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ORIGINAL ARTICLE

Long-term clinical course after catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy

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Abstract
Atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) patients is highly associated with deterioration of their clinical condition, such as worsening heart failure symptoms, and an increased thromboembolic stroke risk and cardiac mortality rate. This study aimed to investigate the long-term clinical course after catheter ablation (CA) in HCM patients with AF. Among 566 primary HCM patients at our institution, 94 who underwent rhythm control therapy to manage AF from 2002 to 2016 were retrospectively analyzed. The eligible patients were divided into two groups: those who managed AF with CA ($n=34$) and those without CA ($n=60$). The endpoints were the incidence of initial clinical events, including HCM-related death or an unplanned heart failure hospitalization, or new-onset thromboembolic strokes. During a mean follow-up of 5.8 years, 6% in the CA group and 28% in the non-CA group had a progression of the AF type into permanent AF (Log-rank: $p=0.012$). In the Kaplan-Meyer curve analyses, the incidence of clinical events was significantly lower in the CA group than non-CA group ($p=0.025$). The annual rates for the incidence of clinical events were 1.2% in the CA group and 6.7% in the non-CA group. In a Cox multivariate analysis, CA therapy (adjusted hazard ratio 0.22; 95% confidence interval: 0.05–0.97; $p=0.046$) was the only independent predictor of the incidence of clinical events. In conclusion, CA may be associated with a favorable long-term clinical course in HCM patients with AF.

Keywords Hypertrophic cardiomyopathy · Atrial fibrillation · Catheter ablation · Heart failure · Stroke

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in patients with hypertrophic cardiomyopathy (HCM) and affects up to 20–25% of this population [1–6]. This arrhythmia is strongly associated with deterioration in the clinical condition including worsening heart failure symptoms, and an increased risk of thromboembolic strokes and cardiac mortality [1–14]. Though the most important goal for improving the clinical condition is to restore and maintain sinus rhythm, anti-arrhythmic drugs (AADs) are frequently not adequate for a rhythm control strategy [15,16]. Over the past decade, radiofrequency catheter ablation (CA) has provided another therapeutic choice for rhythm control in the management of patients with AF [17]. Even in patients with HCM, several reports have suggested that CA of AF might be a valuable option, though more repeat procedures and AADs are needed to prevent AF recurrence [18–21]. However, despite a number of reports demonstrating both the efficacy and safety of CA, there have been a few reports regarding the association between CA and its long-term clinical effect. Therefore, the aim of this study was to investigate the long-term clinical course after CA and validate its clinical effects in HCM patients with AF.

Materials and methods

Study population

In this observational, retrospective cohort study, a total of 566 consecutive primary HCM patients who had been referred to establish a diagnosis and undergo subspecialty therapy at Tokyo Women's Medical University Hospital

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from 2002 to 2016 were analyzed. HCM was diagnosed based on the standard definition [15,16]. The diagnostic process consisted of two-dimensional (2D) echocardiographic identification of a hypertrophied, non-dilated left ventricle in the absence of any other cardiac or systemic diseases capable of producing similar hypertrophy [15,16]. The diagnostic criteria for apical hypertrophy included asymmetric left ventricular hypertrophy that was confined predominantly to the left ventricular apex with an apical wall thickness of ≥15 mm [22]. Among the 566 patients, those who had clinically diagnosed AF were included in the study. Documentation of AF was based on the 12-lead resting electrocardiography or ambulatory electrocardiography obtained either after the acute onset of symptoms or fortuitously during routine examinations of the patients without symptoms. Among the AF patients, those who were already diagnosed with permanent AF at their initial evaluation were excluded from this study. Permanent AF was defined as episodes of AF that the patient and physician made a shared decision to cease any further attempts to restore and/or maintain sinus rhythm, reflecting a therapeutic attitude towards AF [24]. The remaining patients who underwent rhythm control therapy to manage AF during the period of interest were finally analyzed in the present study. The enrolled patients were divided into two groups, patients who underwent CA to manage AF and as a control group, those who managed AF with medications but not CA procedures. The cohort was followed starting from the date of the analytic start time with a prospective review of the outpatient and inpatient medical records. In the CA cohort, the analytic start time was set as the day of the index CA procedure. In the non-CA cohort, the first record of the initial AADs was used as the analytic start time. If patients did not take any AADs due to a low frequency of AF episodes, the analytic start time was set as the first record of taking an initial oral anticoagulant (OAC).

Paroxysmal AF (PAF), persistent AF, and long-standing persistent AF were defined according to the Heart Rhythm Society, European Society of Cardiology, and European Cardiac Arrhythmia Society 2017 Consensus Statement on Catheter and Surgical Ablation of AF [23]. The study was approved by the local institutional ethics board.

