24 |
| Coronary artery disease[b] | 27 (25.2%) | 30 (17.0%) | 0.10 | 13 (16.5%) | 14 (17.7%) | 0.83 | 5.33 |
| History of stroke[b] | 13 (12.1%) | 16 (9.1%) | 0.41 | 10 (12.7%) | 10 (12.7%) | 1.00 | 0 |
| Chronic kidney disease[b] | 50 (46.7%) | 92 (52.3%) | 0.37 | 35 (44.3%) | 35 (44.3%) | 1.00 | 4.31 |
| Left ventricular hypertrophy[b] | 60 (56.1%) | 97 (55.1%) | 0.88 | 42 (53.2%) | 42 (53.2%) | 1.00 | 0 |
| Non-paroxysmal AF[b] | 59 (55.1%) | 118 (67.0%) | 0.045 | 45 (57.0%) | 52 (65.8%) | 0.35 | 14.28 |
| Time since diagnosis of AF, year | 4.6 ± 5.6 | 6.5 ± 7.3 | 0.07 | 5.0 ± 5.3 | 5.5 ± 6.4 | 0.55 | 8.51 |
| Medical treatment at enrollment | | | | | | | |
| ACE-I or ARB[b] | 78 (72.9%) | 102 (58.0%) | 0.03 | 53 (67.1%) | 54 (68.4%) | 0.58 | 4.26 |
| Mineralocorticoid receptor antagonist[b] | 35 (32.7%) | 52 (29.5%) | 0.58 | 25 (31.6%) | 23 (29.1%) | 0.73 | 6.45 |
| Beta-blocker[b] | 76 (71.0%) | 96 (54.5%) | 0.006 | 53 (67.1%) | 52 (65.8%) | 0.87 | 2.11 |
| Calcium-channel blocker[b] | 52 (48.6%) | 75 (42.6%) | 0.33 | 34 (43.0%) | 35 (44.3%) | 0.87 | 2.0 |
| Diuretic agent[b] | 50 (46.7%) | 101 (57.4%) | 0.08 | 36 (45.6%) | 40 (50.6%) | 0.52 | 9.88 |
| Warfarin[b] | 40 (37.4%) | 80 (45.5%) | 0.18 | 33 (41.8%) | 35 (44.3%) | 0.75 | 2.30 |
| Direct oral anticoagulant | 67 (62.6%) | 96 (54.5%) | 0.18 | 46 (58.2%) | 44 (55.7%) | 0.75 | 2.30 |
| Class Ia antiarrhythmic drug | 7 (6.5%) | – | – | 5 (6.3%) | – | – | |
| Class Ic antiarrhythmic drug | 40 (37.4%) | – | – | 31 (39.2%) | – | – | |
| Aprindine | 11 (10.3%) | – | – | 8 (10.1%) | – | – | |
| Amiodarone | 56 (52.3%) | – | – | 44 (55.7%) | – | – | |
| Bepridil | 17 (15.9%) | – | – | 10 (12.7%) | – | – | |
| Biochemical | | | | | | | |
| Hemoglobin, g/dL[b] | 13.6 ± 1.8 | 12.5 ± 2.1 | <0.001 | 13.3 ± 1.8 | 13.4 ± 2.0 | 0.79 | 5.26 |
| Serum sodium, mEq/L[b] | 140 ± 3 | 140 ± 3 | 0.11 | 140 ± 3 | 140 ± 3 | 0.19 | 0 |
| eGFR, mL/min per 1.73m$^2$[b] | 61 ± 17 | 65 ± 28 | 0.29 | 61 ± 17 | 60 ± 27 | 0.65 | 4.32 |
| Serum BNP, pg/mL[b] | 216 [119, 313] | 329 [134, 584] | <0.001 | 233 [137, 331] | 230 [130, 330] | 0.69 | 14.51 |
| Echocardiography | | | | | | | |
| LVEF, %[b] | 65 ± 8 | 63 ± 8 | 0.045 | 65 ± 8 | 65 ± 8 | 0.94 | 0 |
| LV mass index, g/m$^2$[b] | 113 ± 29 | 118 ± 32 | 0.16 | 111 ± 27 | 112 ± 25 | 0.79 | 3.84 |
| GLS, %[b] | −15.8 ± 3.5 | −13.4 ± 4.5 | 0.004 | −14.2 ± 3.0 | −13.9 ± 3.6 | 0.58 | 9.05 |
| LA volume, ml/m$^2$[b] | 50 ± 20 | 58 ± 32 | 0.01 | 51 ± 21 | 51 ± 21 | 0.96 | 0 |
| $E/E'$[b] | 12.1 ± 3.9 | 13.5 ± 6.7 | 0.047 | 12.0 ± 4.6 | 12.5 ± 5.5 | 0.64 | 9.86 |
| TRPG, mmHg[b] | 30 ± 9 | 33 ± 12 | 0.02 | 30 ± 10 | 29 ± 10 | 0.48 | 9.0 |
| Follow-up period, months | 23 [11, 35] | 26 [14, 38] | 0.32 | 24 [12, 36] | 24 [11, 37] | 0.64 | |

