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ORIGINAL RESEARCH

Impact of Atrial Tachyarrhythmia Recurrence on the Development of Long-Term Adverse Clinical Events Following Catheter Ablation in Patients With Atrial Fibrillation With Systolic Impairment: A Single-Center Observational Study

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BACKGROUND: Catheter ablation can improve long-term prognosis of patients with atrial fibrillation with systolic impairment. However, atrial tachyarrhythmia (ATA) recurrence increases during long-term follow-up. We aimed to investigate the impact of ATA recurrence on the development of long-term adverse clinical events following catheter ablation for atrial fibrillation and to identify predictors for the development of adverse clinical events.

METHODS AND RESULTS: This single-center observational study included 75 patients with systolic impairment (left ventricular ejection fraction <50%) who underwent the first catheter ablation procedure for atrial fibrillation at our institution (median follow-up period: 3.5 [range: 2.4–4.7] years). We compared the cumulative incidence of adverse clinical events (all-cause death, heart failure hospitalization, stroke, or acute myocardial infarction) between the groups with and without ATA recurrence following the first and last procedures. Multivariable analyses were performed to identify predictors for developing adverse clinical events. Twenty-one patients (28%) developed adverse clinical events at a median of 2.2 (range: 0.64–2.8) years following the first procedure. The proportion of freedom from adverse clinical events following the first procedure was significantly lower in the ATA recurrence group than in the nonrecurrence group (41% [n=40] versus 95% [n=35], $P<0.0005$); the proportion following the last procedure also showed a similar tendency (35% [n=26] versus 57% [n=49], $P<0.0001$). ATA recurrence emerged as an independent predictor for adverse clinical events following both procedures after multivariable adjustment.

CONCLUSIONS: ATA recurrence following catheter ablation procedure could predict adverse clinical events in patients with atrial fibrillation with systolic impairment.

Key Words: atrial fibrillation ■ atrial tachyarrhythmia recurrence ■ catheter ablation ■ heart failure

The prevalence of atrial fibrillation (AF) is still increasing because of the increase in the aging population worldwide.[1,2] Heart failure (HF) is one of the major complications of AF. Especially in older patients with AF, the incidence of HF was much higher than that of other complications, such as stroke, gastrointestinal bleeding,

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CLINICAL PERSPECTIVE

What Is New?

- We evaluated long-term prognosis in patients with systolic impairment who underwent catheter ablation for atrial fibrillation in contemporary real-world clinical settings.
- The incidence of adverse clinical events was significantly higher among patients with atrial tachyarrhythmia recurrence following the procedure than among those without.

What Are the Clinical Implications?

- Our data showed that catheter ablation for atrial fibrillation in the contemporary clinical setting achieved high safety and efficacy for patients with systolic impairment because of advanced technology.
- Atrial tachyarrhythmia recurrence was a marker of high risk for adverse clinical events in patients with systolic impairment who underwent catheter ablation for atrial fibrillation.
- Watchful follow-up examination after performing the procedure may allow early detection of atrial tachyarrhythmia recurrence, which could help avoid adverse clinical events.

Nonstandard Abbreviations and Acronyms

AFL	atrial flutter
AT	atrial tachycardia
ATA	atrial tachyarrhythmia
CA	catheter ablation
CF	contact force
HFH	heart failure hospitalization
LAD	left atrial diameter
LVDd	left ventricular end-diastolic diameter
PVI	pulmonary vein isolation
SVC	superior vena cava
TTE	transthoracic echocardiography

and myocardial infarction.[3] Although HF and AF are frequently observed together, the optimal therapeutic strategy remains unclear.[4,5] Given that the incidence of AF could confer a higher negative prognostic impact on patients with impaired systolic function than on those with preserved systolic function,[6] the prognostic information for AF patients with systolic impairment is particularly crucial. Recently, a randomized controlled trial (CASTLE-AF [Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation] trial) revealed that compared with standard medical therapy, catheter ablation (CA) for AF reduced the risk of death or worsening HF for selected patients with systolic impairment.[7] However, it remains unknown whether the result could be extrapolated to real-world settings. Furthermore, the rate of recurrence of atrial tachyarrhythmia (ATA) following CA gradually increased with long-term follow-up.[8,9] One may infer that ATA recurrence during long-term follow-up could impair the benefit of sinus restoration by CA and result in poor clinical outcomes, such as worsening HF. To elucidate this issue, we aimed to assess the association between long-term adverse clinical events and ATA recurrence following CA during long-term follow-up in patients with AF with systolic impairment (left ventricular ejection fraction [LVEF] <50%). We also aimed to identify predictors for the development of adverse clinical events.

METHODS

Study Design and Population

The data sets analyzed in this study are available from the corresponding author upon reasonable request. This single-center retrospective observational study

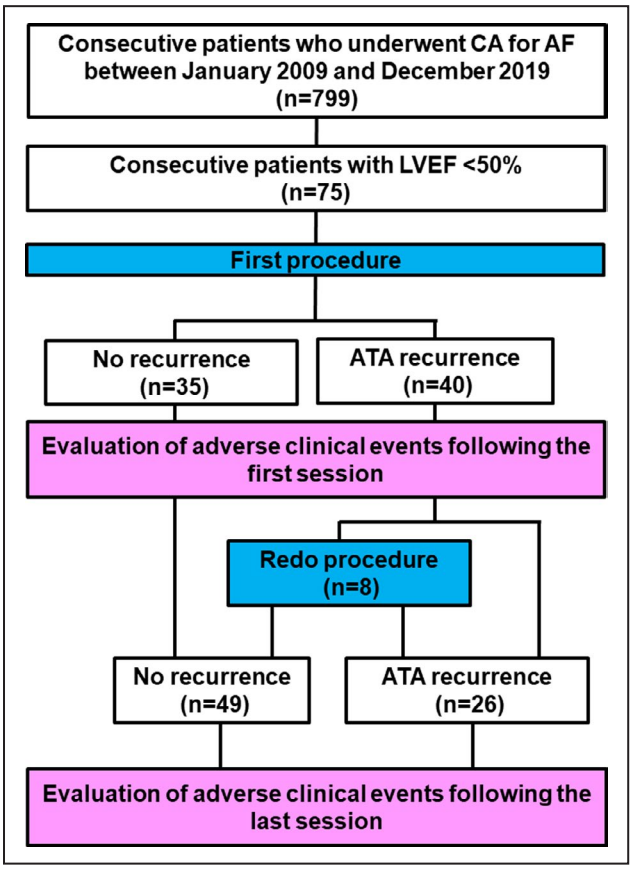

Figure 1. Flow diagram of the study
AF indicates atrial fibrillation; ATA, atrial tachyarrhythmia; CA, catheter ablation; and LVEF, left ventricular ejection fraction.

