ORIGINAL RESEARCH

RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

Transcatheter Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy

A Multicenter Propensity Score-Based Analysis

Alessandro Pierri, MD,[a],* Stefano Albani, MD,[b],* Marco Merlo, MD,[a] Antonia Luisa Buongiorno, MD,[b,c]
Andrea Ricotti, PhD, PharmD,[d] Giulia Grilli, MD,[a] Davide Barbisan, MD,[a] Stefano Grossi, MD,[b] Catia De Rosa, MD,[b]
Barbara Mabritto, MD,[b] Stefania Luceri, MD,[b] Sergio Bongioanni, MD,[b] Francesco Negri, MD,[e] Massimo Burelli, MD,[e]
Michele Millesimo, MD,[f] Federico Biondi, MD,[g] Manuela Cireddu, MD,[h] Jan Berg, MD,[h]
Maria Beatrice Musumeci, MD,[i] Paolo Di Donna, MD,[c] Pier Filippo Vianello, MD,[c] Annamaria Del Franco, MD,[j]
Marco Scaglione, MD,[k] Giulia Barbati, PhD,[l] Sara Urru, MS,[m] Paola Berchialla, PhD,[n] Gaetano Maria De Ferrari, MD,[f]
Vincenzo Russo, MD, PhD,[o] Eustachio Agricola, MD,[g] Massimo Imazio, MD,[e] Italo Porto, MD, PhD,[c]
Marco Canepa, MD, PhD,[c,p] Giovanni Peretto, MD,[h] Pietro Francia, MD,[i] Davide Castagno, MD, PhD,[f]
Camillo Autore, MD,[q] Iacopo Olivotto, MD,[j] Fiorenzo Gaita, MD,[k] Gianfranco Sinagra, MD,[a],†
Giuseppe Musumeci, MD[b],†

ABSTRACT

BACKGROUND The prognostic impact of catheter ablation (CA) of atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) patients has not yet been satisfactorily elucidated.

OBJECTIVES The aim of the study was to assess the impact of CA of AF on clinical outcomes in a large cohort of HCM patients.

METHODS In this retrospective multicenter study, 555 HCM patients with AF were enrolled, 140 undergoing CA and 415 receiving medical therapy. 1:1 propensity score matching led to the inclusion of 226 patients (113 medical group, 113 intervention group) in the final analysis. The primary outcome was a composite of all-cause mortality, heart transplant and acute heart failure exacerbations. Secondary outcomes included AF recurrence and transition to permanent AF. Additionally, an inverse probability weighted (IPW) model was examined.

RESULTS At propensity score matching analysis, after a median follow-up of 58.1 months, the primary endpoint occurred in 29 (25.7%) patients in intervention group vs 42 (37.2%) in medical group ($P = 0.9$). Thromboembolic strokes and major arrhythmic events in intervention vs medical group were 9.7% vs 7.1% ($P = 0.144$) and 4.4 vs 8.0% ($P = 0.779$), respectively. Fewer patients in intervention vs medical group experienced AF recurrences (63.7% vs 84.1%, $P = 0.001$) and transition to permanent AF pattern (20.4% vs 33.6%, $P = 0.026$). IPW analysis showed consistent results. Severe complications related to CA were uncommon (0.7%).

CONCLUSIONS After 5 years of follow-up, CA did not improve major adverse cardiac outcomes in a large cohort of patients with HCM and AF. Nevertheless, CA seems to facilitate the maintenance of sinus rhythm and slow the progression to permanent AF, without significant safety concerns. (JACC Adv 2024;3:100899) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

CA = catheter ablation

CMR = cardiac magnetic resonance

CTI = cavotricuspid isthmus

CV = cardiovascular

HCM = hypertrophic cardiomyopathy

HF = heart failure

HT = heart transplant

ICD = implantable cardioverter-defibrillator

IPW = Inverse probability weighted

LA = left atrium

LV = left ventricular

MR = mitral regurgitation

PSM = propensity score matching

PVI = pulmonary vein isolation

RF = radiofrequency

SCD = sudden cardiac death

SR = sinus rhythm

Hypertrophic cardiomyopathy (HCM) is a primary heart muscle disorder characterized by left ventricular (LV) or biventricular hypertrophy not explained by overload conditions such as hypertension or valvular heart disease.[1,2] Although the clinical course of HCM is variable, higher incidence and earlier onset of supraventricular arrhythmias, especially atrial fibrillation (AF), have been well-documented in HCM patients as compared to general population.[3] Diastolic dysfunction, mitral regurgitation (MR), LV outflow tract obstruction, and intrinsic atrial myopathy represent the most common pathophysiological factors leading to left atrial remodeling and ultimately AF development in HCM.[4,5] As in other conditions associated with impaired diastolic function, AF occurrence and progression are predictive of adverse outcome by increasing the risk of heart failure (HF) exacerbation, thromboembolic events, and inappropriate shocks from implantable cardioverter-defibrillators (ICD).[6] Furthermore, AF tend to significantly affect quality of life and exercise tolerance in patients with HCM, often requiring the implementation of rhythm control strategies to reduce AF-related symptoms. Catheter ablation (CA) is a well-established option to restore and maintain sinus rhythm (SR), particularly after antiarrhythmic drugs failure or intolerance.[7] Furthermore, CA should be considered as first-line rhythm control therapy in selected patients with symptomatic AF, such as those with HF and reduced ejection fraction to decrease mortality and hospitalizations for worsening HF.[8,9]

Current data regarding efficacy, safety, and long-term outcomes of CA in comparison to standard medical therapy are scarce in HCM population, due to the absence of large-scale and comprehensive clinical studies. Therefore, we sought to add knowledge to the existing literature by describing a multicenter experience with transcatheter ablation procedures in a large and well-characterized cohort of patients with HCM and AF.

METHODS

STUDY DESIGN AND POPULATION. We performed an observational retrospective study of adult HCM patients with documented AF followed at 9 Italian referral centers (listed in Supplemental Appendix and Supplemental Figure 1) between January 2000 and December 2021. HCM was diagnosed using standard criteria, namely a maximum wall thickness ≥15 mm in 1 or more LV myocardial segments in the absence of overload conditions, as measured by echocardiography or cardiac magnetic resonance (CMR) imaging. Alternatively, a lower degree of LV hypertrophy (13-14 mm) was enough to diagnose HCM in first-degree family members of HCM patients.[10]

The study included adult patients of both sexes and able to express informed consent. Exclusion criteria were: 1) secondary causes of LV hypertrophy and HCM phenocopies; 2) absence of documented history of AF; 3) continuous AF over 1-year duration considered not amenable to a rhythm control strategy (ie, permanent subtype); 4) age <18 years and