Results are shown as mean ± SD, median [IQR], or as number (%).
[a] $t$-test (normally distributed continuous variables), chi-square test (dichotomous data), Wilcoxon test (skewed data).
[b] Covariates included in the propensity model.
ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; GLS, longitudinal left ventricular global strain; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SR, sinus rhythm; TRPG, peak tricuspid regurgitant pressure gradient.

thyroid function tests were assessed at each visit, as appropriate. A 12-lead electrocardiogram, 24-hour Holter monitoring, and portable electrocardiographic monitoring (HCG-901; OMRON, Kyoto, Japan) was performed at 2 weeks and 1, 3, 6, and 12 months after CA. These modalities were also used anytime the patients reported palpitations. If the electrocardiogram showed any episodes of AF or any other atrial tachyarrhythmias lasting >30 s during the follow-up period, the patients were diagnosed as having a recurrence of AF. However, recurrence of AF within the first 3 months following the ablation was considered transient, and a blanking period of 3 months was applied. A repeat ablation procedure was recommended for recurrences after the blanking period. After antiarrhythmic treatment, the 67 patients who failed to maintain SR had all their AADs discontinued and were included in the rate control group as described above.

In the rate control group, a lenient control target of resting heart rate <110 bpm was applied [20]. During the follow-up period, all patients were examined every 1–3 months and the resting heart rate was assessed by a 12-lead electrocardiogram and appropriate rate control was achieved in all patients. Rate control drugs included β-blockers (bisoprolol, carvedilol), calcium channel blockers (diltiazem, verapamil), and digoxin. Patients simultaneously prescribed rhythm and rate control drugs were classified as rhythm control.

Additional medication for HF including diuretics, mineralocorticoid receptor antagonist, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers was adjusted at the discretion of the attending physician. All patients continued appropriate oral anticoagulation during the entire follow-up period.

### *Assembly of study cohort: propensity score matching*

Because of the non-randomized nature of the study, the predicted probability of rhythm control was estimated by multivariable logistic regression analysis. A model was developed that included 26 clinically relevant variables (Table 1). This model yielded a *c*-statistic of 0.81. To reduce the treatment-selection bias and potential confounding, we adjusted for significant differences in the baseline characteristics with propensity-score (PS) matching using the following: 1:1 optimal match with a ±0.2 caliper and no replacement. We used the standardized difference to measure covariate balance, whereby an absolute standardized difference ≥10% represents meaningful imbalance. As a result, subgroups of 79 patients each were matched from the entire cohort (Fig. 1).

### *Outcome assessment*

The primary outcome was all-cause death. Secondary outcome was a composite of cardiovascular death or hospitalization for HF. Cardiovascular death was defined as death resulting from acute myocardial infarction, sudden cardiac death, HF, stroke, dysrhythmia, pulmonary embolism, aortic aneurysm rupture, or peripheral arterial disease, and other unspecified disorders of the circulatory system.

The beginning of the follow-up period was defined as the point when the final treatment strategy for AF was determined. The median follow-up period was 24 months (interquartile range, 11–37 months). All events were investigated in the outpatient clinic and by telephone and reported by the primary site investigators. Levels of serum brain natriuretic peptides (BNP) were assessed again 12 months after the initial assessment simultaneously with echocardiography.

### *Statistical analysis*

Means were expressed with 1 standard deviation for continuous variables, and medians were presented with interquartile ranges for skewed variables. Differences between two groups were evaluated using a *t*-test (normally distributed continuous variables), chi-square test (dichotomous data), Mann–Whitney's U test, or Wilcoxon signed-rank test (skewed data), as appropriate. The event-free survival probability was estimated by Kaplan–Meier analysis and the two groups were compared using the log-rank test. In the propensity-matched cohort, Cox proportional hazard regression models were analyzed to evaluate the influence of rhythm control or improvements of echocardiographic parameters on clinical outcomes. To validate the findings in the entire cohort, we used multivariable Cox proportional hazard models with adjustment for the PS. To explore the potential heterogeneity of the treatment effect on cardiovascular death or hospitalization for HF, we analyzed the impact of rhythm control in several subgroups according to age (<70 vs. ≥70 years), sex, NYHA functional class (III or IV vs. others), $CHADS_2$ score (<3 vs. ≥3), chronic kidney disease, paroxysmal AF, LV hypertrophy, LA enlargement (mild-moderate vs. severe), longitudinal LV GLS, and serum BNP levels. Medians of longitudinal LV GLS or BNP levels were used as each cut-off value, respectively. We estimated the effect of rhythm control in each of the subgroups using Cox regression models, in each case adjusting for propensity to select rhythm control. Values of $p < 0.05$ and interaction $p < 0.1$ were considered to be statistically significant. All statistical analyses were performed using SPSS software (version 24.0; SPSS Inc., Chicago, IL, USA).

