Very Late Relapse Post Ablation of Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy: A European Observational Multicentre Study

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Abstract

Introduction: Atrial fibrillation (AF) is common in hypertrophic cardiomyopathy (HCM). Data on the mid-term efficacy of catheter ablation of AF in HCM patients are sparse.

Methods: Observational multicentre study in 137 HCM patients (mean age 55.0±13.4, 29.1% female; 225 ablation procedures). We investigated: (i) the efficacy of catheter ablation for AF beyond the initial 12 months; (ii) the available risk scores, stratification schemes and genotype as potential predictors of arrhythmia relapse, and (iii) the impact of cryoballoon vs. radiofrequency in procedural outcomes.

Results: Recurrences after the initial 12-month period post ablation were frequent, and 24 months after the index procedure, nearly all patients with persistent AF had relapsed, and only 40% of those with paroxysmal AF remained free from arrhythmia recurrence. The APPLE score demonstrated some, albeit low, discriminative capacity for AF relapse post-ablation (c-statistic 0.60, 95%CI 0.49-0.71; p=0.004), while the risk stratification schemes for sudden death did not. On multivariate analysis, LA diameter and LV apical aneurysm were independent predictors of recurrence. Despite the small size of the genotyped sample, arrhythmia-free survival was lower in genotype-negative and in those with either MYH7 or MYBPC3 mutations (log-rank p=0.10). Outcome for cryoballoon and radiofrequency ablation was comparable.

Conclusion: Very late AF relapse post ablation appears to be common in the HCM patients, especially in those with persistent AF. LA size, LV apical aneurism, genotype and the APPLE score might contribute to identify subjects at higher risk of arrhythmia recurrence. Cryoballoon technique in the HCM population appears comparable to radiofrequency ablation.

Key words: hypertrophic cardiomyopathy; atrial fibrillation; catheter ablation; genes; cryoballoon.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenic cardiovascular disease and affects 1 out of every 500 individuals [1]. Atrial fibrillation (AF) is common in HCM patients, with an estimated prevalence of 22.5% [1]. AF is associated with adverse clinical outcomes and is usually poorly tolerated in the setting of HCM, often leading to heart failure symptoms and haemodynamic instability requiring prompt treatment with direct current cardioversion [1].

Catheter ablation is an established treatment for symptomatic drug-refractory AF [2]. The HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical AF ablation suggests that similar indications can be used in selected HCM patients as in those without HCM [2]. However, data are sparse regarding patient selection in this setting, with studies based on small cohorts, with short follow-up duration, and presenting sometimes contradictory results [1-2].

Risk scores like the APPLE score have been developed to predict AF recurrences following catheter ablation [3] and have not yet been tested in the HCM population. Furthermore, risk stratification schemes are available for predicting which HCM patients are likely to develop sustained ventricular arrhythmias and should be offered primary prevention implantable cardioverter defibrillator (ICD) [4-5]. Whether these risk scores identify more severe atrial arrhythmia phenotypes which are less likely to respond to catheter ablation and can be used to select patients for ablation remains to be investigated.

Mutations in over 11 genes encoding proteins of the cardiac sarcomere are linked to HCM, with more than 1400 variants described [6]. Whether patient genotype associates with outcomes of AF ablation remains to be determined.

Cryoballon ablation has emerged as an effective alternative to radiofrequency ablation in AF patients [7], having a class of recommendation IIa, level of evidence B in the current guidelines

of the European Society of Cardiology (ESC) for the management of AF [8]. Nonetheless, limited data are available on the use of the cryoballoon technique in the HCM population.

The aim of this study was to investigate in a large cohort of HCM patients: (i) the mid-term efficacy of catheter ablation for AF; (ii) the available risk scores, stratification schemes and genotype as potential predictors of arrhythmia relapse post ablation, and (iii) the impact of cryoballoon vs. radiofrequency technique in the procedural outcomes.

Methods

Non-randomised, observational study in 4 European centres. We included all patients aged over 18 with defined diagnosis of HCM undergoing a catheter ablation for AF between 2006 and 2019. According to the guidelines of the European Society of Cardiology [4], HCM was defined as a wall thickness ≥15 mm in one or more left ventricular myocardial segments (on either echocardiogram or cardiac magnetic resonance imaging) that is not explained solely by loading conditions. All patients provided written informed consent prior to the procedure. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics or audit committees. Procedures were performed under sedation or general anaesthesia, according to each institution's protocol. Venous access was obtained via the femoral vein, with use of vascular ultrasound at operator's discretion. In the absence of patent foramen ovale, a single or dual transseptal puncture was performed under fluoroscopic guidance. Transesophageal echocardiography was used based on operator preference. Patients received intravenous heparin to maintain an activated clotting time of 300–350 seconds. Pulmonary vein isolation (PVI) was the main procedural endpoint, and was performed as a first step in all procedures. If the patient was in AF at the start of the procedure and the arrhythmia organized into an atrial tachycardia this was mapped and ablated. In patients undergoing cryoballoon ablation, if the patient remained in AF after isolation of all four pulmonary veins,