From the ᵃCardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI) and University Hospital of Trieste, Trieste, Italy; ᵇCardiology Department, Azienda Ospedaliera Ordine Mauriziano Umberto I, Turin, Italy; ᶜDepartment of Cardiology, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy; ᵈClinical Trial Unit, Azienda Ospedaliera Ordine Mauriziano Umberto I, Turin, Italy; ᵉCardiothoracic Department, University Hospital Santa Maria della Misericordia, Udine, Italy; ᶠDivision of Cardiology, Department of Medical Sciences, "Città della Salute della Scienza" Hospital, University of Turin, Turin, Italy; ᵍCardiovascular Imaging Unit, Hypertrophic Cardiomyopathy Outpatient Clinic, IRCCS San Raffaele Scientific Institute, Milan, Italy; ʰDepartment of Cardiac Electrophysiology and Arrhythmology, IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁱDivision of Cardiology, Department of Clinical and Molecular Medicine, St. Andrea Hospital, Sapienza University, Rome, Italy; ʲDepartment of Experimental and Clinical Medicine, Careggi University Hospital, University of Florence, Florence, Italy; ᵏDivision of Cardiology, Department of Internal Medicine, Cardinal Massaia Hospital, Asti, Italy; ˡBiostatistics Unit, Department of Medical Sciences, University of Trieste, Trieste, Italy; ᵐUnit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padua, Italy; ⁿDepartment of Clinical and Biological Sciences, Centre for Biostatistics, Epidemiology and Public Health, University of Turin, Turin, Italy; ᵒDepartment of Translational Medical Sciences, University of Campania "Luigi Vanvitelli" - Monaldi and Cotugno Hospital, Naples, Italy; ᵖDepartment of Internal Medicine, University of Genova, Genoa, Italy; and the �q Department of Cardiology and Respiratory Sciences, San Raffaele Cassino (FR), Cassino, Italy. *Drs Pierri and Albani contributed equally as first authors. †Drs Sinagra and Musumeci contributed equally as senior authors.

>80 years; and 5) inability to express informed consent.

The study complied with the Declaration of Helsinki and was approved by the local institutional ethics board.

Eligible patients were divided into 2 treatment groups: those who underwent CA in addition to medical therapy (intervention group) and those who received standard rhythm and/or rate control drugs (medical group). Baseline characteristics including demographics, body mass index, European Society of Cardiology-sudden cardiac death (SCD) risk score (when applicable), cardiovascular (CV) symptoms as defined by the NYHA functional classification, arrhythmia temporal pattern, CV medication use, echocardiographic parameters, and presence of late gadolinium enhancement on CMR imaging were systematically extracted from the electronic medical records and retrospectively analyzed when available. For the aim of the study, arrhythmia temporal pattern was categorized in 3 different subtypes, namely paroxysmal, persistent, and long-standing persistent, according to the 2020 ESC guidelines for AF management.[9]

Notably, baseline characteristics and the start of the follow-up period coincided with the index CA for the intervention group, while dated back to the first evaluation at the referral center for medical group. Clinical follow-up data were manually collected for all patients using hospital records and the information systems used in the cardiology departments.

PRIMARY AND SECONDARY ENDPOINTS. The primary study endpoint was a composite of all-cause death, heart transplant (HT), or acute HF exacerbations (ie, hospitalization or urgent visit with need of intravenous diuretics). Beyond primary outcome components, different secondary outcomes were evaluated: 1) a key composite endpoint, including CV mortality (identified as the following 3 modalities: SCD, with the exclusion of cardiac arrest survivors, end-stage HF-related death and fatal thromboembolic stroke), HT, or HF exacerbations; 2) thromboembolic strokes, including both fatal and nonfatal cerebral accidents; 3) major arrhythmic events, comprehending SCD, major ventricular arrhythmias (including ventricular fibrillation and sustained ventricular tachycardia), and appropriate ICD shocks; 4) AF recurrence; and 5) AF progression, namely the transition from paroxysmal and persistent to permanent patterns.

For each outcome comparison, patients who experienced more than 1 of the component events were counted only once based on the time until the first event.

Finally, any complication related to CA was systematically reported.

IMAGING STUDIES. Comprehensive echocardiographic studies were performed in most of the enrolled patients, according to international guidelines.[11] Details regarding more relevant echocardiographic parameters are provided in the Supplemental Appendix. Additionally, CMR was performed in a subgroup of patients (n = 317; 57.1%) to complete diagnostic assessment, allowing in vivo visualization of myocardial scarring through late gadolinium enhancement. Both echocardiograms and CMR were interpreted locally by cardiac imaging specialists.

TRANSCATHETER ABLATION PROCEDURES. All ablation procedures were targeted to achieve pulmonary vein isolation (PVI) using point-by-point radiofrequency (RF) energy or cryothermy balloon catheters. Electroanatomic mapping systems such as CARTO or NavX were employed. More complex AF ablation schemes, including linear lesions within left atrium (LA) and ablation of complex atrial fractionated electrograms, were variably performed at the discretion of the electrophysiologist. Furthermore, ablation protocols could include right isthmus ablation in case of concomitant cavotricuspid isthmus (CTI)-dependent atrial flutter (AFL).

A 3-month blanking period was considered to determine the arrhythmic recurrence rate following CA. Diagnostic tools for capturing the recurrence included periodic clinical assessments with 12-lead electrocardiograms, Holter recordings, and continuous cardiac monitoring with CV implantable electronic devices such as pacemaker, defibrillator, and loop recorder. Specifically, any AF episode lasting at least 30 seconds when documented by surface electrocardiogram and more than 5 minutes as detected by CV implantable electronic devices was defined as recurrence.

STATISTICAL ANALYSIS. Categorical variables are expressed as counts and percentages and compared among groups using chi-square test or Fisher exact test, as appropriate. Continuous variables are presented as mean ± SD when normally distributed and as median (1st to 3rd IQR) when not normally distributed. Normal distribution of continuous variables under examination was verified with the Shapiro-Wilk test. Significant differences in continuous variables between the groups were assessed using Student's t-test (normally distributed variables)