## Results

### *Study population*

In 172 patients who underwent attempts to restore SR, 105 achieved successful rhythm control and 67 experienced recurrence of AF. Patients with AF recurrence had a longer duration since diagnosis of AF, higher serum BNP levels, and greater LA volume compared to those with successful rhythm control (Supplementary Table 1). In the PS-matched rhythm control group, 66 patients were treated with AADs together with CA and 13 were treated with AADs only (Fig. 1). CA was successfully performed in all patients (single-procedure, $n = 29$; multiple-procedures, $n = 37$) and no major complications occurred during follow-up. The rates of maintenance of SR during observational periods were 72.2% (57 in 79 patients) in PS-matched rhythm control group and 5.1% (4 in 79 patients) in PS-matched rate control group ($p < 0.001$). Although AF was not completely cured in 22 patients of PS-matched rhythm control group, 14 (63.6%) of those reduced the AF burden. On the other hand, 10 of 27 (37.0%) patients with paroxysmal AF in rate control group progressed to persistent AF during observational period.

Baseline characteristics before and after PS-matching are shown in Table 1. Before matching, patients receiving a rate control strategy were significantly older and more likely to have a lower estimated glomerular filtration rate, lower hemoglobin, and higher serum BNP levels. In terms of echocardiographic parameters, a greater LA volume index, $E/E'$, and tricuspid regurgitant pressure gradient, and lower LVEF and LV GLS were seen in the rate control group compared to the rhythm control group. However, the covariate balance between both groups was considerably improved after propensity matching. The standardized differences between the propensity-matched cohorts were

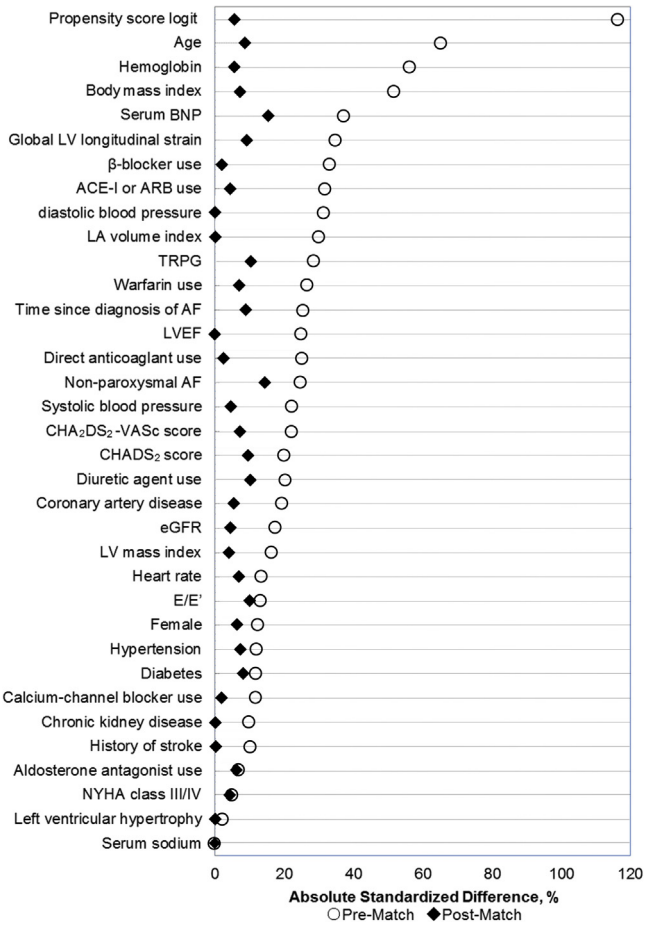



**Fig. 2.** Absolute standardized differences in baseline covariates between the rhythm control and rate control groups before and after propensity score matching. Post-match absolute standardized difference <10% indicates excellent covariate balance.
AF, atrial fibrillation; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TRPG, peak tricuspid regurgitant pressure gradient.

≤10% in absolute value for the majority of baseline covariates (except serum BNP and type of AF), demonstrating optimal matching (Fig. 2).