direct-current cardioversion to sinus rhythm was performed and no further ablation undertaken. Patients were evaluated at 3 and 12 months after the procedure. Information collected during follow-up included a 12-lead electrocardiogram (ECG) and either a 24-hour ECG Holter monitoring or cardiac electronic implantable device interrogation at each visit. Additional visits and further testing were allowed in case of symptoms. The first 3 months post-procedure were considered blanking period. Recurrence was defined as any symptomatic or asymptomatic atrial arrhythmia lasting >30 seconds following the 3 months blanking period. Patients with relapse during the blanking period with no response to pharmacologic or electrical cardioversion were also classified as having a relapse. Very late relapse was defined as any recurrence occurring after 12 months post ablation.

The main efficacy endpoint was freedom from atrial arrhythmias following a blanking period of three months. AF or atrial tachycardia relapse during the initial 3-month blanking period was also documented. With regard to safety, the following complications were systematically recorded: vascular complications (if requiring intervention or prolongation of admission), thromboembolism (transient ischemic attack, stroke and/or systemic embolism during or in the first month after the procedure), phrenic nerve palsy, pericardial effusion (if causing haemodynamic instability and/or requiring pericardiocentesis or prolonged monitoring), oesophageal fistula, and procedure-related death. Other complications were reported at the discretion of the operator.

The risk of sudden cardiac death (SCD) was calculated for each patient using both the HCM-risk SCD score [4] and the stratification model proposed by the American College of Cardiology/American Heart Association (ACC/AHA) for selecting patients for primary prevention implantable cardioverter-defibrillator (ICD) [5].

The chi-square test was used for categorical and t-student test for comparison of means was used for comparison of continuous variables. Levene's test was used to check the homogeneity

of variance; equivalent non-parametric tests were used when Kolmogorov–Smirnov was in favour of the absence of normal distribution. Results with $P < 0.05$ were regarded as significant. Kaplan-Meier curves were traced for illustrating freedom from atrial arrhythmias, and the log rank P test was used for assessing existing differences. Independent predictors of sinus rhythm maintenance after ablation were assessed through Cox regression (Method: Forward Likelihood Ratio, Probability for Stepwise 0.05). Predictive value of clinical scores for sinus rhythm maintenance after ablation were assessed using ROC curves. PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis.

Results

One hundred thirty-seven patients (mean age 55.0±13.4, 29.1% female) underwent a total of 225 catheter ablations for AF (1.7±1.0 per patient). Most patients had paroxysmal AF (57.5%) at baseline, and mean AF duration was 3.3±3.1 years. Mean left atrial diameter was 47±7mm. Maximal left ventricular wall thickness and left ventricular outflow tract gradient were 17±4mm and 14±24mmHg, respectively, and 46.7% of the sample had an ICD or other cardiac rhythm devices.

Based on the HCM-risk SCD score, the 5-year risk of SCD was <4% in more than half of the patients, between 4% and 6% in 16.6%, and >6% in 19.7%. According to the risk stratification model of the ACC/AHA, 41% had no indication for primary prevention ICD, 33.6% should have been considered for an ICD, 17.5% might have been considered, and 8% had a definite indication for an ICD. Baseline population characteristics are reported in Tables 1.

Procedural outcomes

PVI was achieved at the end of the procedure in almost all the patients (97.8%). The cryoballoon technique was utilized in 33.6% of the patients for the first procedure. Freedom from atrial arrhythmia relapse at 12 months was 44.6% after a single procedure (63.3% for

paroxysmal AF vs. 17.1% for persistent AF) and 54.5% after multiple procedure (71.7% for paroxysmal vs. 29.3% for persistent AF).

Very-late relapses (i.e., following the initial 12-month period) were frequent, and at 24-months after the index procedure nearly all patients with persistent AF had relapsed, and only 40% of those with paroxysmal AF remained free from arrhythmia recurrence (Figure 1). Mid-term success rate of cryoballoon ablation was comparable to radiofrequency ablation in both patients with paroxysmal and persistent AF (log-rank p=0.132 and 0.408, respectively; S-Figure 1).

Assessment of independent predictors of AF or atrial arrhythmia relapse is illustrated in Table 3. On multivariate Cox regression, LA diameter and left ventricular apical aneurysm were independent predictors of relapse post ablation. Neither of the risk stratification schemes was identified as a predictor of procedural outcomes.

The rate of peri-procedural complications was 9.3% (Table 2). There was a significant reduction of the rate of complications over time (Figure 3; p=0.002). There was no significant difference in the overall rate of complications between radiofrequency vs. cryoballoon ablation (4.4% vs. 6.7%, respectively; p=0.58).