TABLE 1 Baseline Patient Characteristics

	Before Propensity Score Matching (N = 555)			After Propensity Score Matching (N = 226)		
	Intervention Group (n = 140)	Medical Group (n = 415)	P Value	Intervention Group (n = 113)	Medical Group (n = 113)	P Value
Age (y)	57.00 (49.00-64.00)	60.00 (47.50-67.50)	0.198	57.00 (49.00-65.00)	57.00 (47.00-67.00)	0.894
Male	94 (67.1)	233 (56.1)	0.023	76 (67.3)	78 (69.0)	0.887
BMI (kg/m^2)	26.00 (24.25-27.32)	26.13 (23.86-29.04)	0.678	26.00 (24.07-27.22)	25.71 (23.66-28.70)	0.971
Family history of SCD	33 (23.6)	114 (27.5)	0.438	30 (26.5)	35 (31.0)	0.557
Family history of HCM	44 (31.4)	153 (36.9)	0.262	37 (32.7)	40 (35.4)	0.779
History of CAD	12 (8.6)	42 (10.1)	0.742	11 (9.7)	10 (8.8)	1.000
NSVT	30 (21.4)	93 (22.4)	0.906	28 (24.8)	33 (29.2)	0.549
Major ventricular arrhythmias	12 (8.6)	13 (3.1)	0.002	10 (8.8)	4 (3.5)	0.166
ESC-SCD risk score	2.46 (1.81-4.32)	2.63 (1.78-4.21)	0.896	2.46 (1.82-4.58)	2.88 (2.06-4.86)	0.347
NYHA functional class			0.620			0.738
I	56 (40.0)	145 (34.9)		44 (38.9)	42 (37.2)	
II	67 (47.9)	219 (52.8)		55 (48.7)	60 (53.1)	
III	16 (11.4)	49 (11.8)		14 (12.4)	11 (9.7)	
IV	1 (0.7)	2 (0.5)		0 (0.0)	0 (0.0)	
ICD implanted	29 (20.7)	32 (7.7)	<0.001	22 (19.5)	9 (8.0)	0.119
Prior septal myectomy	14 (10.0)	17 (4.1)	0.002	8 (7.1)	8 (7.1)	1.000
AF subtype			<0.001			0.092
Paroxysmal	66 (47.1)	312 (75.2)		53 (46.9)	49 (43.4)	
Persistent	59 (42.2)	96 (23.1)		46 (40.7)	58 (51.3)	
Long-standing persistent	15 (10.7)	7 (1.7)		14 (12.4)	6 (5.3)	
AF duration (mo)	38.00 (14.00-71.50)	33.00 (9.00-83.00)	0.093	39.00 (21.00-79.00)	33.00 (16.00-77.00)	0.408
Medication						
Oral anticoagulants	119 (85.0)	186 (44.8)	<0.001	93 (82.3)	63 (55.8)	<0.001
VKA	70 (50.0)	127 (30.6)		64 (54.7)	32 (28.4)	
DOAC	49 (35.0)	59 (14.2)		33 (28.2)	31 (27.4)	
Beta-blocker	111 (79.3)	289 (69.6)	0.029	93 (82.3)	90 (79.6)	0.735
Nondihydropyridine CCB	13 (9.3)	57 (13.7)	0.188	13 (11.5)	9 (8.0)	0.502
Antiarrhythmic drugs	83 (59.3)	131 (31.6)	<0.001	69 (61.1)	44 (38.9)	0.001
Sotalol	15 (10.7)	29 (7.0)		15 (13.3)	13 (11.4)	
Amiodarone	39 (27.9)	67 (16.1)		31 (27.4)	21 (18.6)	
Dronedarone	1 (0.7)	5 (1.2)		1 (0.9)	2 (1.8)	
Flecainide	17 (12.1)	10 (2.4)		15 (13.3)	3 (2.7)	
Propafenone	7 (5.0)	4 (1.0)		5 (4.4)	0 (0)	
Disopyramide	4 (2.9)	16 (3.9)		2 (1.8)	5 (4.4)	
Diuretics	41 (29.3)	109 (26.3)	0.510	31 (27.4)	32 (28.3)	1.000
Echocardiographic parameters						
LVEF (%)	60.00 (55.75-65.00)	60.00 (60.00-65.00)	0.054	60.00 (56.00-65.00)	60.00 (58.00-66.00)	0.744
Maximum LVWT (mm)	19.00 (16.00-21.00)	19.00 (17.00-23.00)	0.152	19.00 (16.00-22.00)	20.00 (17.00-24.00)	0.162
Not available	3 (2.1)	4 (1.0)				
Obstructive HCM	25 (17.9)	158 (38.2)	<0.001	22 (19.5)	26 (23.0)	0.626
Diastolic dysfunction			0.276			0.929
Not available	6 (4.3)	4 (1.0)				
None	16 (12.0)	32 (7.8)		13 (11.5)	13 (11.5)	
Mild	47 (35.3)	146 (35.6)		39 (34.5)	40 (35.4)	
Moderate	44 (33.1)	164 (40.0)		39 (34.5)	42 (37.2)	
Severe	26 (19.5)	68 (16.6)		22 (19.5)	18 (15.9)	
Mitral regurgitation			0.263			0.416
None	18 (12.9)	62 (14.9)		8 (7.1)	3 (2.7)	
Mild	86 (61.4)	219 (52.8)		75 (66.4)	82 (72.6)	
Moderate	35 (25.0)	123 (29.6)		29 (25.7)	27 (23.9)	
Severe	1 (0.7)	11 (2.7)		1 (0.9)	1 (0.9)	
SAM of mitral valve	32 (23.2)	202 (50.6)	<0.001	29 (25.7)	40 (35.4)	0.148
Not available	2 (1.4)	14 (3.8)				
Left atrial diameter (cm)	5.00 (4.40-5.50)	4.70 (4.20-5.20)	0.003	5.00 (4.40-5.50)	4.80 (4.40-5.40)	0.564
Not available	10 (7.1)	8 (1.9)				

TABLE 1 Continued						
	Before Propensity Score Matching (N = 555)			After Propensity Score Matching (N = 226)		
	Intervention Group (n = 140)	Medical Group (n = 415)	P Value	Intervention Group (n = 113)	Medical Group (n = 113)	P Value
LV LGE on CMR imaging	66 (75.9)	160 (73.7)	0.772	53 (72.6)	52 (78.8)	0.434
Not available	44 (31.4)	196 (47.2)				

Values are median (IQR) or n (%).

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blockers; CMR = cardiac magnetic resonance; DOAC = direct-acting oral anticoagulants; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; LVWT = left ventricular wall thickness; NSVT = nonsustained ventricular tachycardia; SAM = systolic anterior motion; SCD = sudden cardiac death; VKA = vitamin K antagonists.

or the Mann-Whitney rank-sum test (non-normally distributed variables).

Subsequently, a 1:1 propensity score matching (PSM) analysis was performed by adjusting for a set of baseline covariates which could play a role when evaluating treatment options for AF: age, body mass index, NYHA functional class, arrhythmia pattern, LV ejection fraction, maximum LV wall thickness, obstructive HCM, diastolic dysfunction, MR grade, and LA diameter (Supplemental Figure 2). Therefore, 2 matched well-balanced cohorts were obtained and included in the final analysis for outcome measures. Additionally, we used the propensity score to elaborate further analysis by weighting each patient by the inverse probability of undergoing CA. This inverse probability weighted (IPW) model was employed to confirm or disprove the results obtained with PSM technique.

For all analyses, time-to-first event data were evaluated with the use of Kaplan-Meier and groups were compared using the Cox proportional hazard model. 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. The proportional hazard assumption was verified by the log minus log method and the analysis of Schoenfeld residuals.

For all tests, 2-sided P values <0.05 were considered to indicate statistical significance.

Statistical calculations were performed using software R (R 4.2.0, R Development Core Team).