All 79 patients in the PS-matched rhythm control group were taking AADs at the starting period of observation and 19 received more than 1 drug. During the study period, 3 patients (3.8%) experienced an adverse effect from the AADs. In patients taking amiodarone and flecainide, thyroid toxicity was found in 1 patient and 1 developed severe bradycardia (heart rate <40 beats/min). A marked prolongation of the QT interval (corrected QT >500 ms) was found in 1 patient taking bepridil and flecainide. All of the above cases recovered fully after discontinuation of amiodarone or bepridil and continued taking the class I AAD alone. At the final follow-up, a low-dose AAD was prescribed in 39 (49.4%) patients.

*Primary outcome*

Table 2 and Fig. 3 show the association of rhythm control on primary outcome. Overall, 27 patients (9.5%) died during the median follow-up period of 24 months. Of these deaths, 19 (6.7%) were from cardiovascular causes and 8 (2.8%) were non-cardiovascular deaths (5 patients died of sepsis, 1 of cancer, 1 of suicide, and 1 of unknown cause). Across the entire cohort, all-cause mortality was lower in the rhythm control group than in the rate control group [hazard ratio (HR), 0.14; 95% confidence interval (CI), 0.03–0.59; $p = 0.007$]; however, that difference was no longer significant after adjustment with PS (adjusted HR, 0.31; 95% CI, 0.07–1.39; $p = 0.13$). In the propensity-matched cohort, there were 10 (6.3%) all-cause deaths. There was no significant difference in all-cause mortality between the PS-matched groups (HR, 0.50; 95% CI, 0.10–2.45; $p = 0.39$).

*Secondary outcomes*

The impact of rhythm control on secondary outcome is shown in Table 2 and Fig. 3. In the entire cohort, there were 65 (23.0%) events of cardiovascular deaths or HF worsening requiring hospitalization during the follow-up period. The 19 (6.7%) cases of cardiovascular deaths included 14 from progressive HF, 4 from presumed arrhythmic causes, and 1 from fatal myocardial infarction. The rhythm control group had a lower incidence of the composite endpoint even after adjustment with PS (adjusted HR, 0.27; 95% CI, 0.12–0.61; $p = 0.002$).

In the propensity-matched cohort, the rhythm control group also achieved a significant decrease in the rate of secondary outcome (HR, 0.42; 95% CI, 0.18–0.99; $p = 0.048$). To ensure that these results were not confounded by sub-optimally matched baseline covariates, we analyzed them after adjusting for covariates with post-matching absolute standard-

**Table 2**
Impact of Rhythm Control on clinical outcomes.

| Events | Event rates | | | Unadjusted risk | | Adjusted risk[a] | |
|---|---|---|---|---|---|---|---|
| | Total | Rhythm control | Rate control | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Entire cohort (*n* = 283) | | | | | | | |
| All-cause death | 27 (9.5%) | 2 (1.9%) | 25 (14.2%) | 0.14 (0.03–0.59) | 0.007 | 0.31 (0.07–1.39) | 0.13 |
| Cardiovascular death or HF hospitalization | 65 (23.0%) | 7 (6.5%) | 58 (33.0%) | 0.20 (0.09–0.44) | <0.001 | 0.27 (0.12–0.61) | 0.002 |
| Cardiovascular death | 19 (6.7%) | 2 (1.9%) | 17 (9.7%) | 0.22 (0.05–0.94) | 0.04 | 0.47 (0.10–2.18) | 0.33 |
| HF hospitalization | 46 (16.3%) | 5 (4.7%) | 41 (23.3%) | 0.19 (0.08–0.49) | 0.001 | 0.22 (0.08–0.58) | 0.002 |
| PS-matched cohort (*n* = 158) | | | | | | | |
| All-cause death | 10 (6.3%) | 2 (2.5%) | 8 (10.1%) | 0.50 (0.10–2.45) | 0.39 | 0.41 (0.08–1.95) | 0.26 |
| Cardiovascular death or HF hospitalization | 31 (19.6%) | 7 (8.9%) | 24 (30.4%) | 0.42 (0.18–0.99) | 0.048 | 0.30 (0.18–0.98) | 0.04 |
| Cardiovascular death | 8 (5.1%) | 2 (2.5%) | 6 (7.6%) | 0.52 (0.09–2.74) | 0.44 | 0.57 (0.22–2.91) | 0.50 |
| HF hospitalization | 23 (14.6%) | 5 (6.3%) | 18 (22.8%) | 0.34 (0.13–0.97) | 0.04 | 0.34 (0.13–0.94) | 0.04 |

Values are *n* (%) unless otherwise indicated.
CI, confidence interval; HF, heart failure; HR, hazard ratio; PS, propensity score.
HR and CI were derived from Cox proportional hazard models.
[a] In the entire cohort analyses, adjustment was performed for the PS; in the PS-matched cohort analyses, adjustment was performed for the covariates with ≥10% absolute standardized difference between the PS-matched groups (Fig. 2).