Table 1. Comparison of Demographics Between the Nonrecurrence and ATA Recurrence Groups Following the First Procedure

	Total (n=75)	Nonrecurrence (n=35)	ATA recurrence (n=40)	*P* value
Age (y), mean±SD, [0]	65±11	64±10	66±11	0.15
Female sex, n (%), [0]*	20 (27)	5 (14)	15 (38)	0.02
Persistent AF, n (%), [0]	46 (61)	22 (63)	24 (60)	0.98
AF duration (mo), median (IQR), [0]	12 (4, 36)	11 (4, 22)	21 (4, 53)	0.20
BMI (kg/m^2), mean±SD, [0]	23±4	23±4	23±4	0.85
SBP (mm Hg), mean±SD, [0]	121±17	121±17	121±18	0.68
HR (/min), mean±SD, [0]	77±18	75±16	78±19	0.70
NYHA class, mean±SD, [0]	1.8±0.7	1.7±0.7	1.9±0.8	0.51
History of HFH, n (%), [0]	35 (47)	15 (43)	20 (50)	0.69
CTR, mean±SD, [0]	51±5	50±5	51±5	0.30
CHA_2DS_2-VASc, mean±SD, [0]	2.6±1.8	2.4±1.9	2.7±1.6	0.29
ICD/CRT, n (%), [0]	12 (16)	3 (9)	9 (23)	0.12
Echocardiographic parameter				
LVDd (mm), mean±SD, [0]	54±7	53±6	55±8	0.22
LVEF (%), mean±SD, [0]	39±8	40±7	39±8	0.78
LAD (mm), mean±SD, [0]	44±8	41±7	45±8	0.21
LAVI (mL/m^2), mean±SD, [10]	58±19	53±15	62±21	0.11
Mitral E/e' ratio, mean±SD, [10]*	11±6	9±3	13±6	0.01
Therapeutic agent				
ACEI/ARB, n (%), [0]	54 (72)	26 (74)	28 (70)	0.88
β-Blocker, n (%), [0]	66 (88)	29 (83)	37 (93)	0.35
MRA, n (%), [0]	25 (33)	11 (31)	14 (35)	0.93
Diuretics, n (%), [0]	37 (49)	16 (46)	21 (53)	0.72
AAD, n (%), [0]*	19 (25)	5 (14)	14 (35)	0.04
Amiodarone, n (%), [0]	17 (23)	5 (14)	12 (30)	0.1
Laboratory data				
eGFR (mL/min per 1.73 m^2), mean±SD, [0]	54±18	59±15	51±21	0.08
BNP level (pg/mL), median (IQR), [0]	167 (82, 358)	147 (83, 284)	192 (81, 411)	0.16
Structural heart disease				
IHD, n (%), [0]	13 (17)	9 (26)	4 (10)	0.16
DCM/DHCM, n (%), [0]	8 (11)	4 (11)	4 (10)	0.86
HCM, n (%), [0]	3 (4)	0	3 (8)	0.29
VHD, n (%), [0]	2 (3)	2 (6)	0	0.42
CHD, n (%), [0]	2 (3)	1 (3)	1 (3)	0.53
Cardiac sarcoidosis, n (%), [0]	6 (8)	1 (3)	5 (13)	0.27

Numerical data are expressed as means±SDs or medians (IQRs; first quartile, third quartile). Categorical data are expressed as percentages and numbers. The numbers of missing data are presented in square brackets.

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ATA, atrial tachyarrhythmia; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; CTR, cardiothoracic ratio; DCM, dilated cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HFH, heart failure hospitalization; HR, heart rate; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; IQR, interquartile range; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; and VHD, valvular heart disease.

*Indicates statistical significance (P<0.05).

was conducted at Yamaguchi University Hospital. This study was approved by the institutional review board. Informed consent was waived owing to the opt-out system. The tenets of the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation were followed.

Consecutive patients with systolic impairment (LVEF <50%) who underwent their first session of CA

Table 2. Comparison of CA-Related Variables Between the Nonrecurrence and ATA Recurrence Groups Following the First Procedure

	Total (n=75)	Nonrecurrence (n=35)	ATA recurrence (n=40)	*P* value
Radiofrequency PVI (non-CF-guided), n (%), [0]	6 (8)	1 (3)	5 (13)	0.12
Radiofrequency PVI (CF-guided), n (%), [0]	56 (75)	27 (77)	29 (73)	0.64
Cryoballoon PVI, n (%), [0]	13 (17)	7 (20)	6 (15)	0.57
SVCI, n (%), [0]	32 (43)	17 (49)	15 (38)	0.33
CTI ablation, n (%), [0]	24 (32)	11 (31)	13 (33)	0.92
Posterior wall isolation, n (%), [0]	0	0	0	>0.99
CFAE ablation, n (%), [0]	0	0	0	>0.99
Performed by less-experienced operator, [0]	3 (4)	2 (6)	1 (3)	0.47

Categorical data are expressed as percentages and numbers.
ATA indicates atrial tachyarrhythmia; CA, catheter ablation; CF, contact force; CFAE, complex fractionated atrial electrogram; CTI, cavo-tricuspid isthmus; PVI, pulmonary vein isolation; and SVCI, superior vena cava isolation.

for AF between January 2009 and December 2019 were included. LVEF was measured using transthoracic echocardiography (TTE). Patients whose preprocedural TTE data were not available were excluded. The 3-month period following the CA procedure was defined as the blanking period. We dichotomized the whole population into (1) patients without ATA recurrence after the blanking period following the first/last procedure (nonrecurrence group) and (2) those with ATA recurrence (ATA recurrence group).

Study End Points

The primary end point of this study was a comparison of the cumulative incidence of adverse clinical events between both groups. In addition, the predictors for the development of adverse clinical events were evaluated using univariate and multivariable analyses.

CA Procedure

During the first CA procedure, all patients underwent pulmonary vein isolation (PVI) by radiofrequency energy (Navistar Thermocool; Biosense Webster, Diamond Bar, CA) or second-generation cryoballoon energy (Arctic Front Advance, Medtronic, Inc., Minneapolis, MN). The procedural protocol and strategy of our group have been previously described.[10,11] In brief, the procedural end point was the disappearance or dissociation of all pulmonary vein (PV) potentials. Patients with paroxysmal AF underwent radiofrequency or cryoballoon PVI using a 3-dimensional electroanatomical mapping system (CARTO, Biosense Webster). Patients with persistent AF since October 2015 underwent empiric superior vena cava (SVC) isolation in addition to PVI. Cavotricuspid isthmus ablation was performed for patients who had a documented common atrial flutter (AFL). Ablation for complex fractionated atrial electrograms was not performed. Regarding the redo procedure, all patients were assessed for PV reconnection during sinus rhythm. The closure of all PV conduction and electrical re-isolation gaps was performed using radiofrequency energy. If electrical isolation of all PVs was already achieved, SVC isolation was performed. For patients who underwent SVC isolation in the previous procedure, SVC re-isolation was also performed when SVC reconnection was obtained. Regarding patients who were clinically confirmed as having common/uncommon AFL or atrial tachycardia, ablation for the targeted the AFL/atrial tachycardia was also performed.