RESULTS

STUDY SAMPLE. A total of 631 HCM patients with AF were originally screened. Out of these, 76 patients were excluded from the study because of permanent arrhythmia pattern. Of the remaining 555 patients, 140 (25.2%) were included in the intervention group and 415 (74.8%) in the medical group. At baseline (Table 1), patients in medical group were characterized by a greater proportion of female (182 [43.9%] females in the medical group vs 46 [32.9%] females in the intervention group; $P = 0.023$). A lower proportion of patients in the medical group suffered from persistent and long-standing persistent AF (24.8% in the medical group vs 52.9% in the intervention group, $P < 0.001$). The median (25th, 75th percentiles) arrhythmia duration was 38 months (14, 71.5 months) for intervention group and 33 months (9, 83 months) for medical group ($P = 0.093$), measured from the first detection of AF to the index ablation and to the first outpatient clinic visit at the referral center, respectively. Median LV ejection fraction was preserved in both groups, and no significant differences in diastolic function and maximum LV wall thickness were found. Conversely, higher proportions of obstructive HCM and systolic anterior motion of the mitral valve were observed in the medical group. Remarkably, median LA diameter was slightly larger in the intervention group ($P = 0.003$). Despite a higher prevalence of ICD carriers as well as a larger use of betablocker and antiarrhythmic agents in the intervention group, the 5-year risk score for primary prevention of SCD did not significantly differ between the 2 groups.

After applying 1:1 PSM, 113 patients treated by CA and 113 patients receiving medical treatment were coupled. Consequently, no significant differences in any of the assessed baseline characteristics were identified between groups, except for more frequent use of anticoagulant and antiarrhythmic drugs in the intervention group (Table 1). A substantial covariate balance was also achieved by applying IPW, with the advantage to preserve the original sample size more than PSM. Precisely, 113 patients in intervention group and 383 patients in medical group were compared after weighting procedure.

CA PROCEDURAL DETAILS. Detailed procedural aspects were evaluated within the entire ablation cohort (n = 140) and are summarized in Table 2. At baseline, 68 patients (48.6%) were in SR and 72 patients (51.4%) had AF/AFL. Only 22 patients (15.7%) had undergone ≥1 previous ablation procedure in other centers.

TABLE 2 Index Transcatheter Ablation Procedural Details (N = 140)

Rhythm at hospital admission	
SR	68 (48.6)
AF/AFL	72 (51.4)
Transcatheter ablation scheme	
Not available	*3 (2.1)*
PVI alone	70 (50.0)
PVI + CTI ablation	12 (8.6)
PVI + additional lesion sets	34 (24.3)
PVI + CTI ablation + additional lesion sets	21 (15.0)
PVI technique	
Not available	*3 (2.1)*
RF ablation	130 (92.9)
Cryoablation	7 (5.0)
Sinus rhythm restoration	
During ablation procedure	42 (58.3)
After electrical cardioversion	30 (41.7)
Procedure time (min)	150 (120-200)
Rhythm at hospital discharge	
Not available	*10 (7.1)*
SR	116 (82.9)
AF/AFL	14 (10.0)
Repeat ablation procedure	47 (33.6)
AF ablation	22 (15.7)
CTI ablation	11 (7.9)
AF ablation + CTI ablation	14 (10.0)
Periprocedural complications	11 (7.8)
Mild pericardial effusion	7 (5)
Cardiac tamponade	1 (0.7)
Femoral hematoma	1 (0.7)
Pleural effusion	1 (0.7)
Hemidiaphragm paralysis	1 (0.7)

Values are n (%) or median (IQR).

AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation; RF = radio frequency; SR = sinus rhythm.

The ablation scheme encompassed PVI alone in 70 patients (50.0%), PVI and additional lesion sets such as complex atrial fractionated electrograms ablation and linear lines in 34 patients (24.3%), PVI and CTI ablation in 12 patients (8.6%), PVI, additional lesion sets, and CTI ablation in 21 patients (15.0%). PVI was achieved by RF energy in most of the patients (n = 130, 92.9%), while cryoablation was executed in 7 patients (5.0%). A schematic view of ablation schemes is reported in **Figure 1**.

The median (25th, 75th percentiles) procedure time was 150 minutes (120, 200 minutes).

Among patients in whom the index ablation was performed during AF/AFL, SR restoration required electrical cardioversion at the end of the procedure in 30 patients (41.7%). 116 patients (82.9%) were in SR at hospital discharge.

After the blanking period, repeat ablation procedures were performed in 47 patients (33.6%) by virtue of favorable clinical profile and symptomatic improvement after the index CA.

Overall, index ablation-related complications were recorded in 11 out of 140 patients (7.8%); however, serious adverse events were uncommon (<1%). Specifically, 8 patients developed a pericardial effusion, but only 1 required pericardiocentesis. One patient had hemidiaphragm paralysis due to damage to the phrenic nerve and 1 pleural effusion without respiratory compromise. Lastly, 1 patient developed a small hematoma at the femoral puncture site that was treated conservatively.

PRIMARY ENDPOINT AT MID-TERM FOLLOW-UP. Considering the PSM analysis, over a median follow-up of 58.1 (IQR: 26.0-104.1) months, the primary outcome event occurred in 29 out of 113 patients (25.7%) in the intervention group and 42 out of 113 patients (37.2%) in the medical group (HR: 0.97 [95% CI: 0.60-1.57]; $P = 0.90$) (**Table 3**, **Figure 2**).

SECONDARY CV ENDPOINT. Among the secondary endpoints, a key outcome including CV mortality, HT and acute HF exacerbations occurred in 24 patients (21.2%) in the intervention group and in 37 patients (32.7%) in the medical group (HR: 0.86 [95% CI: 0.51-1.46]; $P = 0.581$). There were 6 (5.3%) deaths from CV causes in the intervention group and 5 (4.4%) in the medical group (HR: 1.65 [95% CI: 0.5-5.45]; $P = 0.414$) (**Table 4**, **Figure 3**).

There were 11 patients (9.7%) in the intervention group who suffered from thromboembolic cerebral events, including 2 stroke-related deaths. On the other hand, in the medical group, there were 8 thromboembolic strokes, almost all nonfatal (HR: 2.00 [95% CI: 0.79-5.05]; $P = 0.144$) (**Table 4**). Although anticoagulation levels were unbalanced at baseline, the number of anticoagulated patients at the time of embolic cerebrovascular events did not significantly differ between the 2 groups (Supplemental Table 1).

During follow-up, a major arrhythmic event occurred in 5 patients (4.4%) in the intervention group and in 9 patients (8.0%) in the medical group [HR: 0.85 [95% CI: 0.28-2.59]; $P = 0.779$) (**Table 4**). Analogously to anticoagulant therapy, antiarrhythmic drug use at the last medical contact preceding the event was comparable between the groups (Supplemental Table 1).