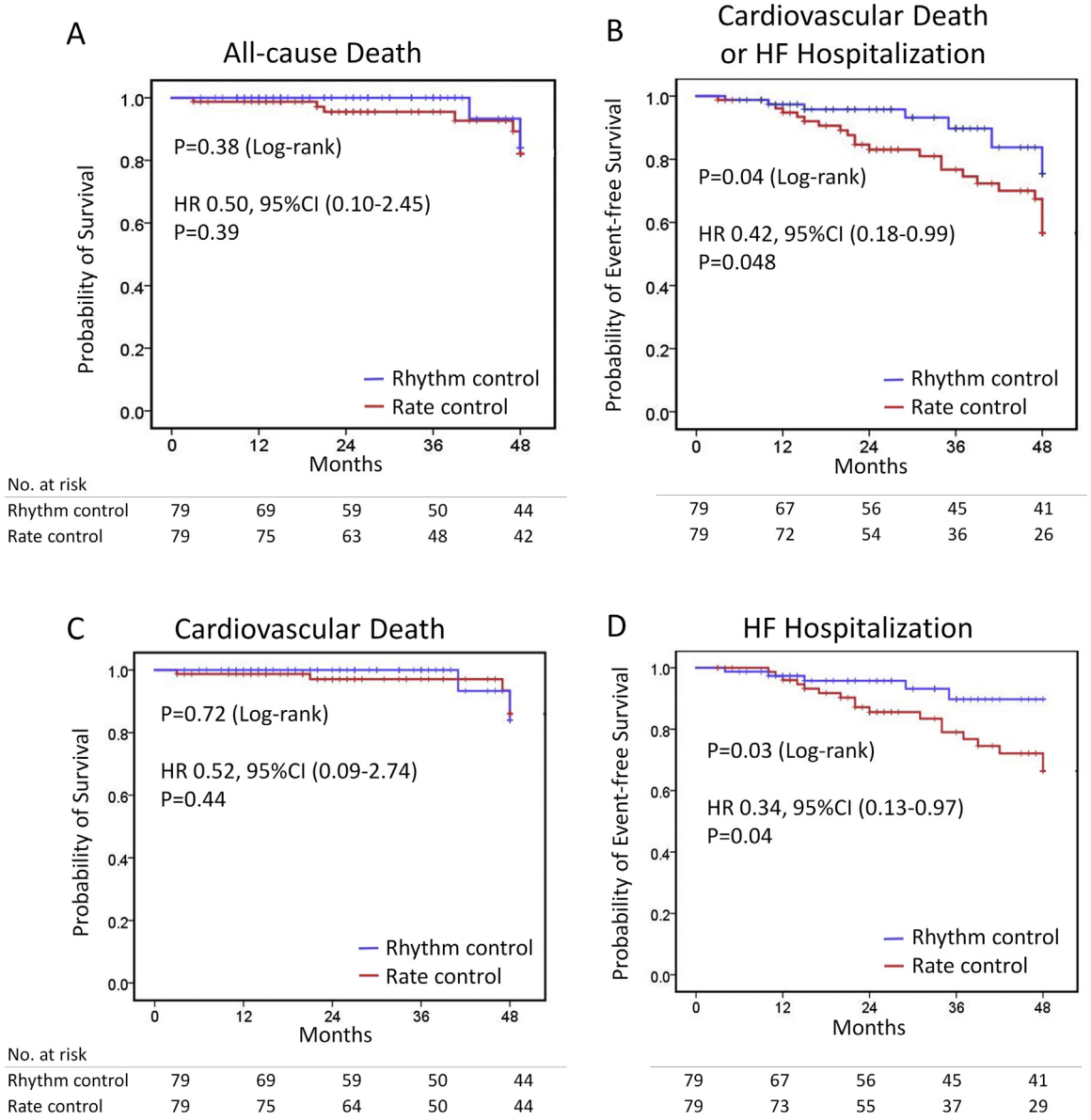



**Fig. 3.** Impact of rhythm control on primary and secondary endpoints in the propensity score-matched population. Event-free rates from all-cause death (A); from a composite of cardiovascular death or hospitalization for heart failure (HF) (B); from cardiovascular death (C); and from hospitalization for HF in the rhythm control group (blue line) versus the rate control group (red line) in the propensity score matched population. Patients at risk at different times are reported below each figure.
CI, confidence interval; HR, hazard ratio.