Definition of Clinical Events

Adverse clinical events were defined as composite events of all-cause death, HF hospitalization (HFH), stroke, and acute myocardial infarction. Events that occurred within the blanking period were excluded. HFH was defined as hospitalization that required unplanned medical treatments, such as the intravenous administration of diuretics, renal replacement therapy, and cardiac pacing for decompensated HF. Stroke was defined as ischemic stroke that required unplanned hospitalization for manifest neurological symptoms.

Patient Follow-up

All patients underwent blood analysis, chest radiography, electrocardiography, transesophageal echocardiography, and TTE within 1 month before CA. After the procedure, electrocardiography was continuously performed for at least 3 days. In outpatient settings, electrocardiography and/or 24-hour Holter electrocardiography recordings were obtained by the referring physician at 1, 3, 6, and 12 months after the procedure. Event monitoring using 24-hour Holter electrocardiography or a cardiac event recorder was performed when patients complained of symptoms indicative of ATA recurrence. ATA recurrence was defined as the detection of >30 s of AF/AFL after the

Table 3. Characteristics of Patients Who Developed Adverse Clinical Events

Patient no.	Age (y)	Sex	Total CA sessions	ATA recurrence following the first procedure		First event following the first procedure		ATA recurrence following the last procedure		First event following the last procedure		Trigger of worsening HF
				Y/N	Months	Type	Months	Y/N	Months	Type	Months	
1	77	Male	1	Y	31	HFH	31	…	…	…	…	ATA
2	71	Female	1	Y	28	HFH	29	…	…	…	…	ATA
3	64	Female	1	Y	7	HFH	7	…	…	…	…	Volume overload
4	82	Male	1	Y	38	HFH	5	…	…	…	…	Hypoperfusion, MR
5	75	Male	1	Y	17	HFH	14	…	…	…	…	Hypoperfusion
6	77	Female	1	Y	31	HFH	30	…	…	…	…	Bradycardia
7	43	Male	1	Y	3	HFH	30	…	…	…	…	Poor compliance, ATA
8	66	Female	1	N	…	Stroke	31	…	…	…	…	…
9	70	Female	2	Y	7	HFH	26	Y	13	HFH	15	MR, ATA
10	70	Male	2	Y	9	HFH	43	Y	16	HFH	32	Pneumonia, ATA
11	79	Female	2	Y	4	HFH	12	Y	9	HFH	26	ATA
12	67	Male	2	Y	3	HFH	7	N	…	HFH	4	Hypoperfusion
13	67	Female	2	Y	3	HFH	8	Y	6	HFH	27	ATA
14	71	Male	2	Y	3	HFH	132	N	…	HFH	77	ATA
15	73	Male	2	Y	3	HFH	10	Y	3	HFH	5	Volume overload
16	58	Male	2	Y	20	Stroke	24	N	…	…	7	…
17	82	Female	2	Y	4	Stroke	7	Y	11	HFH	11	ATA
18	67	Female	3	Y	4	HFH	6	Y	14	HFH	28	Bradycardia, Hypoperfusion
19	74	Male	3	Y	3	HFH	71	Y	10	HFH	25	VA
20	71	Male	3	Y	3	HFH	55	N	…	HFH	68	ATA
21	66	Female	4	Y	3	HFH	51	Y	28	HFH	33	Volume overload, bradycardia

ATA indicates atrial tachyarrhythmia; CA, catheter ablation; HF, heart failure; HFH, heart failure hospitalization; MR, mitral regurgitation; and VA, ventricular arrhythmia.

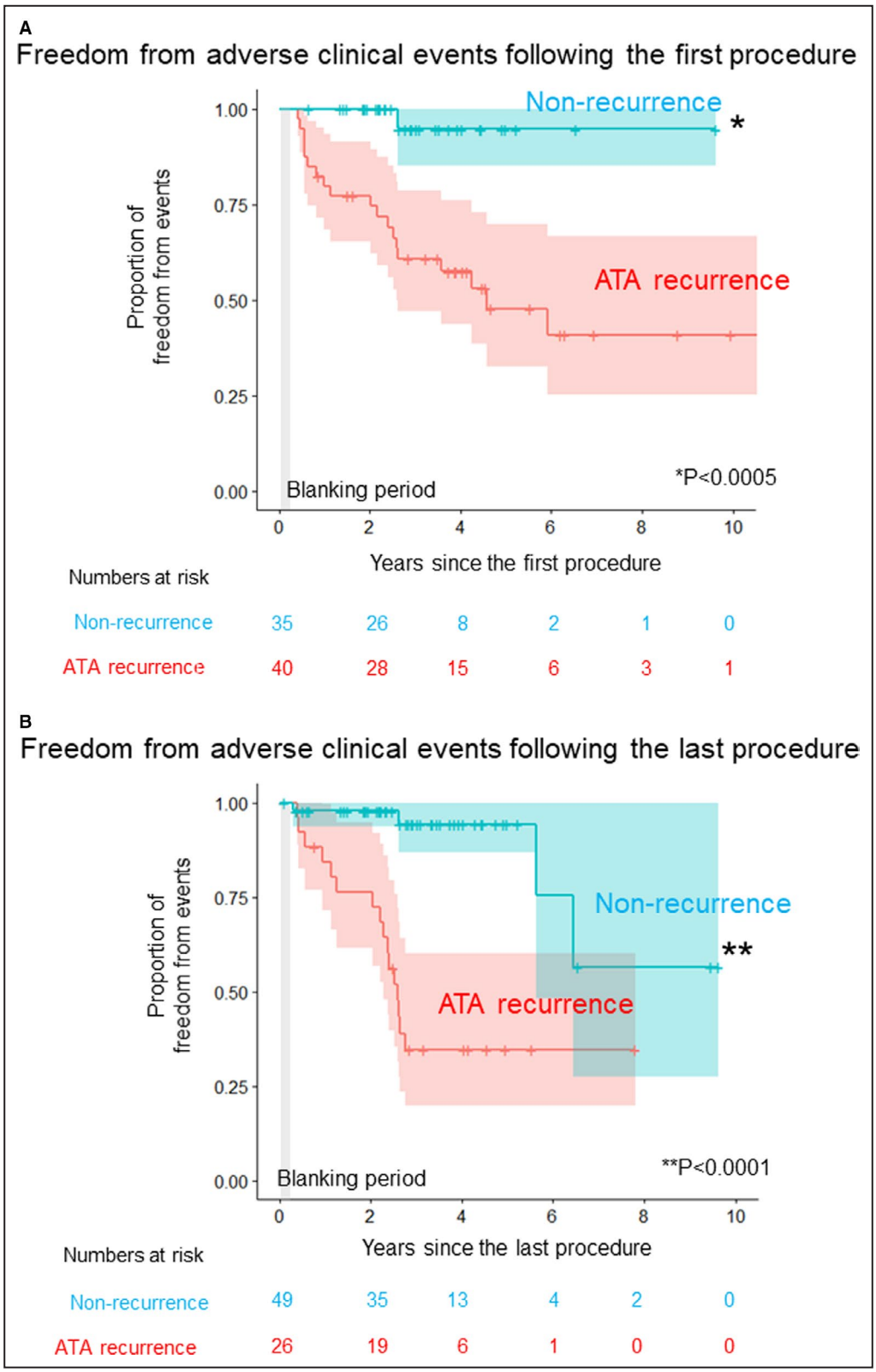

Figure 2. Comparison of the cumulative incidence of adverse clinical events
A, The Kaplan–Meier curve shows a cumulative proportion with the 95% CI of adverse clinical events following the first procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **B,** The Kaplan–Meier curve shows a cumulative proportion with 95% CI of adverse clinical events following the last procedure in the nonrecurrence (blue) and ATA recurrence groups (red). The asterisk indicates statistical significance (*P<0.0005, **P<0.0001). ATA indicates atrial tachyarrhythmia.