AF RECURRENCE AND PROGRESSION. At the end of follow-up, a significantly lower AF burden was found in the intervention arm as compared to the medical group (OR: 0.73 [95% CI: 0.17-0.62]; $P = 0.001$)

(Figure 4A). Indeed, 72 patients (63.7%) vs 95 patients (84.1%) experienced AF recurrences in the intervention and medical group, respectively. Focusing on the intervention group, stable SR was found in 27 (50.9%) patients with paroxysmal AF and 14 (23.3%) patients with persistent/long-persistent AF (OR: 3.41 [95% CI: 1.53-7.63]; $P = 0.002$).
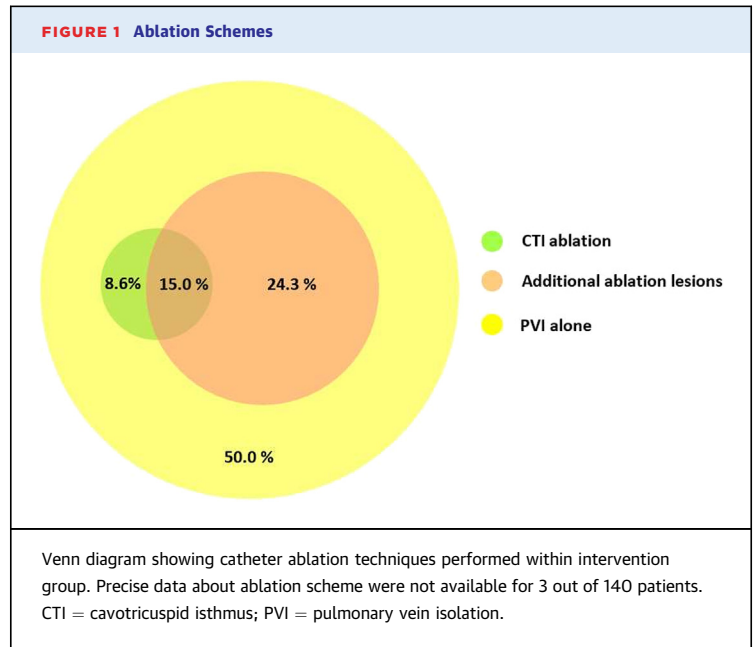
In the intervention group, 23 patients (20.4%) finally progressed to permanent AF pattern, while there were 38 permanent AF (33.6%) in the medical group at the end of follow-up (OR: 0.50 [95% CI: 0.27-0.91]; $P = 0.026$) (Figure 4B). Among patients experiencing arrhythmic recurrences in the intervention group, a substantial part (38 out of 72 patients, 52.8%) underwent redo procedures to regain freedom from AF.

COVARIATE ADJUSTED IN PROPENSITY SCORE-MATCHED SAMPLES. We performed further analyses for primary and secondary outcomes by adjusting for those variables that remained unbalanced after 1:1 PSM, namely anticoagulant and antiarrhythmic drug therapy. As shown in Supplemental Table 2, this adjustment did not change the estimated effect of intervention treatment.

COMPLEMENTARY ANALYSIS BASED ON IPW MODEL. IPW analysis substantially confirmed the results obtained by PSM method, with the only exception of supraventricular arrhythmia progression because of the loss of statistical significance (Supplemental Table 3).

DISCUSSION

MAIN FINDINGS. Current guidelines have pointed out the key role of CA in the management of AF in the general population, and even more in certain categories of patients such as those with HF and reduced ejection fraction[8] or tachycardia-induced cardiomyopathy.[12] Conversely, the existing data concerning the optimal management and treatment modalities of AF in HCM patients are scarce and fragmentary due to the absence of large-scale clinical studies and randomized trials. In this challenging scenario, our study shows for the first time that the implementation of CA for AF in HCM patients with a median pre-ablation arrhythmia duration close to 3 years is not associated with a significantly lower rate of death, HT and HF exacerbations during a 5-year follow-up period. CA strategy might result in a significantly lower AF burden, either by reducing arrhythmia recurrence and the progression to permanent pattern (Central Illustration). Furthermore, the procedure was safe, with a limited number of nonfatal complications across participating center. These findings have

FIGURE 1 Ablation Schemes

- CTI ablation
- Additional ablation lesions
- PVI alone

8.6% 15.0% 24.3%

50.0%

Venn diagram showing catheter ablation techniques performed within intervention group. Precise data about ablation scheme were not available for 3 out of 140 patients. CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation.

potential implications for the management of HCM patients with AF.

PROGNOSTIC ROLE OF CA STRATEGIES. CA does not seem to significantly reduce the occurrence of CV death, nor the incidence of thromboembolic stroke or major arrhythmic events. These results have a pathophysiological rationale that relates to the complexity and heterogeneity of patients with HCM. A vast multitude of well-recognized pathophysiological features, ranging from dynamic obstruction, MR, diastolic dysfunction with a rise in ventricular filling pressure, autonomic dysregulation, myocardial ischemia to atrial and ventricular arrhythmias, can promote clinical deterioration of HCM patients.[1] Thus, the potential hemodynamic benefit resulting from the restoration of the atrial contraction may be

TABLE 3 Primary Composite Outcome and Its Components (Propensity Score Matching Analysis)

	Intervention Group (n = 113)	Medical Group (n = 113)	HR (95% CI)	P Value
Primary composite outcome	29 (25.7)	42 (37.2)	0.97 (0.60-1.57)	0.900
All-cause mortality	13 (11.5)	15 (13.3)	0.97 (0.34-2.65)	0.933
Heart transplant	2 (1.8)	4 (3.5)	0.95 (0.11-5.83)	0.831
Acute HF exacerbations	23 (20.4)	28 (24.8)	1.11 (0.61-2.04)	0.718
HF hospitalization	16 (14.2)	21 (18.6)		
HF urgent visit	10 (8.8)	15 (13.3)		

Values are n (%) unless otherwise indicated. Multistate regression models were used to analyze the components of the composite endpoint.

HF = heart failure.