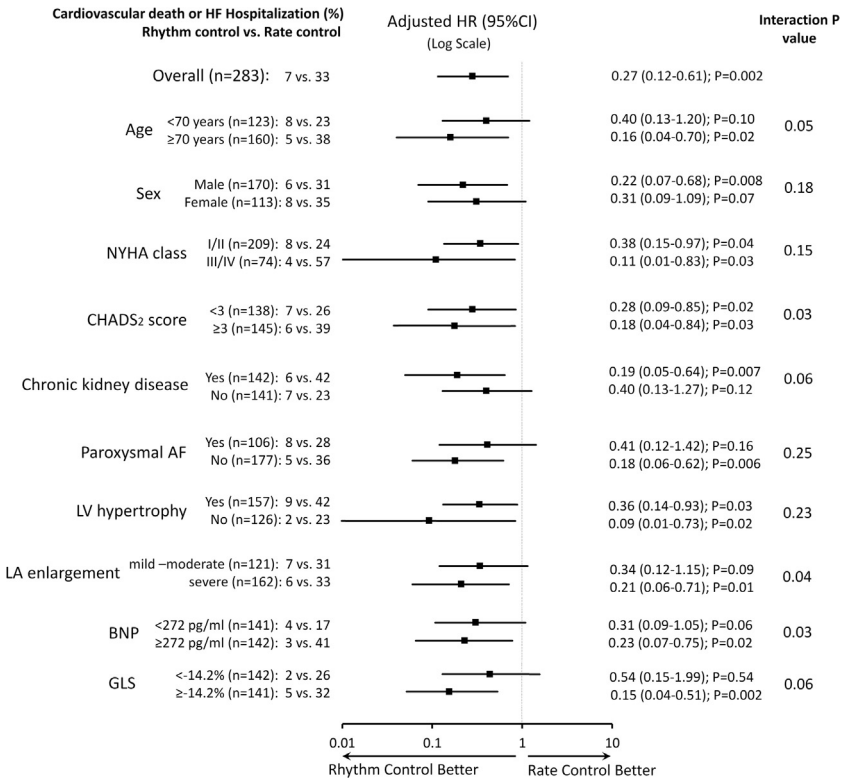
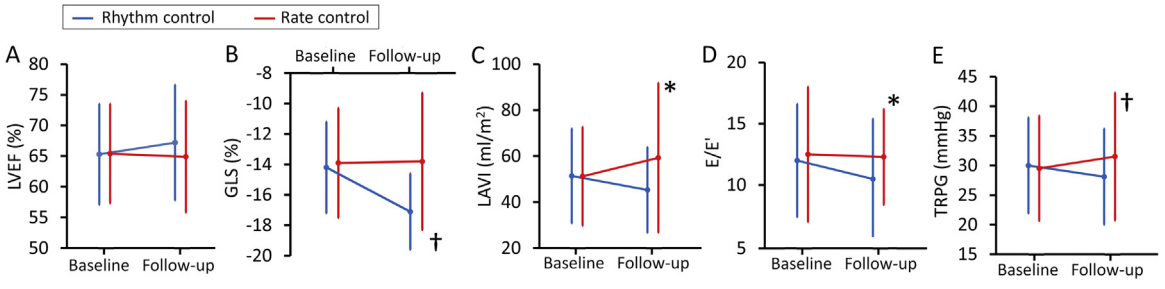



**Fig. 4.** Impact of rhythm control on a composite endpoint of cardiovascular death or hospitalization for heart failure by subgroup. To test the impact of rhythm control and each subgroup in terms of the composite endpoint of cardiovascular death or hospitalization for heart failure (HF), we used multivariable Cox regression models adjusted for the propensity score in the entire cohort ($n$ = 283). Left ventricular (LV) hypertrophy was defined as an echocardiographic LV mass index ≥116 g/m$^2$ (males) and ≥96 g/m$^2$ (females). Mild to moderate left atrial (LA) enlargement was defined as an LA volume index within 35–48 ml/m$^2$ and severe LA enlargement was defined as ≥48 ml/m$^2$.
AF, atrial fibrillation; BNP, brain natriuretic peptide; CI, confidence interval; GLS, longitudinal left ventricular global strain; HR, hazard ratio; NYHA, New York Heart Association.




| | PS-matched rhythm control group | | | PS-matched rate control group | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | P | Baseline | Follow-up | P |
| LVEF, % | 65±8 | 67±9 | 0.048 | 65±8 | 65±9 | 0.56 |
| GLS, % | -14.2±3.0 | -17.1±2.5 | <0.001 | -13.9±3.6 | -13.8±4.5 | 0.10 |
| LAVI, ml/m$^2$ | 51±21 | 45±3 | 0.005 | 51±21 | 59±33 | 0.006 |
| E/E′ | 12.0±4.6 | 10.4±4.9 | 0.048 | 12.5±5.5 | 12.6±3.9 | 0.83 |
| TRPG, mmHg | 30±10 | 28±8 | 0.03 | 29±10 | 31±11 | 0.06 |
| BNP, pg/ml | 233[137-331] | 116[43-182] | <0.001 | 230[144-344] | 186[94-377] | 0.48 |

The P value indicates intragroup statistical difference in each parameter.