Table 4. Comparison of Demographics Between the Nonrecurrence and ATA Recurrence Groups Following the Last Procedure

	Total (n=75)	Nonrecurrence (n=49)	ATA recurrence (n=26)	*P* value
Age (y), mean±SD, [0]*	65±11	64±12	69±9	0.03
Female sex, n (%), [0]*	20 (27)	6 (12)	14 (54)	0.0001
Persistent AF, n (%), [0]	46 (61)	30 (61)	16 (62)	0.98
AF duration (mo), median (IQR), [0]	12 (4, 36)	11 (4, 25)	25 (5, 54)	0.20
BMI (kg/m^2), mean±SD, [0]	23±4	23±4	23±4	0.69
SBP (mm Hg), mean±SD, [0]	121±17	122±17	117±17	0.18
HR (/min), mean±SD, [0]	77±18	74±15	82±21	0.12
NYHA class, mean±SD, [0]	1.8±0.7	1.7±0.6	2±0.8	0.15
History of HFH, n (%), [0]	35 (47)	20 (41)	15 (58)	0.16
CTR, mean±SD, [0]*	51±5	49±5	53±4	0.003
CHA_2DS_2-VASc, mean±SD, [0]*	2.6±1.8	2.3±1.7	3.1±1.7	0.027
ICD/CRT, n (%), [0]	12 (17)	7 (14)	5 (19)	0.58
SHD, n (%), [0]	34 (45)	23 (47)	11 (42)	0.70
Echocardiographic parameter				
LVDd (mm), mean±SD, [0]	54±7	53±6	56±8	0.46
LVEF (%), mean±SD, [0]	39±8	40±7	38±8	0.67
LAD (mm), mean±SD, [0]	44±8	43±7	46±8	0.09
LAVI (mL/m^2), mean±SD, [10]	58±19	55±19	63±19	0.08
Mitral E/e'ratio, mean±SD, [10]*	11±6	9±4	15±7	0.0004
Therapeutic agent				
ACEI/ARB, n (%), [0]	54 (72)	35 (71)	19 (73)	0.88
β-Blocker, n (%), [0]	66 (88)	41 (84)	25 (96)	0.11
MRA, n (%), [0]	25 (33)	15 (31)	10 (38)	0.49
Diuretics, n (%), [0]	37 (49)	22 (45)	15 (58)	0.29
AAD, n (%), [0]	19 (25)	9 (18)	10 (38)	0.056
Amiodarsone, n (%), [0]	17 (23)	8 (16)	9 (35)	0.07
Laboratory data				
eGFR (mL/min per 1.73 m^2), mean±SD, [0]	54±18	57±16	50±21	0.10
BNP level (pg/mL), median (IQR), [0]*	167 (82, 358)	148 (77, 286)	242 (113, 429)	0.038
Structural heart disease				
IHD, n (%), [0]	13 (17)	9 (18)	4 (15)	0.99
DCM/DHCM, n (%), [0]	8 (11)	5 (10)	3 (12)	0.83
HCM, n (%), [0]	3 (4)	1 (2)	2 (8)	0.57
VHD, n (%), [0]	2 (3)	2 (4)	0	0.77
CHD, n (%), [0]	2 (3)	1 (2)	1 (4)	0.57
Cardiac sarcoidosis, n (%), [0]	6 (8)	5 (10)	1 (4)	0.60

Numerical data are expressed as means±SDs or medians (IQRs; first quartile, third quartile). Categorical data are expressed as percentages and numbers.

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ATA, atrial tachyarrhythmia; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; CTR, cardiothoracic ratio; DCM, dilated cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HFH, heart failure hospitalization; HR, heart rate; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; IQR, interquartile range; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SHD, structural heart disease; and VHD, valvular heart disease.

*Indicates statistical significance ($P<0.05$).

blanking period. During the follow-up visit at 3 months after the procedure, blood analysis, chest radiography, and TTE were performed as the postprocedural assessment for all patients. Redo procedure was recommended for patients who developed ATA recurrence. Data regarding clinical events were collected