CA treatment cohort

The CA treatment was offered to patients whose quality of life was regarded to be significantly impairing due to multiple symptomatic episodes of AF and in whom AADs failed to control the frequency of AF or were not tolerated. All patients gave their written informed consent before the procedure. All patients underwent a pulmonary vein isolation (PVI). Since 2009, a 3.5-mm cooled-tip catheter (Navistar ThermoCool or ThermoCool SF, Biosense Webster Inc., Diamond Bar, CA, USA) was utilized for mapping and ablation guided by electroanatomical mapping combined with image integration. Inducible atrial tachycardias (ATs) or reproducible premature atrial contractions (PACs) were additionally mapped and ablated. Since 2012, an empirical superior vein (SVC) isolation was additionally undergone after achieving the PVI [24]. During the entire period, no empirical substrate modification targeting linear lesions or complex fractionated electrograms was performed. Following a first ablation procedure, the discontinuation of the AADs after the CA depended on any AT/AF recurrences or the referring physician's decision. If AT/AF recurrences were documented by the symptoms, electrocardiography recordings, 24-h ambulatory monitoring, or interrogation of the implanted devices after a 2-month blanking period from the procedure, a repeat ablation was offered to the patients. During the repeat procedures, a re-isolation of all PVs and SVC potentials was performed by targeting the recovery of the electrical potentials along the previous ablation line. Just as in the initial procedures, if any sustained ATs or frequent PACs were induced, they were mapped and ablated. However, basically, no empirical substrate modification was performed even during the repeat procedures.

Non-CA treatment cohort

A separate cohort consisted of patients who were treated for AF with medical treatment but not CA during the follow-up period. The selection of the AADs depended on the attending physician's decision, based on a shared decision model taking into account the risk and benefits of each AAD [17].

Clinical events

The primary interest of the clinical course was whether there were clinical events that appeared to be associated with HCM and AF during the follow-up interval. The "clinical events" were defined as the combined incidence of the initial events including HCM-related death or heart failure hospitalization, or the thromboembolic strokes per each patient. HCM-related death was defined as the following 3 modes: (1) sudden and unexpected death, which meant a collapse in the absence or < 1 h after the onset of symptoms in a patient who had previously been relatively stable (including resuscitated cardiac arrest), (2) heart failure-related death, which was defined as occurring after progressive cardiac decompensation, particularly if complicated by pulmonary edema or the evolution to end-stage HCM, and (3) stroke-related death, which was defined as death from ischemic strokes [2,15,16]. In patients with implantable cardioverter-defibrillators (ICD), an appropriate defibrillator discharge triggered by ventricular fibrillation or rapid ventricular tachycardia was also defined as an event of sudden cardiac death. However, those with

resuscitated cardiac arrest or an appropriate ICD intervention that occurred before the analytic start time were excluded from the survival analysis calculations of sudden death events. Heart failure events were defined as initial unplanned inpatient hospital admissions for advanced heart failure symptoms to New York Heart Association functional classes III/IV [7–10]. Thromboembolic stroke events were defined as a permanent neurological disability or impairment caused by vascular causes such as an ischemic stroke [11–14].

Statistical analysis

The continuous variables are described as the mean ± standard deviation (SD). A Student's *t* test, Fisher's exact test, and Mann–Whitney *U* test were used to compare the differences across the two groups. Variables with a p value < 0.10 for univariate associations were entered into a stepwise multivariable Cox proportional hazards model to identify any independent predictors. All tests were two-sided, and statistical significance was set at a value of $p < 0.05$. For the analysis of the combined clinical events and progression to permanent AF, the fraction at each follow-up interval was estimated by the Kaplan–Meier method. The follow-up time for each patient was calculated from the date of the initial analytic start time to the most recent contact or incidence of targeting clinical events, or death. Differences in the survival or clinical events between the patient groups were assessed using the log-rank test. The data were analyzed by SPSS software version 23.0 (SPSS Inc, Chicago, IL).

Results

Baseline characteristics

The patient selection method is illustrated in Fig. 1. There were 34 patients in the CA group and 60 in the non-CA group. The baseline characteristics of the two study groups are summarized in Table 1. Briefly, the patients in the CA group had a lower age ($p = 0.02$) and higher prevalence of long-standing persistent AF ($p = 0.04$) as compared to the non-CA group. The prevalence of the phenotypes of HCM, including an outflow tract obstruction or apical hypertrophy, did not significantly differ between the two groups. The echo parameters such as the left atrial dimension, left ventricular ejection fraction, and maximum left ventricular wall thickness were nearly identical. The proportion of those who took β-blockers and OACs was also similar between the two groups.