**Fig. 5.** Changes in echocardiographic parameters and serum brain natriuretic peptide levels. Serum brain natriuretic peptide (BNP) and echocardiographic measurements in patients treated with rhythm control and rate control therapy are shown. Plotted values are means ± standard deviation. Baseline and follow-up (over 12 months after enrollment) data of left ventricular ejection fraction (LVEF) (A), global left ventricular longitudinal strain (GLS) (B), left atrial volume index (LAVI) (C), $E/E'$ ratio (D), peak tricuspid regurgitant pressure gradient (TRPG), (E) and serum BNP levels (F) are compared. *$p < 0.05$ and †$p < 0.01$ compared with rhythm control group at follow-up. The $p$-values shown in the table indicate the statistical significances between baseline and follow-up.

ized difference >10% (serum BNP level and type of AF). Even after adjustment, maintenance of SR was still associated with a decreased risk of the composite endpoint (adjusted HR, 0.30; 95% CI, 0.18–0.98; $p = 0.04$). In particular, there was significant reduction in the probability of hospitalization for HF in the rhythm control group (adjusted HR, 0.34; 95% CI, 0.14–0.94; $p = 0.04$).

We also evaluated the association between AADs and cardiac prognosis in the entire cohort. Kaplan–Meier survival analysis and multivariable Cox proportional hazard model showed that use of any AADs or class Ic AADs did not show significant increased risk of cardiac death or a composite of cardiac death and HF hospitalization (Supplementary Fig. 1).

*Subgroup analysis*

An association between rhythm control and reduction of cardiovascular death or hospitalization for HF was noted across a wide spectrum of HFpEF patients across the entire cohort after adjustment with PS (Fig. 4). The consistency of the favorable effect of rhythm control is illustrated by the overlap of CIs in the subgroups with that of the overall cohort.

*Changes in cardiac function and natriuretic peptides*

Changes in echocardiographic parameters and serum BNP level in the PS-matched cohort are illustrated in Fig. 5. In the PS-matched cohort, follow-up echocardiographic and BNP data (over 12 months after observation) were available for 138 (72 in the rhythm control group and 66 in the rate control group) after 10 patients died and 10 were found to lack follow-up data. The baseline values of all parameters were comparable between both treatment arms. From baseline to follow-up, LA reverse remodeling was seen in the rhythm control group, while LA remodeling progressed in the rate control group. In the PS-matched rhythm control group, LVEF and GLS significantly improved and the $E/E'$ ratio and peak tricuspid regurgitation pressure gradient were significantly reduced at follow-up compared with baseline values. In contrast, no changes were seen in the PS-matched rate control group. Serum BNP levels were found to be significantly decreased from baseline to follow-up in the rhythm control group only. In the PS-matched cohort, 75 patients experienced improvement of echocardiographic parameters and 83 did not. Rate of use of class Ic AADs did not show significant difference between patients with and those without improvement of echocardiographic parameters (14.7% vs. 14.5%, $p = 1.00$). Patients with improvement of echo parameters showed lower probability of cardiac events (Supplementary Fig. 2).

## Discussion

*Major findings*

This is one of the first studies to date to report a potential advantage when SR is able to be maintained among patients with HFpEF. In patients with concomitant HFpEF and AF, determining the relationships between maintenance of SR and clinical outcomes compared with rate control has been problematic due to treatment strategies being commonly set at the attending physician's discretion, which makes unbiased comparisons challenging. We employed PS matching to overcome these limitations and demonstrated that: (1) there was no evidence that maintenance of SR is associated with lower all-cause mortality, (2) maintenance of SR was associated with the lower occurrence of a composite endpoint of cardiovascular death or hospitalization for HF in the overall study population and across a wide spectrum of subgroups, and (3) maintenance of SR had favorable effects on cardiac function and natriuretic peptide secretion at 12 months of follow-up.

*Efficacy of maintenance of sinus rhythm in patients with concomitant AF and HFpEF*