FIGURE 2   Time-to-Event Curves for Primary Composite Outcome, All-Cause Death, and Acute HF Exacerbations
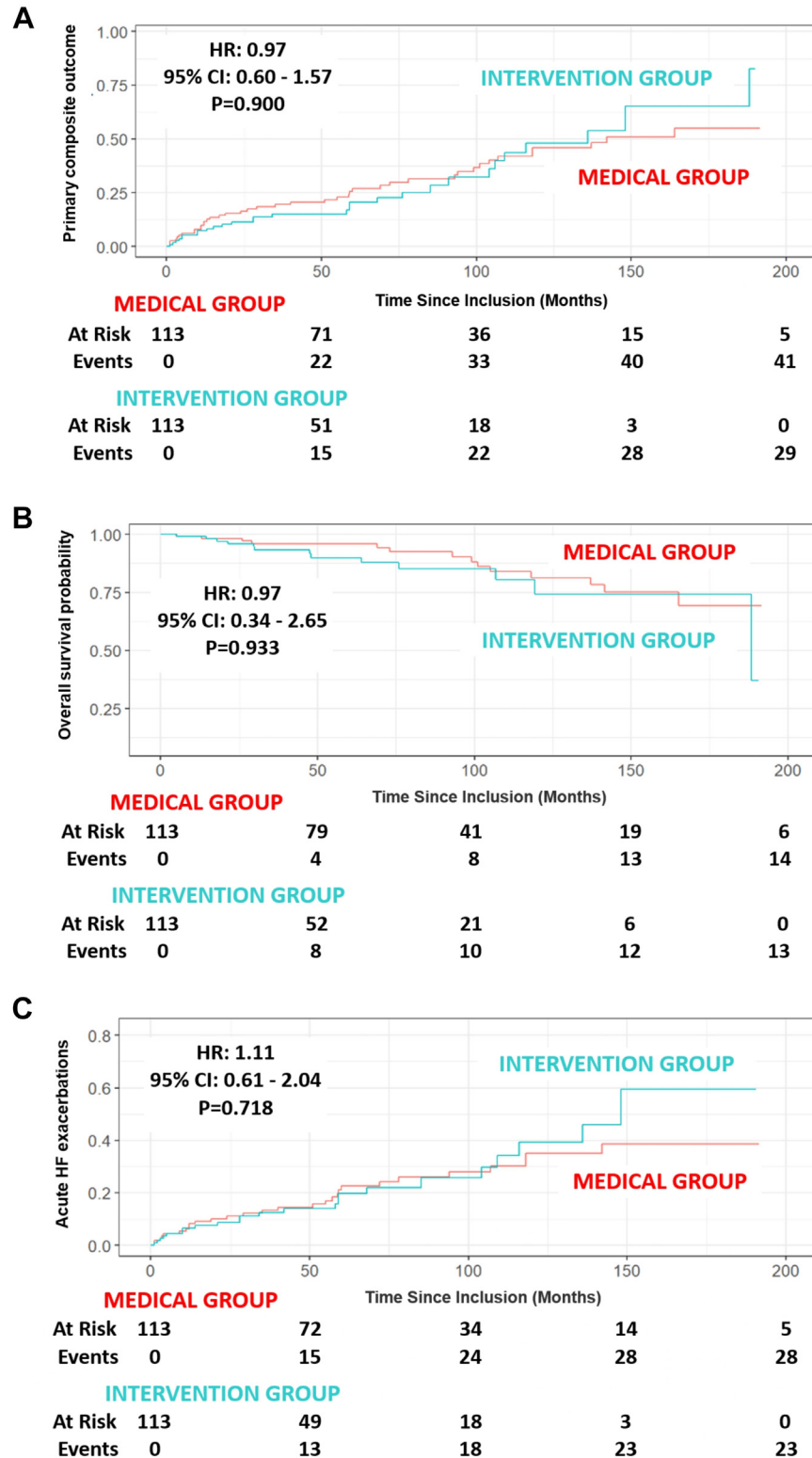
(A) Kaplan-Meier curve for the primary composite outcome of all-cause death, heart transplant, and acute HF exacerbations. (B) Kaplan-Meier curve for all-cause mortality. (C) Kaplan-Meier curve for acute HF exacerbations. HF = heart failure.

nullified by the development, worsening, and convergence of the other pathophysiological mechanisms over a mid-term follow-up period. Interestingly, by observing the trajectory of the primary outcome curve, a beneficial trend for ablation therapy can be noticed only within the first few years after the procedure, and then is lost during the following monitoring period.

Moreover, various baseline characteristics such as moderate-to-severe degree of LA dilation, important rate of diastolic impairment, and median pre-ablation arrhythmia duration exceeding 3 years probably reflect an advanced stage of the disease for most ablated patients of our cohort. Besides, before PSM, the majority of patients in the medical group suffered from paroxysmal AF (75.2%), while more than half of ablated patients (52.9%) were affected from persistent and long-standing persistent forms. This difference, albeit mitigated after PSM, averagely reflects a long-time interval from AF onset to CA, as often happened in the first decade of the 2000s. Notably, retrospective studies investigating the time-dependent clinical impact of CA for AF in HCM subjects have not been published, and a more consistent benefit from early invasive strategy following arrhythmia onset cannot be excluded.

The results from our study appear discordant with those deriving from other observational research evaluating the long-term clinical effects of CA in HCM patients with AF. Specifically, in a recent publication from Zheng et al,[13] a total of 120 HCM patients undergoing CA were compared with HCM patients who managed AF pharmacologically. During a 5-year follow-up, the composite of clinic events including all-cause mortality, unplanned HF hospitalizations, and new-onset thromboembolic strokes occurred in 18 patients (15%) in the CA group and in 12 patients (37.5%) in the medical group (P = 0.023). Likewise, Higuchi et al[14] found that the incidence of clinical events, including HCM-related deaths, HF hospitalizations, and new-onset strokes, was reduced significantly by CA compared to medical therapy (P = 0.025). However, single-center sources of data, small study samples, omission of pre-ablation arrhythmia duration, and lack of propensity score adjustment make these results difficult to compare to ours. To our knowledge, this is the largest multicenter study offering an all-round view of the clinical course of HCM patients after ablation of AF, adopting 2 propensity score-based methods. PSM represents a reliable statistical technique that attempts to reduce the confounding factors secondary to the different baseline characteristics of observational cohorts.[15] In our study, after applying 1:1 PSM, 2 well-balanced groups of HCM patients were generated. The consistency of the results by IPW analysis confirmed the reliability of our findings.

TABLE 4 Secondary Outcomes (PSM Analysis)

	Intervention Group (n = 113)	Medical Group (n = 113)	HR (95% CI)	P Value
Key secondary CV endpoint	24 (21.2)	37 (32.7)	0.86 (0.51-1.46)	0.581
CV death	6 (5.3)	5 (4.4)	1.65 (0.50-5.45)	0.414
Heart transplant	2 (1.8)	4 (3.5)	0.95 (0.11-5.83)	0.831
HF exacerbations	23 (20.4)	28 (24.8)	1.11 (0.61-2.04)	0.718
Thromboembolic stroke	11 (9.7)	8 (7.1)	2.00 (0.79-5.05)	0.144
Fatal stroke	2 (1.8)	1 (0.9)		
Nonfatal stroke	9 (8.0)	7 (6.2)		
Major arrhythmic event	5 (4.4)	9 (8.0)	0.85 (0.28-2.59)	0.779
Sudden cardiac death	0 (0)	2 (1.8)		
Appropriate ICD shock	3 (2.7)	3 (2.7)		
Major VA	5 (4.4)	7 (6.2)		

Values are n (%) unless otherwise indicated.

CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator; PSM = propensity score matching; VA = ventricular arrhythmias.