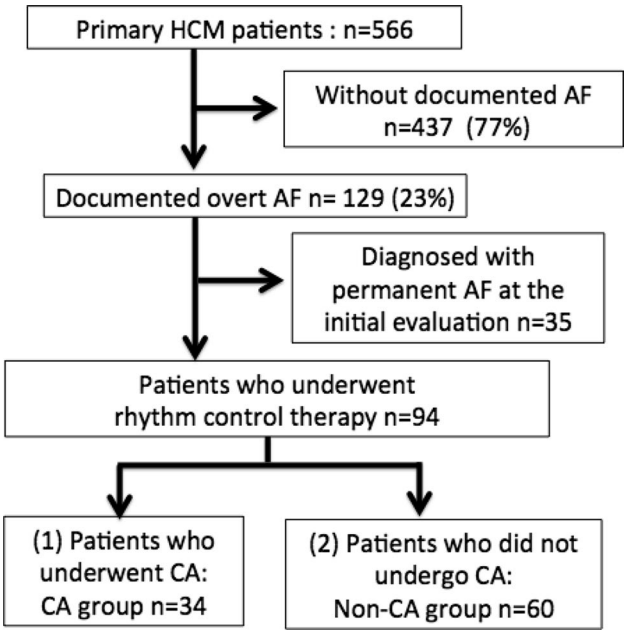

Fig. 1 Flow chart of the enrolled hypertrophic cardiomyopathy patients. *HCM* hypertrophic cardiomyopathy, *AF* atrial fibrillation, *CA* catheter ablation

AF control

The details of the ablation procedures in the CA group are summarized in Table 2. A PVI was successfully achieved in all 34 patients during the initial procedures. An SVC isolation was performed in 17 patients (50%), an AT ablation in 15 (44%), and reproducible PACs (3%) were induced but successfully ablated in one. During a mean follow-up of 2.3 years after the initial procedure, only 9 patients (26%) had no AT/AF recurrences without any AADs. However, in the arrhythmia control, defined as the maintenance of sinus rhythm with or without AADs, those who maintained sinus rhythm significantly increased to 22 patients (65%) during the follow-up period (Log-rank $p = 0.002$) (Fig. 2a). Repeat procedures were performed in 20 patients (59%). There were 19 patients (95%) who had a left atrium-PV reconnection and they were all re-isolated. After the second procedures, 5 patients (15%) underwent a third procedure and 3 (9%) underwent a fourth procedure for further AF recurrences. Finally, during a mean follow-up of 3.0 years after the last procedure (median 1.8 procedures), 20 patients (59%) had no AT/AF recurrences without any AADs and arrhythmia control was achieved in 28 patients (82%) (Log-rank, $p = 0.031$) (Fig. 2b).

In the non-CA group, the details of the total number and type of AADs taken for managing AF during the period of interest are summarized in Table 3. There were 10 patients (17%) who did not require any AADs due to a low frequency of AF episodes. Amiodarone was the

Table 1 Baseline characteristics

Variable	CA group, ($n=34$)	Non-CA group, ($n=60$)	*P* value
Age (years)	59.3 ± 9.8	64.9 ± 12.1	0.02
Male, sex (%)	25 (74)	41 (68)	0.65
OTO (%)	7 (21)	19 (32)	0.34
APH (%)	10 (29)	21 (35)	0.65
Family history of SCD (%)	3 (9)	6 (10)	1.00
AF type			
Paroxysmal (%)	17 (50)	41 (68)	0.12
Persistent (%)	14 (41)	19 (32)	0.37
Long-standing persistent (%)	3 (9)	0 (0)	0.04
Hypertension (%)	17 (50)	29 (48)	1.00
Diabetes (%)	2 (6)	9 (15)	0.32
Prior stroke (%)	6 (18)	8 (13)	0.56
Prior NYHA III or IV episode (%)	8 (24)	11 (18)	0.60
ICD implantation (%)	7 (21)	8 (13)	0.40
NSVT (%)	14 (41)	27 (45)	0.83
BNP (pg/ml)	240.9 ± 222.3	312.6 ± 279.0	0.22
LAD (mm)	42.0 ± 6.5	42.2 ± 9.3	0.91
LVDd (mm)	45.6 ± 5.8	45.0 ± 5.2	0.66
LVEF (%)	55.5 ± 9.2	55.1 ± 10.3	0.84
Maximum LV wall thickness (mm)	18.6 ± 3.8	19.2 ± 4.3	0.58
β-blockers (%)	28 (82)	43 (72)	0.32
Warfarin (%)	30 (88)	51 (85)	0.76
DOAC (%)	4 (12)	5 (8)	0.72

All data are expressed as the mean ± SD or *n* (%)

CA catheter ablation, *OTO* outflow tract obstruction, *APH* apical hypertrophy, *SCD* sudden cardiac death, *AF* atrial fibrillation, *NYHA* New York Heart Association, *ICD* implantable cardioverter defibrillator, *NSVT* non-sustained ventricular tachycardia, *BNP* brain natriuretic peptide, *LAD* left atrial dimension, *LVDd* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *LV* left ventricular, *DOAC* direct oral anticoagulants

most frequently used drug taken in 29 patients (48%). Among the Class I agents, disopyramide (27%), pilsicainide (22%), and flecainide (20%) were the commonly used AADs.