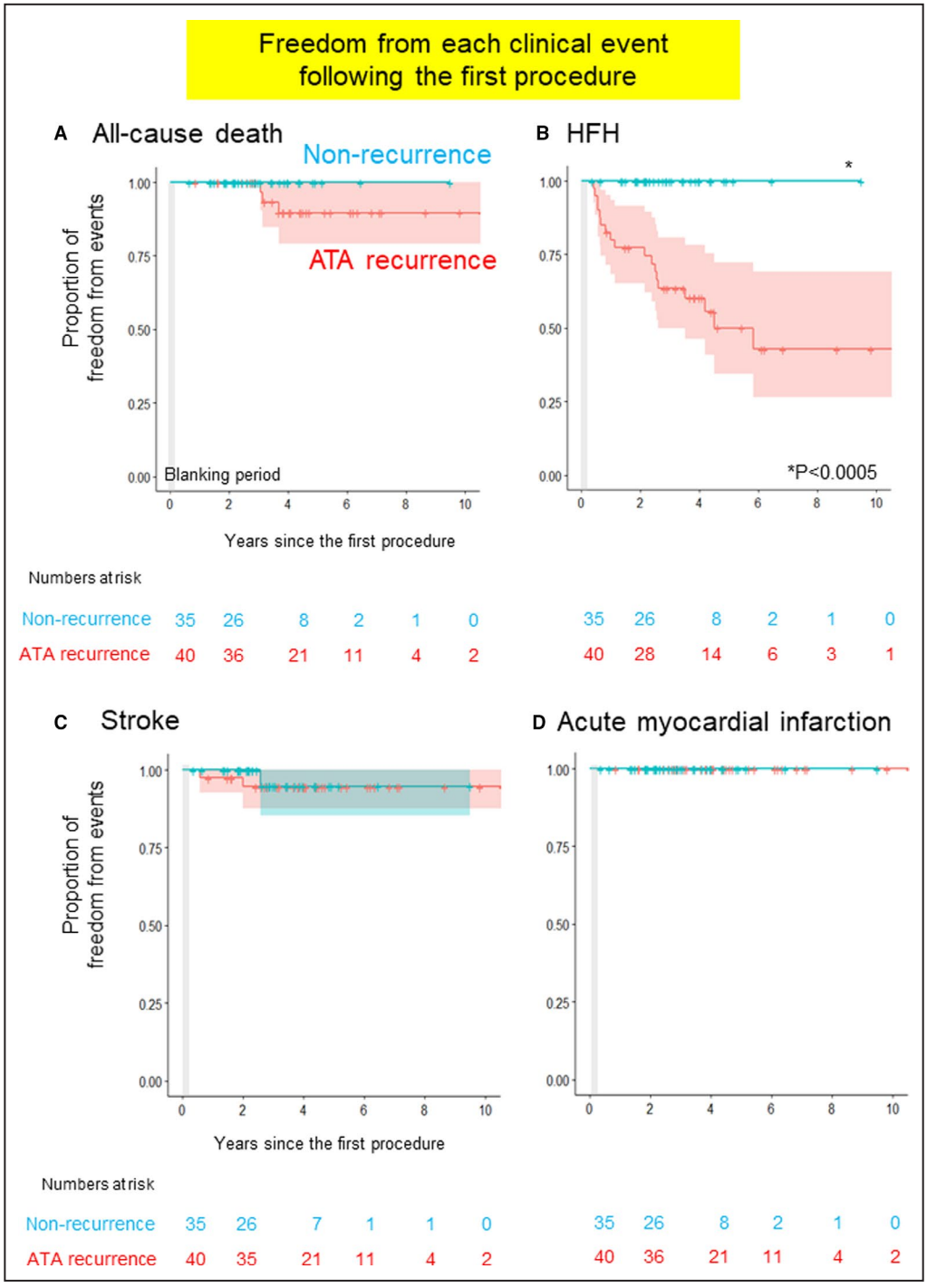

Figure 3. Comparison of the cumulative incidence of each adverse clinical event following the first procedure

A, The Kaplan–Meier curve shows cumulative proportion with 95% CI for all-cause death following the first procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **B,** The Kaplan–Meier curve shows cumulative proportion with the 95% CI for HFH following the first procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **C**, The Kaplan–Meier curve shows cumulative proportion with 95% CI for stroke following the first procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **D,** The Kaplan–Meier curve shows cumulative proportion with 95% CI for acute myocardial infarction following the first procedure in the nonrecurrence (blue) and ATA recurrence groups (red). The asterisk indicates statistical significance (*P<0.0005). ATA indicates atrial tachyarrhythmia; and HFH, heart failure hospitalization.

by contacting the primary care physicians of each patient in April 2021.

Statistical Analysis

Normally distributed variables are expressed as means±SDs, whereas non-normally distributed variables are expressed as medians and interquartile (first and third) ranges. Differences in continuous variables between the groups were evaluated using the Mann–Whitney test. Categorical variables are presented as frequency and proportion (%) and were compared using the χ^2 test. Differences in echocardiographic parameters before and after the first procedure were compared using the Wilcoxon signed rank test.

The differences in the cumulative incidence of adverse clinical events following the first and last procedures between the groups were compared using the log-rank test. Cox proportional hazards regression analysis was performed to identify predictors for developing adverse clinical events following the first and last procedures. Variables with *P* values ≤0.1 in the univariate analysis were selected as potential predictors. Among the variables, predictors that were considered prognostic factors in previous studies[7,12] or clinically important factors for patients with systolic impairment were selected into multivariable analysis. Variables that met proportional assumption using Schoenfeld residuals were analyzed. Univariate and multivariable analyses were used to identify predictors for developing ATA recurrence following the first and last procedures. To precisely evaluate the association between ATA recurrence and adverse clinical events, the log-rank test for the population, in which the patients who developed adverse clinical events before ATA recurrence were excluded, was also performed as a sensitivity analysis. The results are expressed as hazard ratios and 95% CIs. All analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY), and results with a *P* value <0.05 were considered statistically significant.

RESULTS

Study Population and CA Procedure

A flow diagram of the present study is presented in Figure 1. In total, 799 patients underwent their first session of CA for AF during the whole study period. In all patients, cardiac function was evaluated using TTE before the initial procedure. We collected the data of 75 patients with an LVEF <50%. Most of the procedures (72/75 patients, 96%) were performed by experienced surgeons (>25 procedures/y).[13] Among those patients, 35 and 40 patients were categorized in the nonrecurrence and ATA recurrence groups, respectively, during a median follow-up period of 3.5 (range: 2.4–4.7) years. The success rates at 6 and 12 months following the first procedure were 68% and 60%, respectively. The success rates without antiarrhythmic drug administration were 71% (6 months) and 65% (12 months). Patients with ATA recurrence developed recurrence at 0.33 (range: 0.25–1.3) years following the initial procedure. Eighty-eight percent of patients developed AF (35/40 patients), and the remaining patients (12%, 5/40 patients) developed common/uncommon AFL or atrial tachycardia. A comparison of patient demographics is presented in Table 1. A comparison of CA-related variables is presented in Table 2. Most patients (69/75 patients, 92%) underwent contact force–guided radiofrequency PVI or cryoballoon PVI. There were no complications during the periprocedural period. In the ATA recurrence group, 28 patients (70%) underwent redo procedure following the initial procedure (additional 1.4±0.6 sessions). After the last procedure, 49 and 26 patients were categorized into the nonrecurrence and ATA recurrence groups, respectively. The success rates at 6 and 12 months following the last procedure were 89% and 78%, respectively, and the success rates without antiarrhythmic drugs were 89% (6 months) and 82% (12 months). A comparison of patient demographics is presented in Table 3. Patients with ATA recurrence developed recurrence at 0.78 (range: 0.31–2.4) years following the last procedure.

Table 5. Proportion of Freedom from Each Clinical Event Following First Procedure

	No recurrence	ATA recurrence	*P* value
Adverse clinical events, % (95% CI)*	95 (85, 100)	41 (21, 61)	<0.0005
All-cause death, % (95% CI)	100	86 (72, 100)	0.2
HFH, % (95% CI)*	100	44 (23, 65)	0.0003
Stroke, % (95% CI)	95 (85, 100)	94 (85, 100)	0.63
AMI, % (95% CI)	100	100	N/A

AMI indicates acute myocardial infarction; ATA, atrial tachyarrhythmia; HFH, heart failure hospitalization; and N/A, not available.
*Indicates statistical significance (*P*<0.05).