THE IMPACT OF CA ON AF RECURRENCES AND PROGRESSION. Despite no difference in the major outcomes, CA strategy was associated to a significantly lower AF burden during follow-up, either by suppressing arrhythmia recurrence or, potentially, by slowing down the progression to permanent pattern. Similarly, in their recent study analyzing the efficacy of RF ablation in a cohort of HCM patients with concomitant AF, Castagno et al[16] demonstrated a positive impact of intervention strategy with respect to long-term SR maintenance and freedom from arrhythmia recurrence. Notably, such benefit was obtained by performing the ablation procedure approximately 5 years after the first diagnosis of the arrhythmia, and this time frame was even shorter in our cohort. As highlighted by Castagno et al, the higher suppression of AF recurrences suggests potential advantages from ablation therapy in terms of better quality of life, since atrial tachyarrhythmias are usually not tolerated in HCM patients, especially if diastolic function is compromised.[17] This concept is corroborated by the significant percentage of redo CA procedures in the intervention group of our study sample. Almost half of these patients underwent a repeat ablation due to recurring AF during follow-up, possibly reflecting the patient-perceived symptomatic benefits following the index CA. Overlapping proportions of redo procedures in HCM patients undergoing AF ablation are reported in literature, ranging from 39% to 72%. In addition, we found that among all HCM patients those with paroxysmal AF

FIGURE 3   Time-to-Event Curve for the Key Secondary Cardiovascular Endpoint

Kaplan-Meier curve for the key secondary cardiovascular endpoint of cardiovascular death, heart transplant, and acute HF exacerbations. HF = heart failure.

FIGURE 4   AF Recurrence and Progression

(A) Schematic view of AF recurrence rates in patients receiving medical therapy-only or catheter ablation. (B) Schematic view of progression rates from paroxysmal and persistent to permanent AF receiving medical therapy-only or catheter ablation. AF = atrial fibrillation.

CENTRAL ILLUSTRATION Transcatheter Ablation of Atrial Fibrillation vs Medical Therapy in Patients With Hypertrophic Cardiomyopathy
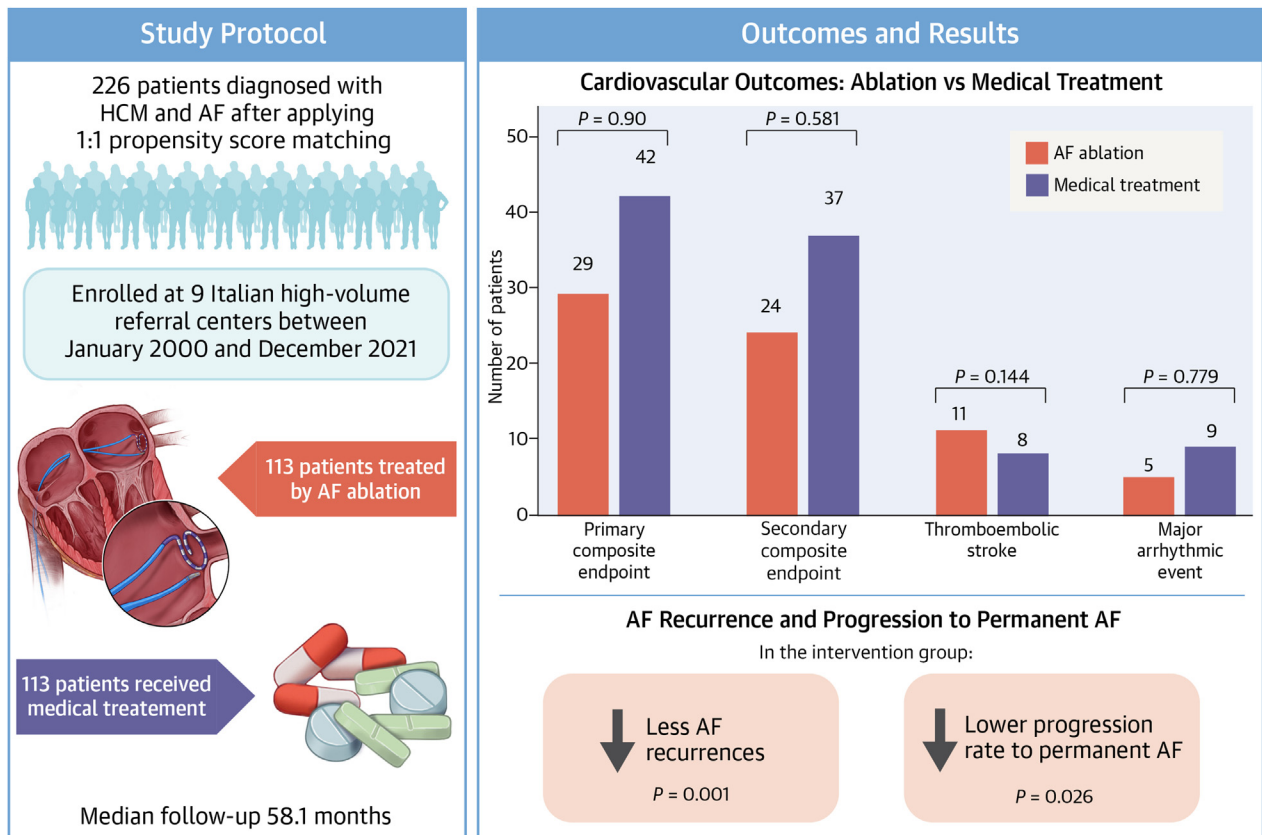
Pierri A, et al. JACC Adv. 2024;3(5):100899.

HCM is strongly associated with an increased risk of AF, with subsequent adverse outcomes. The prognostic impact of CA for AF was assessed by applying a 1:1 PSM algorithm to our cohort of HCM patients. CA did not significantly improve the main clinical outcomes but was associated with lower risk of AF progression and recurrence at mid-term follow-up. AF = atrial fibrillation; CA = catheter ablation; HCM = hypertrophic cardiomyopathy; PSM = propensity score matching.

undergoing CA were less prone to have arrhythmia relapses and progress to permanent pattern during the mid-term follow-up, thus emphasizing the opportunity of performing CA in the first phases of the disease and after the first episodes of AF. These findings are in line with those from recent single-arm studies exploring the impact of CA in patients with HCM,[18,19] particularly revealing that ablation of paroxysmal AF was associated with a significantly lower rate of arrhythmia recurrences as compared with persistent and long-standing persistent forms. Remarkably, the favorable impact of CA on AF recurrences and progression was obtained despite a reduction of antiarrhythmic drug use at follow-up (48.7%) as compared to baseline (61.1%), while no

change in antiarrhythmic administration was noticed in the medical group during the observation period. In summary, these considerations may suggest that earlier and broader implementation of CA following the onset of AF may lead to better results and favorable effects in quality of life of HCM patients. Such hypothesis, however, requires further and focused investigations.