Incidence of AF progression to permanent AF

In the CA group, during a mean follow-up of 5.0 years, 2 patients (6%) finally progressed to permanent AF even after 3 procedures in one person and 4 procedures in another. In contrast, in the non-CA group, 17 patients (28%) progressed to permanent AF, including 7 with PAF and 10 with persistent AF at the beginning of the follow up during a mean follow-up of 6.4 years. Figure 3 shows the Kaplan–Meier survival plots showing time to the incidence of AF progression to permanent AF in the two groups. The CA group had a significantly higher rate of freedom from AF progression than the non-CA group ($p=0.012$).

Incidence of clinical events

Over a mean of 5.0 years of follow-up, combined clinical events, including HCM-related death, heart failure hospitalizations and new-onset strokes occurred in 2 patients (6%) in the CA group. On the other hand, over a mean of 6.4 years of follow-up, combined clinical events occurred in 25 patients (42%) in the non-CA group. The overall annual rates of the incidence of clinical events were 1.2% in the CA group and 6.7% in the non-CA group (Fig. 4a). In creating a Kaplan–Meier curve for the incidence of combined clinical events, the event free rates were significantly higher in the CA group than non-CA group ($p=0.025$) (Fig. 5a). Furthermore, in analyzing the incidence of combined clinical events according to the phenotype of non-obstructive HCM, the CA group also demonstrated significantly higher rates of freedom from combined clinical events than the non-CA group (Log-rank $p=0.004$) (Fig. 5b). On the contrary, among the patients with obstructive HCM, there was no significant

Table 2 Details of the ablation procedures

1st procedure	$n=34$
PVI	34 (100)
SVC isolation	17 (50)
CTI linear ablation	12 (35)
AT ablation	3 (9)
Non-PV foci ablation	1 (3)
2nd procedure	$n=20$ (59%)
PVI	19 (95)
SVC isolation	8 (40)
CTI linear ablation	9 (45)
AT ablation	4 (20)
Non-PV foci ablation	2 (10)
3rd procedure	$n=5$ (15%)
PVI	2 (40)
SVC isolation	2 (40)
AT ablation	4 (80)
Non-PV foci ablation	2 (40)
CFAE ablation	1 (20)
4th procedure	$n=3$ (9%)
PVI	1 (33)
SVC isolation	2 (67)
AT ablation	1 (33)
Non-PV foci ablation	1 (33)
CFAE ablation	1 (33)

All data are expressed as the *n* (%)

PVI pulmonary vein isolation, *SVC* superior vena cava, *CTI* cavo-tricuspid isthmus, *AT* atrial tachycardia, *PV* pulmonary vein, *CFAE* complex fractionated atrial electrograms