Cumulative Incidence of Adverse Clinical Events

We obtained data from all patients regarding clinical events. Figure 2A shows the comparison of the cumulative incidence of adverse clinical events following the first procedure between the nonrecurrence and ATA recurrence groups. The proportion of freedom from adverse clinical events was significantly lower in the ATA recurrence than in the nonrecurrence group (41% [95% CI, 21–61] versus 95% [95% CI, 85–100], *P*<0.0005). In total, 21 patients developed adverse clinical events at a median of 2.2 (range: 0.64–2.8)

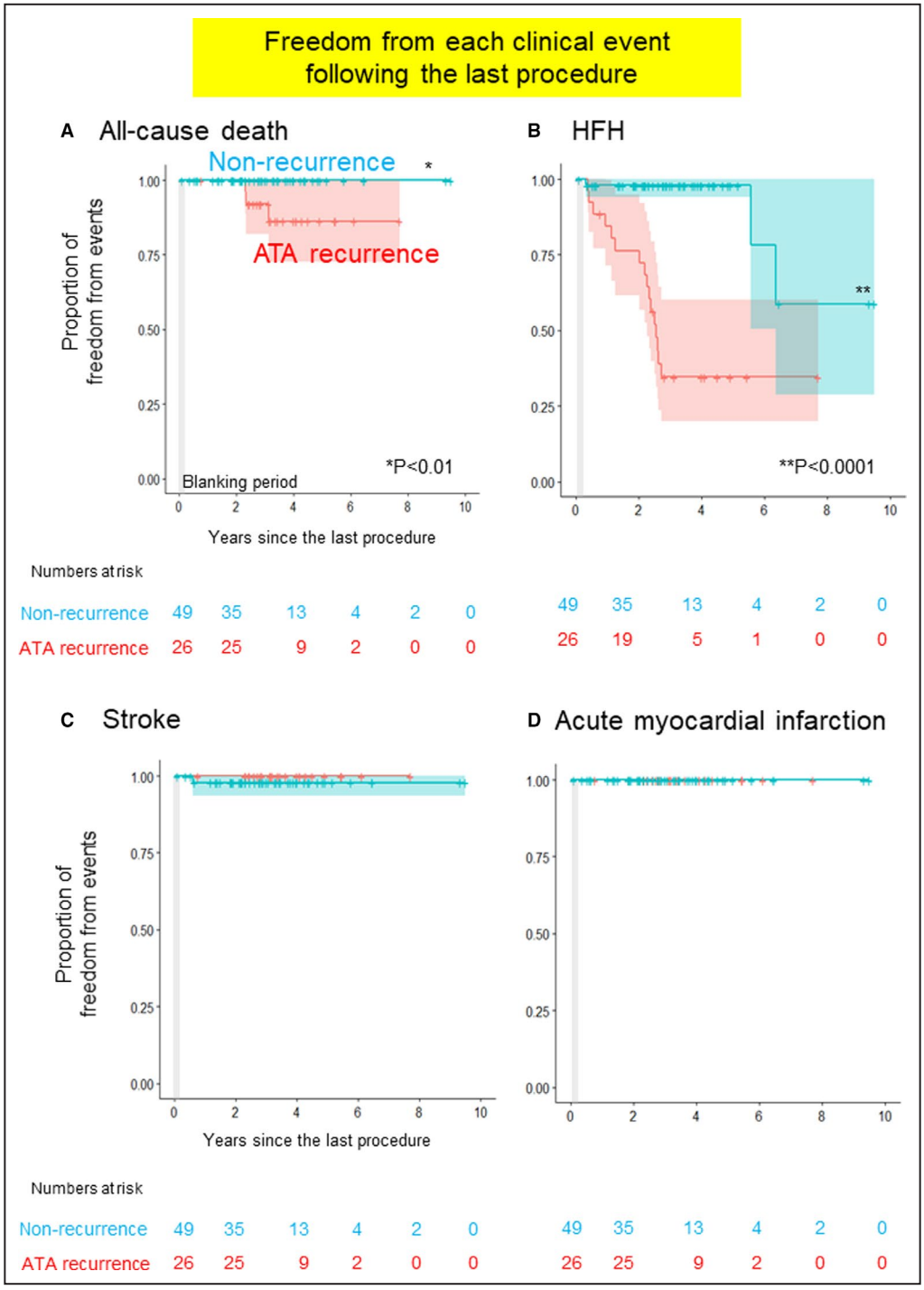

Figure 4. Comparison of the cumulative incidence of each adverse clinical event following the last procedure

A, The Kaplan–Meier curve shows cumulative proportion with 95% CI for all-cause death following the last procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **B,** The Kaplan–Meier curve shows cumulative proportion with 95% CI for HFH following the last procedure in the nonrecurrence (blue) and ATA recurrence group (red). **C,** The Kaplan–Meier curve shows cumulative proportion with 95% CI for stroke following the last procedure in the nonrecurrence (blue) and ATA recurrence groups (red). **D**. The Kaplan–Meier curve shows cumulative proportion with 95% CI for acute myocardial infarction following the last procedure in the nonrecurrence (blue) and ATA recurrence group (red). The asterisk indicates statistical significance (*P<0.01, **P<0.0001). ATA indicates atrial tachyarrhythmia; and HFH, heart failure hospitalization.

Table 6. Proportion of Freedom from Each Clinical Event Following the Last Procedure

	No recurrence	ATA recurrence	*P* value
Adverse clinical events, % (95% CI)*	57 (16, 97)	35 (16, 54)	<0.0001
All-cause death, % (95% CI)*	100 (0)	73 (44, 100)	0.009
HFH, % (95% CI)*	59 (17, 100)	35 (16, 54)	<0.0001
Stroke, % (95% CI)	96 (90, 100)	100 (0)	0.53
AMI, % (95% CI)	100 (0)	100 (0)	N/A

AMI indicates acute myocardial infarction; HFH, heart failure hospitalization; and N/A, not available.

*Indicates statistical significance (*P*<0.05).

years following the initial procedure. Table 4 presents a list of patients with adverse clinical events. The cumulative incidence of each clinical event following the first procedure is presented in Figure 3 and in Table 5. The adverse clinical events mainly comprised HFH (18/21 patients, 86%). All-cause death was noted in 3 patients (Patients 6, 17, and 18; Table 3). No patient developed acute myocardial infarction during the follow-up period. ATA was attributed to worsening HF in half of the patients with HFH (9/18 patients; Table 4). Three patients developed HFH before ATA recurrence (Patients 4–6; Table 4). Figure 2B shows a comparison of the cumulative incidence of adverse clinical events following the last procedure between the nonrecurrence and ATA recurrence groups. The proportion of freedom from adverse clinical events was significantly lower in the ATA recurrence than in the nonrecurrence group (35% [16–54] versus 57% [16–97], *P*<0.0001). Patients who underwent a redo procedure developed adverse clinical events at a median of 2.3 (range: 1.0–2.6) years following the last procedure. The cumulative incidence of each clinical event following the last procedure is presented in Figure 4 and in Table 6. The proportion of freedom from all-cause death was significantly lower in the ATA recurrence than in the nonrecurrence group (73% [44–100] versus 100%, *P*=0.009). In the sensitivity analysis, the comparison of the incidence of adverse clinical events following the first and last procedures was reanalyzed in the population in which patients who developed adverse clinical events before ATA recurrence were excluded. After reanalysis, the significant difference persisted (both *P*<0.0005).