In patients with HFpEF, those with concomitant AF have significantly greater exertional intolerance, higher LV filling pressure [21,22], and worse prognosis [5,7] than those with SR. Although it has been suggested that restoration of SR has a positive impact on exercise hemodynamics, symptom severity, and quality of life [10,12,13], the data regarding the association of rhythm control and the adverse cardiac events of HFpEF has been limited. In the present study, we demonstrate that rhythm control for AF might be associated with better cardiovascular outcomes in patients with HFpEF in comparison with rate control. Although AF recurred in some patients of PS-matched rhythm control group, the majority of those reduced the AF burden despite reduced dose of AADs during follow-up. That might contribute to the better cardiac prognosis in the rhythm control group. On the contrary, more than one-third of patients with paroxysmal AF in the rate control group progressed to persistent AF during the observational period as a natural course and that might be associated with increase of worsening of HF [23]. Ventricular stiffening and impaired LV relaxation are the major pathophysiological mechanisms in HFpEF [15]. To compensate for such LV diastolic dysfunction and prevent pulmonary edema, the contribution and importance of LA function significantly increases [24] and further compromise of LA function is directly associated with new-onset dyspnea [25]. Thus, rhythm control to preserve both LA and LV function may, in theory, lead to greater hemodynamic improvement and may prevent exacerbation of HF in HFpEF patients. We have previously demonstrated that maintenance of SR leads to functional improvement of the LA and LV in HFpEF [9]. Our present study also showed that the $E/E'$ ratio, LA volume, and peak tricuspid regurgitant pressure gradient, which are key echocardiographic parameters associated with diastolic function in patients with HFpEF [15,26], improved in the rhythm control group. In addition, we found these favorable changes of cardiac function were associated with the lower prevalence of cardiac adverse events in the present study. To date, there are no proven therapies for HFpEF; therefore, targeted therapy aimed at AF in HFpEF is an appealing consideration. The results of subgroup analysis suggest that there were significant interactions between rhythm control and age, $CHADS_2$ score, chronic kidney disease, severity of LA enlargement, BNP levels, and GLS. This finding may be a quantitative interaction indicating that the treatment effect varies in magnitude by subgroup since each CI across subgroups was almost overlapping and in the same direction [27]. Overall, our results showed that rhythm control seems to have a favorable impact on all subgroups of HFpEF patients.

However, despite the improvement in cardiac function and lower incidence of cardiovascular events in patients with maintenance of SR, reduction in all-cause mortality was not seen in the present study. The plausible explanations for the result are the small sample size and low mortality rate in the present study and the complex pathophysiology of HFpEF involving multiple organ systems failure in addition to cardiac dysfunction [15]. Therefore, randomized trials in large cohorts are mandatory to confirm

the clinical impact of maintenance of SR in patients with both HFpEF and AF.

*Catheter ablation based rhythm control in HFpEF*

To maintain SR in the long-term, the majority of patients in the rhythm control group required CA. Since HF induces atrial fibrosis/remodeling leading to the development of the AF substrate [6,28], rhythm control with AADs alone has shown unsatisfactory results [11,19,29]. CA is an effective and safe therapeutic option to overcome this limitation and eliminate AF, even in patients with HF [9,11,30]. In addition, our results showed that ablation-based rhythm control enabled the discontinuation of AADs in approximately half of the rhythm control group and dose reduction in the remaining cases. It has been recognized that AADs prescribed for AF are associated with increased mortality, and the adverse effects of AADs offset the benefit of maintenance of SR in a previous study [31]. In particular, the current guidelines discourage use of class Ic AADs in patients with congestive HF because of their cardiodepressant effects [15]. In the present study, prescription of any AADs except amiodarone were carefully performed for patients with hemodynamically stable condition after enough decongestion therapy and patients were closely followed-up. As a result, lethal complications of AADs did not occur in our study and there was no increase in cardiac adverse events in patients taking class Ic AADs. Dose-reduction of AADs after successful CA, and regular examination by trained cardiologists might contribute to rare adverse events relating to AADs in the present study.

*Limitations*

First, precise diagnosis of HFpEF in the context of AF remains challenging since the clinical symptoms and signs overlap [15]. Second, since this is a nonrandomized study including a relatively small number of patients, biases related to unmeasured or hidden confounders might potentially limit the findings despite PS matching. Third, it is possible that matching process excluded patients who were older and had more advanced HF from our analysis. That might limit generalizability to patients dissimilar to those included in our analysis.

Fourth, changes in the prescribed medication (except for AADs) during the observation period were not recorded. Although the treatments administered for HF were comparable at the starting point of observation, patients treated with rhythm control might have received potentially better overall medical care during the study period. Finally, intermittent or symptom-based monitoring is less effective for the detection of asymptomatic recurrence of atrial arrhythmias, compared with implantable loop recorders.

## Conclusions

In patients with concomitant HFpEF and AF, maintenance of SR was independently associated with a lower risk of a composite endpoint of cardiovascular death or hospitalization for HF but had no association with all-cause mortality during long-term follow-up. Rhythm control could be an effective therapeutic option to improve cardiovascular outcomes in patients with HFpEF. A randomized trial is required to definitively confirm our results.

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## Conflicts of interest

Dr. Aonuma received endowments from Boston Scientific Japan, Japan Lifeline, Nihon Kohden, Biotronik Japan, Toray Industries, Century Medical, and Boehringer Ingelheim Japan. Dr. Nogami received honoraria from Medtronic, Japan Lifeline, Daiichi Sankyo, and St. Jude Medical, and an endowment from Medtronic and DVx. Dr. Sekiguchi received an endowment from St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.02.014.

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