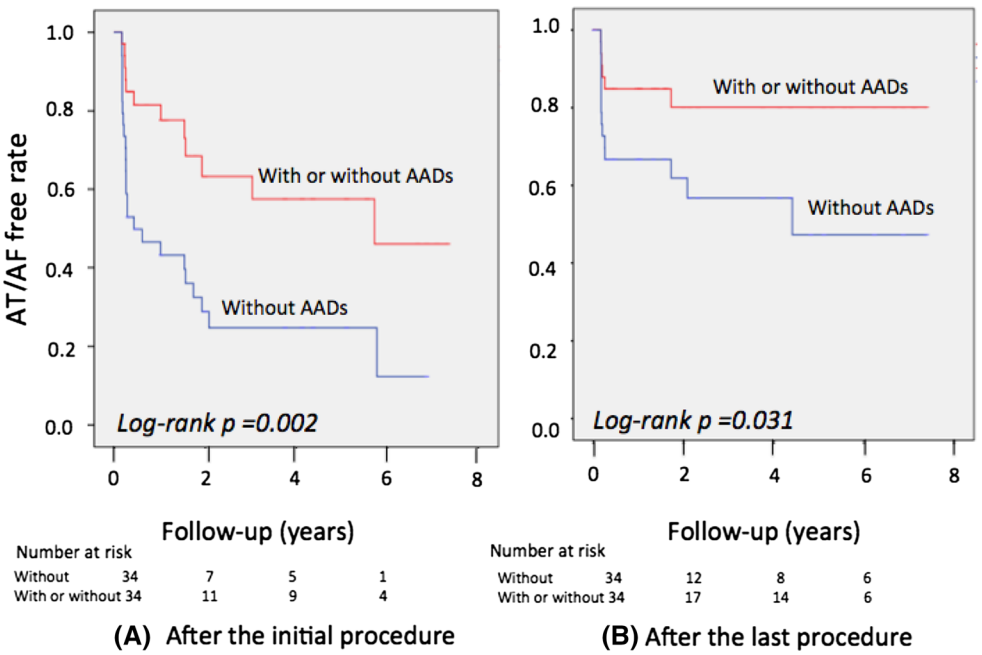

Fig. 2 Kaplan–Meier curve showing the long-term atrial tachyarrhythmia-free survival **a** after the initial ablation procedure and **b** after the last ablation procedure. *Blue line* without antiarrhythmic drugs, r*ed line* with or without antiarrhythmic drugs. *AADs* antiarrhythmic drugs, *AT* atrial tachycardia, *AF* atrial fibrillation

Table 3 Details of the total number of antiarrhythmic drugs in the non-CA group

Variable	$n=60$
Number of AADs	
0	10 (17)
1	23 (38)
2	19 (32)
3	4 (7)
≥4	4 (7)
Class I	
Disopyramide	16 (27)
Pilsicainide	13 (22)
Flecainide	12 (20)
Cibenzoline	9 (15)
Pirmenol	7 (12)
Class III	
Amiodarone	29 (48)
Sotalol	3 (5)
Class IV	
Bepridil	3 (5)

All data are expressed as the *n* (%)

CA catheter ablation, *AAD* antiarrhythmia drug

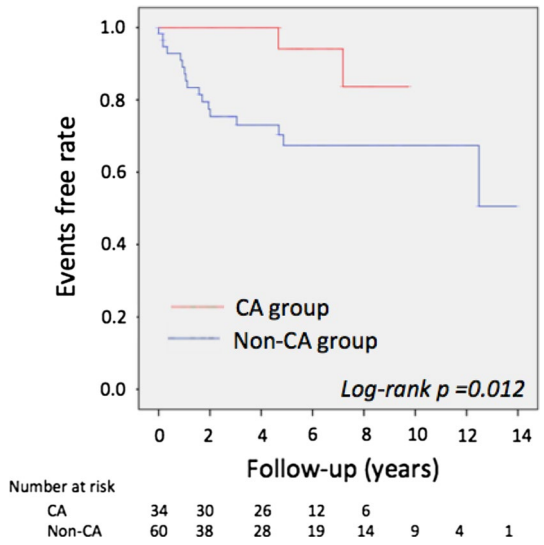

Fig. 3 Kaplan–Meier curve of the association with a progression to permanent atrial fibrillation according to whether or not catheter ablation therapy was performed. *CA* catheter ablation

difference in the event free rates between the two groups (Log-rank $p=0.687$) (Fig. 5c).

Clinical events-1: HCM-related death

There were no HCM-related deaths in the CA group, whereas 8 patients (13%) in the non-CA group had HCM related deaths, including 5 sudden and unexpected deaths (one resuscitated out-of-hospital cardiac arrests, 3 sudden deaths, and one appropriate ICD intervention), one heart failure-related death, and 2 stroke-related deaths. One heart failure-related death was during a persistent AF status and two stroke deaths were during a permanent AF status. In contrast, among 5 patients with sudden and unexpected deaths, one had a persistent AF status, but 4 had a PAF status at the time of the events. The overall annual death rates were 0% in the CA cohort and 1.8% in the non-CA cohort (Fig. 4b).

Clinical events-2: heart failure hospitalization

There were 2 patients (6%) in the CA group who required an unplanned heart failure hospitalization. Both of them had AF recurrences after the initial procedure even while taking post-procedural amiodarone and were in AF rhythms at the onset of the advanced heart failure. One patient could finally maintain sinus rhythm after undergoing repeat procedures following the event, while in one patient the AF finally progressed to permanent AF despite repeat procedures. Over a mean of 3.5 years of follow-up after the last procedure, there were no heart failure events in the CA group. In the non-CA group, there were 15 patients (25%) who required an unplanned heart failure hospitalization. Among those patients, 7 were in persistent AF while all taking amiodarone, 4 were in a PAF status and 4 had already shifted to permanent AF at the time of the events. One patient died with a worsening heart failure condition during an initial unplanned hospitalization, while in the remaining 14, the heart failure symptoms improved and they were discharged from the hospital. The overall annual rate of unplanned heart failure hospitalizations was 1.2% in the CA cohort and 3.9% in the non-CA cohort (Fig. 4c).