Changes in Echocardiographic Parameters Following the First Procedure

Figure 5 shows a comparison of the left ventricular end-diastolic diameter, LVEF, and left atrial diameter between before the procedure and at 3 months following the first procedure. Both groups showed a significant reduction in left ventricular end-diastolic diameter (Figure 5A; nonrecurrence group: 53±6 versus 51±7 mm, *P*<0.0001; ATA recurrence group: 55±8 versus 53±8 mm, *P*=0.002). Although both groups showed significant improvement in LVEF, the magnitude of improvement was higher in the nonrecurrence than in the ATA recurrence group (Figure 5B; nonrecurrence group: 40±7% versus 49±9%, *P*<0.0001; ATA recurrence group: 39±8% versus 45±13%, *P*<0.0001). A significant shortening of the left atrial diameter was also observed in both groups (Figure 5C; nonrecurrence group: 42±7 versus 39±7 mm, *P*=0.0005; ATA recurrence group: 45±8 versus 43±7 mm, *P*=0.04).

Predictors for Developing Adverse Clinical Events

The results of the univariate and multivariable analyses of predictors for developing adverse clinical events are summarized in Tables 7 and 8. Regarding the adverse clinical events following the first procedure, the following emerged as significant factors in the univariate analysis: female sex, ATA recurrence, left atrial diameter >45 mm, LVEF <35%, mitral E/e' ratio ≥12, an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, and brain natriuretic peptide >300 pg/mL. After multivariable adjustment, ATA recurrence remained the independent predictor for adverse clinical events following the first session (Table 7). Even regarding the adverse clinical events following the last procedure, ATA recurrence remained the significant predictor after multivariable adjustment (Table 8).

DISCUSSION

Main Findings

The important findings of the present study are as follows. First, the cumulative incidence of adverse clinical events following the CA procedure was significantly higher in patients with systolic impairment who developed ATA recurrence than in those with no recurrence. Second, ATA recurrence was an independent predictor for adverse clinical events following the first and last CA procedures after adjustment in the multivariable analysis including low LVEF.

CA for Patients With AF With Systolic Impairment and Impact of ATA Recurrence

Given that a certain number of patients with systolic impairment had reversible cause (arrhythmia-induced cardiomyopathy),[14] it seems rational to choose sinus restoration therapy. However, previous trials have showed that pharmacological rhythm control therapy failed to have a prognostic impact.[15,16] Hence, the long-term adverse effect of antiarrhythmic agents may

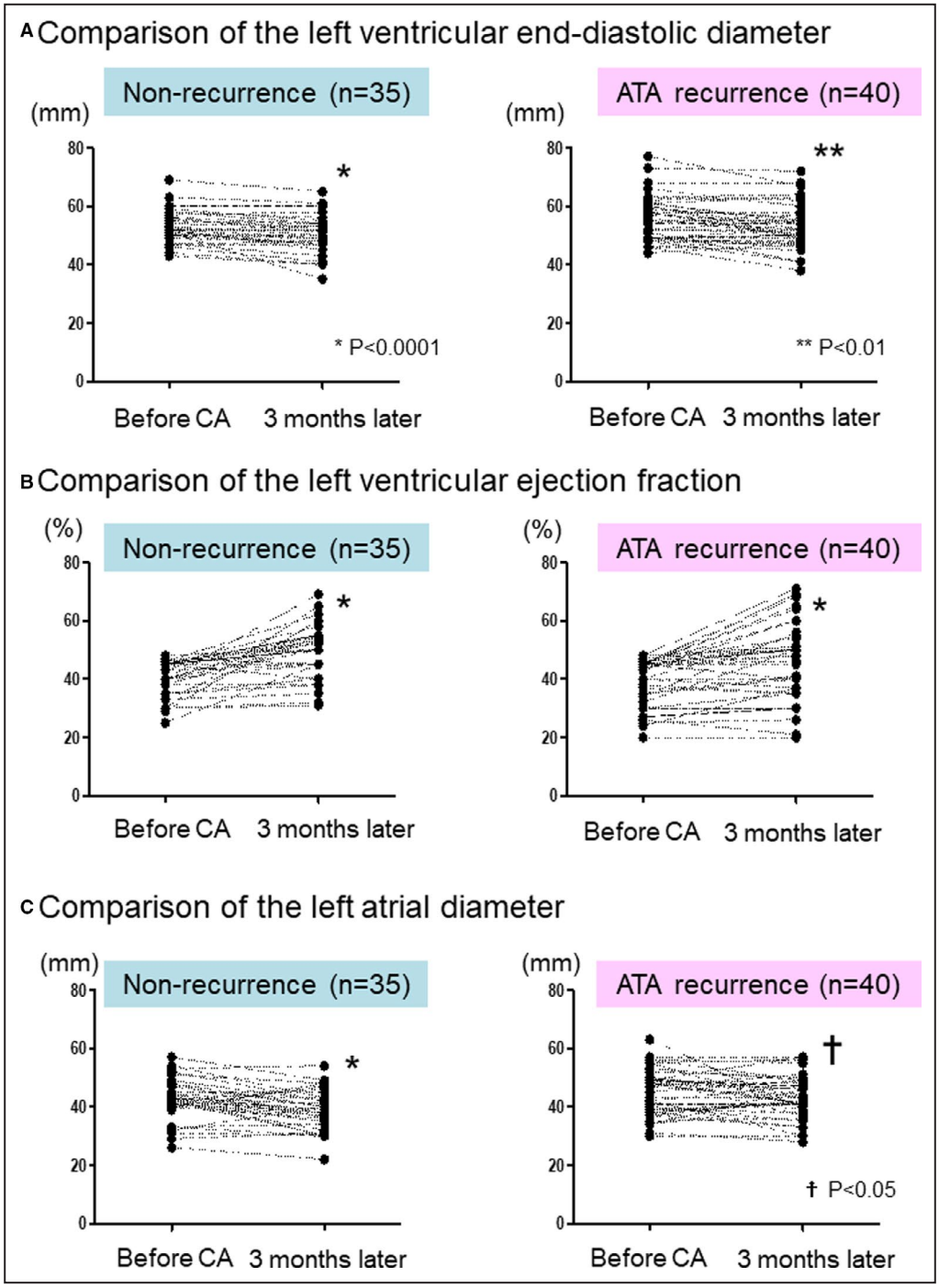

Figure 5. Comparison of echocardiographic parameters between before CA and at 3 months following the first procedure (A)

The plots show a comparison of the left ventricular end-diastolic diameter between before CA and at 3 months following the first procedure in the nonrecurrence (left panel) and ATA recurrence groups (right panel). **B,** The plots show a comparison of the left ventricular ejection fraction between before CA and at 3 months following the first procedure in the nonrecurrence (left panel) and ATA recurrence groups (right panel). **C,** The plots show a comparison of the left atrial diameter between before CA and at 3 months following the first procedure in the nonrecurrence (left panel) and ATA recurrence groups (right panel). The asterisk and dagger indicate statistical significance (*P<0.0001, **P<0.01, †P<0.05). ATA indicates atrial tachyarrhythmia; and CA, catheter ablation.