FOCUS ON MEDICAL THERAPY MANAGEMENT. Evolution of ablation strategies proceeded in parallel with that of medical treatment over the past decades. In our study, the drastic reduction in the use of Class Ic agents at follow-up in comparison with baseline represents a striking demonstration, since nowadays these drugs are extensively contraindicated in

patients with significant LV hypertrophy due to proarrhythmic risk.[9] Interestingly, although not associated with an excess of major arrhythmic events, a larger use of flecainide and propafenone was maintained in the intervention group at follow-up. Specific considerations are reserved to anticoagulant and antiarrhythmic treatment. In our study, after applying 1:1 PSM, 2 well-balanced groups of HCM patients were generated, with the only exception of anticoagulant and antiarrhythmic drugs. The explanation for this difference is probably related to the analytic start time: the start of the follow-up period dated back to the first outpatient clinic visit for non-ablated patients, when anticoagulant and antiarrhythmic agents had yet to be introduced in many cases. In contrast, the analytic start time was set as the last record before the index procedure for ablated patients, in a phase where oral anticoagulant therapy for stroke risk management is strongly encouraged irrespective of CHA_2DS_2-VASc score.[20] In addition, the larger use of antiarrhythmic drugs in this group may depend on a worse arrhythmia-related symptom status consistent with the subsequent decision to perform CA in these patients. Antiarrhythmic and anticoagulant regimens have gradually changed over the years, achieving a balance between the groups at follow-up.

STUDY LIMITATIONS

Our investigation has some limitations. First, although PSM allows to mimic the conditions of randomized studies through recognition and adjustment of unbalanced baseline characteristics, it is difficult to identify all the possible confounding and interacting factors that intervene in the clinical management and may influence the outcomes of patients.[15] Particularly, potential bias due to confounding by indication cannot be ruled out. Moreover, PSM is usually not able to smooth out all the differences in baseline characteristics. In our study, even if not statistically significant, a higher prevalence of long-standing persistent forms of AF and a broader use of ICDs remained in the intervention group and could have affected outcomes. Thus, further randomized studies as well as large prospective registries would be desirable to confirm our results. Second, this research comes from referral centers with expertise in HCM management and electrophysiology procedures; therefore, the generalizability to other realities is limited. Third, due to the retrospective nature of the study, valuable data concerning the decision-making on ablation strategies were not always obtainable. Similarly, arrhythmia-related symptoms

as established by the European Heart Rhythm Association symptoms scale were not reported, thus symptom status influence on treatment decisions could only be inferred. Fourth, we enrolled HCM patients with different patterns of AF, therefore ablation techniques and approaches were very heterogeneous and determined by operator preference, as well as drug therapies have changed over the course of a long study, potentially affecting outcomes. For the small minority of previously ablated patients in the intervention group, the prior outside ablation was never considered as time zero for purposes of survival analysis because of the paucity of procedural data. On the other hand, our study represents a real-world experience, and this could be considered a strength point. Fifth, the AF recurrence data lack for precise temporal collocation during the observation period. Finally, the evaluation of inappropriate shocks in ICD carriers was omitted from this research: although the misinterpretation of supraventricular arrhythmias by the device was the most common mechanism of inappropriate interventions, accurate data about potential lead defects and ICD programming with respect to discrimination algorithms were not available.

CONCLUSIONS

In our multicenter cohort of HCM patients with AF, when compared with medical treatment, CA was not associated with a reduction in all-cause mortality, HTs, HF-related hospitalizations, and HF-related urgent visits during a 5-year follow-up. However, our study suggests a potential benefit from CA in terms of lower rates of AF recurrence, especially in patients with paroxysmal AF. Whether earlier and more aggressive implementation of CA, preceding severe atrial remodeling and disease progression, may impact the outcome of HCM patients, remains unresolved.

ADDRESS FOR CORRESPONDENCE: Dr Marco Merlo, Cardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Ospedale di Cattinara, Polo Cardiologico, Via Valdoni, 7, Trieste 34149, Italy. E-mail: marco.merlo79@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:
Compared with the general population, HCM patients usually represent a very challenging group to manage once atrial arrhythmias, particularly AF, develop. Given paucity of outcome reports, the ablative strategy for AF is currently an object of considerable controversy in HCM patients. Based on our multicenter retrospective data, AF ablation does not appear to achieve a significant effect on hard clinical endpoints during a 5-year follow-up.

TRANSLATIONAL OUTLOOK: AF recurrences usually result in poorer health-related quality of life and disabling symptoms, especially when the diastolic ventricular filling is impaired. From this perspective, the lower AF burden after ablation may translate into symptom improvement and reduction in emergency room visits, with possible related economic benefits. Furthermore, there are some clues that performing ablation in the early phase of the HCM may confer adjunctive advantages. Future studies are needed to confirm our results and to establish the optimal timing of ablation in reference to the time of AF diagnosis in HCM patients.

REFERENCES

1. Ali JM, Braunwald E. Hypertrophic cardiomyopathy genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res.* 2017;121: 749-770.

2. Force T, Bonow RO, Houser SR, et al. Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute. *Circulation.* 2010;122:1130-1133.

3. Spirito P. Atrial fibrillation in hypertrophic cardiomyopathy, new light on an old problem. *Circulation.* 2017;136(25):2437-2439.

4. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart.* 2014;100:465-472.

5. Liu T, Li GP. Potential mechanisms between atrial dilatation and atrial fibrillation. *Am Heart J.* 2006;151(2):e1.

6. Liew R. Inappropriate defibrillator shocks and mortality. *Heart.* 2013;99:1223-1224.

7. Gaita F, Di Donna P, Olivotto I, et al. Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol.* 2007;99(11):1575-1581.

8. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;378(5):417-427.

9. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373-498.

10. Elliot PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35(39): 2733-2779.

11. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:1321-1360.

12. Prabhu S, Costello BT, Taylor AJ, et al. Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: a substudy of the CAMERA MRI trial. *J Am Coll Cardiol EP.* 2018;4:999-1007.

13. Zheng S, Jiang W, Dai J, et al. Five-year outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol.* 2020;31:621-628.

14. Higuchi S, Ejima K, Minami Y, et al. Long-term clinical course after catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Heart Ves.* 2019;34:527-537.

15. Reiffel JA. Propensity score matching: the "devil is in the details" where more may be hidden than you know. *Am J Med.* 2020;133(2):178-181.

16. Castagno D, Di Donna P, Olivotto I, et al. Transcatheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy: long-term results and clinical outcomes. *Cardiovasc Electrophysiol.* 2021;32:657-666.

17. O'Neill L, Duytschaever M, Knecht S. Atrial fibrillation ablation in patients with hypertrophic cardiomyopathy: do not throw in the towel too fast!. *Europace.* 2021;23:1334-1335.

18. Dinshaw L, Münkler P, Schäffer B, et al. Ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: treatment strategy, characteristics of consecutive atrial tachycardia and long-term outcome. *J Am Heart Assoc.* 2021;10(3):e017451.

19. Creta A, Elliott P, Earley MJ, et al. Catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a European Observational Multicentre Study. *Europace.* 2021;23(9): 1409-1417.

20. Calkins H, Hindriks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017;14(10):e275-e444.

KEY WORDS atrial fibrillation, catheter ablation, hypertrophic cardiomyopathy, propensity score matching

APPENDIX For the supplemental appendix, tables, and figures, please see the online version of this paper.