Clinical events-3: new-onset thromboembolic strokes

There were no stroke events in the CA group. In contrast, 8 patients (13%) in the non-CA group had a new-onset thromboembolic stroke. Among those, 2 patients did not take any OACs when the events occurred and the remaining 6 had been taking warfarin at that time. When the events occurred, 5 patients were already in permanent AF.

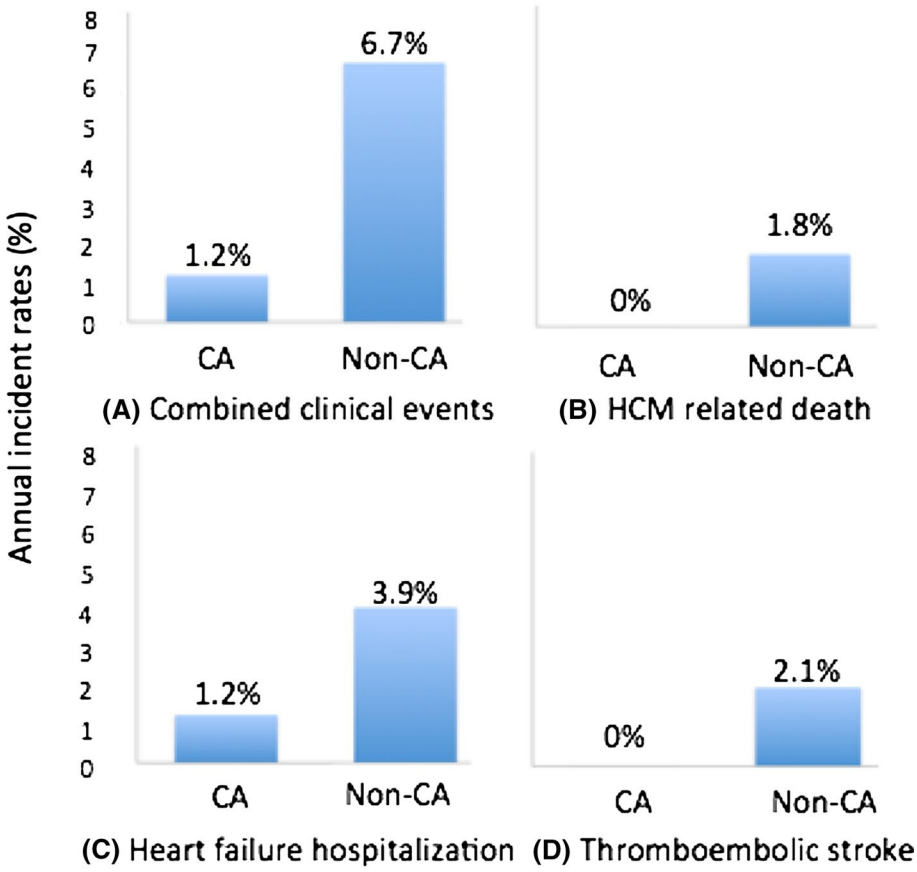

Fig. 4 The annual incidence rate of each event according to whether or not catheter ablation therapy was performed. **a** Combined clinical events. **b** HCM-related deaths. **c** Heart failure hospitalizations. **d** New-onset thromboembolic strokes. *CA* catheter ablation