Table 7. Identification of Predictive Factors for Adverse Clinical Events Following the First Procedure

	Univariate analysis			Multivariable analysis		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Age >75 y	1.6	0.6–4.3	0.38			
Female sex	3.2	1.3–7.6	0.01			
ATA recurrence*	15.2	2–114	0.007	10.8	1.4–81.9	0.02
LAD >45 mm*	4.6	1.7–12.9s	0.003	3.6	1.3–10.4	0.02
LVEF <35%	2.9	1.2–6.9	0.02	1.8	0.64–4.8	0.27
Mitral E/e' ratio ≥12	2.8	1.2–7.1	0.02			
eGFR <30 mL/min per 1.73 m^2	5.9	2.1–17	0.001	3.2	0.83–12.1	0.09
BNP level >300 pg/mL	3.1	1.3–7.5	0.01	1.6	0.51–4.6	0.43

ATA indicates atrial tachyarrhythmia; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAD, left atrial diameter; and LVEF, left ventricular ejection fraction.

*Indicates statistical significance after adjustment in the multivariable analysis ($P<0.05$).

cancel the benefit of maintaining sinus rhythm,[17] but CA could overcome this issue. Rhythm control therapy by CA for patients with systolic impairment demonstrated efficacy in terms of surrogate outcomes, such as cardiac function, exercise capacity, and quality of life when compared with medical therapy.[18–20] In addition, the results of recent trials revealed the benefits of CA for hard outcomes, such as mortality and HFH for selected patients.[7,21,22] Our findings demonstrated the efficacy of CA for patients with systolic impairment in a contemporary clinical setting, in which most patients underwent CA by an advanced technology (contact force–guided radiofrequency or second-generation cryoballoon) and were prescribed cardioprotective agents (renin-angiotensin-system-acting agents and β-blocker). Our population had success rates without antiarrhythmic drugs that were comparable with those reported in previous trials.[23] In addition, our data showed significant improvement in cardiac function, regardless of ATA recurrence, which suggested that nearly all patients in our population could benefit from CA. Several observational studies assessed the association between the adverse clinical events following CA and ATA recurrence. Ullah et al. reported that AF recurrence strongly predicted the long-term incidence of stroke and death following CA in patients with systolic impairment (LVEF ≤45%).[24] In line with these findings, our data indicated that ATA recurrence had independent predictability with long-term adverse clinical events, especially HFH. We also demonstrated that ATA was attributed to worsening HF in half of the patients with HFH in our study population. Yazaki et al. and Kawaji et al. also assessed the association between ATA recurrence and death/HFH. Although the univariate analysis revealed ATA recurrence as a potential predictor in both studies, it did not show independent predictability after adjustment in the multivariable analysis.[12,25] The difference might have originated from the lower incidence of events in the previous studies (12%[12] and 18%[25] versus 28% in our population). The significance of ATA recurrence might have been amplified in the population with a large number of high-severity patients. However, a recent subanalysis of the CASTLE-AF trial showed that AF burden, rather than ATA recurrence, was associated with clinical outcomes.[26] Given that ATA recurrence in our population depended on patient symptom because

Table 8. Identification of Predictive Factors for Adverse Clinical Events Following the Last Procedure

	Univariate analysis			Multivariable analysis		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Age >75 y	1.7	0.6–4.9	0.3			
Female sex	3.4	1.3–8.9	0.01			
ATA recurrence*	8.6	2.8–26	0.0001	12.9	3.5–48.2	0.0001
LAD >45 mm*	4.3	1.5–12	0.005	5.5	1.8–17.5	0.003
LVEF <35%*	3.7	1.4–9.7	0.006	4.4	1.1–17.1	0.03
Mitral E/e' ratio ≥12	2.5	0.96–6.5	0.058			
eGFR <30 mL/min per 1.73 m^2	7.2	2.5–21	0.0003	2.4	0.52–10.9	0.26
BNP level >300 pg/mL	3.3	1.3–8.1	0.009	1.8	0.6–5.5	0.27

ATA indicates atrial tachyarrhythmia; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAD, left atrial diameter; and LVEF, left ventricular ejection fraction.

*Indicates statistical significance after adjustment in the multivariable analysis ($P<0.05$).

of the limited number of patients in whom a monitorable device (ie, pacemaker, insertable cardiac monitor) was implanted, we could have missed cases of asymptomatic ATA recurrence. The disparity between the study by Brachmann et al.[26] and our study may imply that symptomatic ATA recurrence could have a better association with adverse clinical events than asymptomatic ATA recurrence. Further studies investigating the association between AF burden and symptoms are warranted.

Clinical Implications

Our study revealed the association between ATA recurrence and adverse clinical events following CA in patients with systolic impairment in a contemporary clinical setting. Although technical advances enabled CA to be performed safely and effectively in patients with AF with systolic impairment, clinicians should be cautious about using such a CA procedure because such patients have a high risk of adverse clinical events if they develop ATA recurrence. Watchful follow-up examination after performing the CA procedure may allow early detection of ATA recurrence, which could help avoid adverse clinical events, especially worsening HF.

Limitations

The present study had several limitations. First, because the data were collected retrospectively, our population was heterogeneous (ie, patients with paroxysmal and persistent AF and those who underwent both radiofrequency PVI and cryoballoon PVI were included); therefore, it remains unclear whether our results could be generalized to a homogeneous population (ie, patients with paroxysmal AF only). Furthermore, we also might have missed unmeasured variables associated with clinical events. For instance, exercise capacity could influence the development of adverse clinical events following the procedure. Second, the sample size of our population was relatively small because of the single-center observational study design.

In addition, our institution is not categorized as a high-volume center; therefore, it remains unclear whether our results could be generalized to the outcomes in such centers. Third, although the proportion of systolic impairment (9%) was comparable to that in other studies in Japan[12,25] and Europe,[24] it was relatively lower than that in the United States.[27] Hence, it remains unclear whether our results could be applicable to such a population. Fourth, most adverse clinical events in the present study comprised HFH. The number of patients with other events (stroke and all-cause death) was very small. Hence, it remains unclear whether ATA recurrence would truly predict the events. Thus, future studies, in which a large number of patients developing such events would be included, may be helpful to validate our findings. Fifth, ATA recurrence largely depended on patient symptom because the diagnosis of recurrence was obtained using 24-hour Holter ECG and/or a cardiac event recorder rather than using cardiac implantable electronic devices that monitor AF burden. It remains uncertain whether our results could be extrapolated to a population in which a large proportion of patients are asymptomatic for ATA recurrence.

CONCLUSIONS

Our data suggested the association between ATA recurrence and adverse clinical events following the CA procedure in patients with AF with systolic impairment in a contemporary clinical setting. Watchful follow-up examination after the CA procedure may allow for the early detection of ATA recurrence, which could help avoid adverse clinical events, especially worsening HF.

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