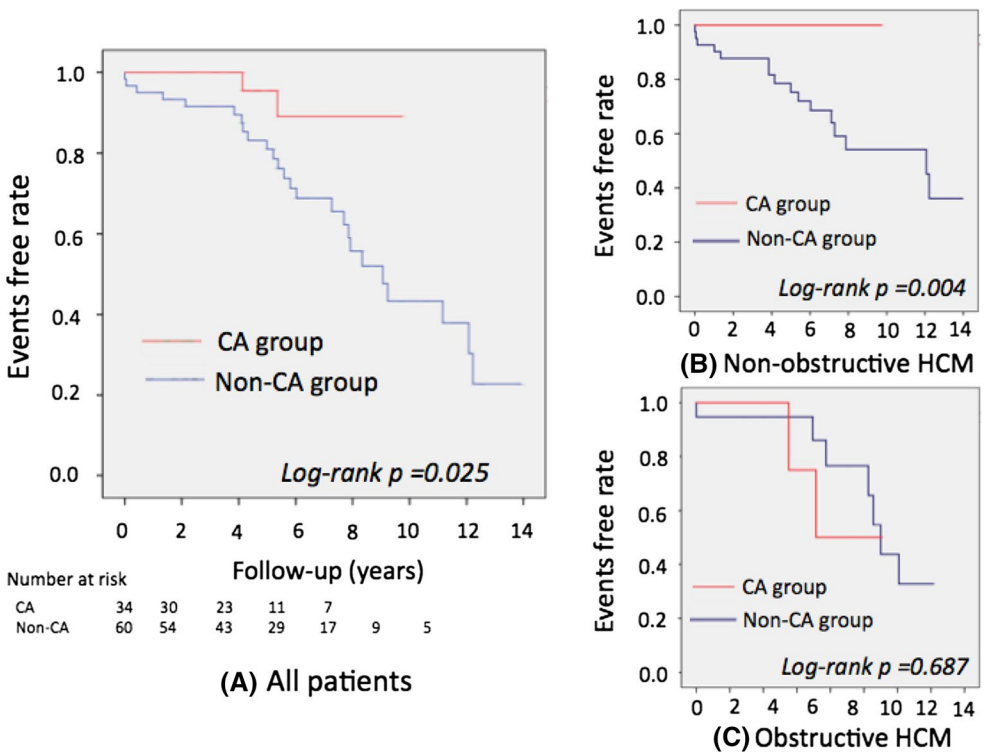

Fig. 5 Kaplan–Meier curve for the incidence of combined clinical events according to whether or not catheter ablation therapy was performed. **a** All patients. **b** Patients with non-obstructive HCM. **c** Patients with obstructive HCM. *HCM* hypertrophic cardiomyopathy, *CA* catheter ablation

Two patients died from the initial stroke events. The overall annual rate in the non-CA cohort was 2.1% (Fig. 4d).

Predictors of the incidence of clinical events

The predictors of the incidence of clinical events were analyzed using a Cox proportional hazards model among all the cohort patients. In the univariate model, the CA therapy exhibited a significant association with the occurrence of clinical events (Table 4). After adjusting for covariates in multivariable Cox model, only CA therapy (adjusted hazard ratio 0.22; 95% confidence interval: 0.05–0.97; $p = 0.046$) was indicated as an independent predictor of the incidence of clinical events.

Discussion

Major findings

The major findings of this study were that undergoing CA in HCM patients with AF had a significant association with fewer clinical events as compared to that in those who did not undergo CA. The CA group was associated with lower rates of progression into permanent AF than the non-CA group. To the best of our knowledge, this is the first report investigating the long-term clinical course after CA in HCM patients with AF.

Advantages of CA therapy in rhythm control management

Recently, Rowin et al. reported that in over 6 years of follow-up, 26% of HCM patients with PAF evolved to a permanent state of AF [3]. Also in our study, 28% in the non-CA group evolved to permanent AF during the 6 year follow-up. Permanent AF has been considered as a more advanced disease complication for patients with HCM, due to their potentially adverse consequences attributed to the chronic absence of an atrial contraction and its contribution to LV filling [2,3]. On the contrary, only 6% of the CA group had AF progression into a permanent AF phase after the CA therapy. This difference suggested a potential benefit of preventing AF progression with CA therapy.

Furthermore, though freedom from atrial arrhythmias without AADs after single-procedures was only achieved in 26% in our study, it increased to 59% after multiple procedures. Zhao et al. reported in a meta-analysis that the single-procedure success rate without AADs was only 33% and 50% after multiple procedures [18]. Since, the AFFIRM study demonstrated that AADs seemed to be associated with an increased mortality due to their pro-arrhythmic and negative inotropic effects [29], discontinuing or reducing AADs after CA therapy might have another advantage in managing AF in these populations.

Effects of the CA on HCM-related deaths

Several reports have indicated that HCM patients who develop AF have a higher risk of mortality and cardiac deaths as compared to those without AF [1,2,5–8]. Masri et al. performed a meta-analysis and reported that patients with AF had a 2.8-fold higher odds ratio of cardiac mortality as compared to those without AF [1]. On the contrary, the latest report demonstrated that with the current HCM management initiatives, AF is associated with a low cardiovascular mortality with respect to heart failure, arrhythmic sudden death, or thromboembolisms [3].

In the present study, 80% of the sudden cardiac death, which was the major cause of death, occurred in those during the PAF phase. We previously reported that an AF phase in PAF patients was a higher risk of the incidence of sudden cardiac death as compared to that in non-PAF patients [6]. Patients with HCM are more susceptible to myocardial ischemia because of small vessel abnormalities, such as

Table 4 Predictors of clinical events

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex, male	1.02 (0.44–2.37)	0.958		
Age at analytic start time	1.02 (0.98–1.06)	0.344		
Outflow tract obstruction	1.99 (0.89–4.46)	0.093	1.55 (0.69–3.51)	0.291
Apical hypertrophy	1.19 (0.54–2.66)	0.668		
BNP	1.00 (1.00–1.00)	0.345		
Left atrial dimension	1.02 (0.97–1.07)	0.453		
Non-sustained ventricular tachycardia	2.10 (0.95–4.64)	0.066	2.12 (0.95–4.76)	0.068
Catheter ablation therapy	0.22 (0.05–0.94)	0.041	0.22 (0.05–0.97)	0.046

HR hazard ratio, *CI* confidence interval, the other abbreviations are as in Table 1.

thickened walls and a limited luminal area, and this has been regarded as one of the most essential pathophysiological features that promotes ischemic damage to the ventricular myocardium [26,27]. The acute hemodynamic changes and sudden increase in the ventricular rate with the onset of AF would promote ischemia of the ventricular myocardium and lead to fatal ventricular arrhythmias [26,28]. Thus, though it seemed to frequently require multiple procedures or post-procedural AADs, CA might be able to reduce AF attacks and contribute to the prevention of sudden cardiac death.

Effects of the CA on heart failure hospitalizations

In our study, 73% of those with advanced heart failure in the non-CA group had a persistent or permanent AF status. Also in the CA group, all heart failure events occurred in those who had persistent AF recurrences after the initial procedure. Previous reports indicated that during higher rates of AF, patients with HCM are often unable to maintain an appropriate stroke volume due to a shorter time for cardiac filling, leading to a poorly relaxing and non-compliant ventricle and increased risk of worsening heart failure conditions [2,4,5,9,10]. Furthermore, in patients with obstructive HCM, since the stroke volume relies on the left atrial contraction for left ventricular filling to relieve the obstruction, higher rates of AF might emphasize a risk of heart failure events [2]. All these findings suggested that a high AF burden might be a risk of advanced heart failure. In the CA group, among patients with persistent or long-standing persistent AF who had AF recurrences after the initial procedure, 64% could change the recurrent AF type into PAF, while the remaining 36% still had persistent AF recurrences. Since recurrences as persistent AF still accounted for a relative proportion even after undergoing CA procedures, this might be one of the limitations.

Nonetheless, in the present study, the annual event rate in the CA group was 1.2% while in the non-CA group it was 3.9%. In the general HCM population, Maron et al. reported that, the annual rate of progressive heart failure was 1.6% in the nonobstructive HCM patients and 7.4% in the HCM patients who had an outflow obstruction [6]. Olivotto et al. previously reported that patients with AF were associated with a 2.8-fold higher odds ratio of progressive heart failure compared to those without AF [2]. These findings suggested that the annual rate of progressive heart failure in the CA group might be relatively lower than that of the natural course of HCM patients with AF.

Effects of CA on new-onset thromboembolic strokes

We previously reported that in the HCM cohort without documented AF, the incidence of strokes and embolic events was 1.0% per year [11]. In HCM patients with AF, Guttmann et al. reported in a systemic-review in which the incidence of thromboembolisms was 3.8% per year [13]. The usual CHA_2DS_2-VASc score to predict the risk of thromboembolic events did not appear to be correlated with the incidence of embolic events in HCM patients [3,12,16], and the guidelines recommend that AF patients should be anticoagulated regardless of the CHA_2DS_2-VASc score [17]. However, several reports including our previous one suggested that in the HCM cohort, an advanced age and larger LA dimension might be highly associated with the risk of the incidence of embolic events [11,13,14]. In the present study, 63% of those with stroke events were $\geq$75 years and 38% had a larger LA dimension of $\geq$48 mm [11]. Furthermore, 63% of the stroke patients had permanent AF. Olivotto et al. previously reported that in the HCM population, patients developing chronic AF might be associated with a higher probability of stroke events as compared to those with PAF [2]. Since CA therapy seems to be highly associated with preventing AF progression, this effect may contribute to a decrease in the thromboembolic stroke risk in HCM patients with AF.

Limitations

Several limitations must be taken into account when interpreting this study. First, the non-CA group had a higher age and this might have been associated with the incidence of the clinical events. However, since the multivariable Cox model showed that age was not independently shown to be a predictor of the clinical events, we thought this bias would not have affected our conclusion. Second, it is likely that we underestimated the true prevalence of AF, since subclinical AF could not be completely detected. Finally, this was a nonrandomized, observational, single-center study and the sample size was small. Therefore, to confirm and extend our findings, further multicenter and prospective studies validated in a larger group of patients are required.

Conclusions

CA may be associated with a favorable long-term clinical course in HCM patients with AF. This therapeutic option may be highly associated with lower long-term clinical events and lower rates of those who progress into permanent AF. Further studies are required to clarify these findings.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

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