Procedural outcomes in genotyped patients

Among 51 patients undergoing genetic screening, gene mutations responsible for HCM were identified in 41 patients, and the remaining were genotype negative. As many as 18 patients had a mutation of the MYH7 gene, 15 of the MYBPC3, 4 of the TNNT2, 2 of the TPM1, 1 of the ACTC1, and 1 of the FHL1. On a Kaplan-Meier analysis of this small subset of patients, numerically lower arrhythmia-free survival was observed in genotype-negative patients and in those with either MYH7 or MYBPC3 mutations (log-rank p=0.10; Figure 3).

Predictive value of clinical scores for atrial arrhythmia relapses post-ablation

The APPLE score demonstrated some, albeit low, discriminative capacity for predicting atrial arrhythmia relapses post ablation (c-statistic 0.60, 95%CI 0.49-0.71; p=0.004). The performance of HCM-risk SCD score, ACC/AHA risk stratification system, CHA_2DS_2VASc and HAS-BLED was poor (c-statistic 0.55, 95%CI 0.45-0.66, p=0.342; 0.50, 95%CI 0.39-0.60, p=0.964; 0.53, 95%CI 0.42-0.64, p=0.457; 0.48, 95%CI 0.36-0.59, p=0.648; respectively). These results are shown in Figure 4 and 5 and S-Table 1.

Discussion

The main findings of this multicentre study are that mid-term success rate of catheter ablation for AF in HCM is much lower than what is reported for the general population, especially for patients with persistent AF. Relapses tend to be more frequent not only in the initial 12 months post ablation, but also longer term. Cryoballoon and radiofrequency technique performs comparably in HCM patients. The APPLE score can be used for predicting atrial arrhythmia recurrence, however its discriminative performance is only low. Clinical scores for SCD are not useful in predicting mid-term success rate, however left atrial diameter and left ventricular apical aneurism are independently associated with relapse. Furthermore, genotype-negative patients and those with mutation in MYH7 and MYBC3 gene tend to have a lower arrhythmia-free survival.

Previous small observational studies have evaluated the efficacy and safety of AF ablation in HCM, with conflicting results. A systematic review and meta-analysis from our group [1] showed that catheter ablation might be a valuable option in this setting, however risk of relapse was two-fold higher compared to the general population; in addition, a sensitivity analyses suggested that the outcome in HCM patients with smaller atria and paroxysmal AF might be

more comparable to the general population. Notably, the largest cohort in that systematic review included only 61 participants and the median cohort size was only 27 patients.

To the best of our knowledge, our multicentre data constitute the largest cohort of HCM patients undergoing AF ablation. In keeping with previous evidence, the 12-month success rate of ablation for paroxysmal AF appears comparable to what is observed in the general population [9]. However, a significant proportion of patients required more than one procedure. On a multivariate analysis, paroxysmal AF was associated with a 63% lower rate of arrhythmia relapses.

Performance of catheter ablation for persistent AF was extremely poor, with a success rate after single or multiple procedures as low as 29.3% at the 12 months follow-up, and nearly all patients having relapsed before the end of the second year. Considering the non-negligible rate of complications, our findings rise some concerns about the role of ablation in this group of HCM patients.

It is conceivable that the relevant degree of atriopathy in HCM patients with persistent forms of AF significantly affects the success rate of the ablation. Indeed, the physio-patological connection between HCM and AF is complex and multifactorial. HCM is associated with diastolic disfunction, which results in an increase of the end diastolic left ventricular pressure and subsequently of the left atrial afterload. As a consequence, the left atrium undergoes a process of remodelling and dilatation with proarrhythmic implications. HCM patients have also a high prevalence of mitral regurgitation, which can promote a structural atrial remodelling [1]. Furthermore, atrial fibrosis is common in HCM [1, 10] and may play a key role of substrate for AF by promoting slow conduction and inter-atrial re-entry. Other possible mechanisms include abnormal calcium handling which could account for triggered activity, atrial ischemia due to microvascular dysfunction, and polymorphisms in the angiotensin receptor gene [1].

Previous studies showed that only less than 10% of patients undergoing AF ablation suffer from very late recurrences [11-12]. Interestingly, our data suggest that the latter may be much more frequent in HCM population; in fact, as many as 20% of the patients relapsed after the initial 12-month period in our cohort. Progression of atrial fibrosis, enlargement of left atrium and adverse electrical and molecular remodelling of myocardial tissue might account for this finding [13].

PVI was the main procedural endpoint in our series. Whether a more extensive ablation might improve outcomes in this population has not been established. Of note, on a multivariate analysis creation of atrial lines or ablation of complex fractionated electrograms were not associated with a reduction of arrhythmia relapses. Scar homogenisation [11] or ablation of non-pulmonary vein triggers [12] in the left and/or right atrium might represent alternative approaches beyond PVI.

Another relevant finding of the present study is that cryoballoon ablation appears to be effective and safe in HCM patients, showing comparable results with the radiofrequency technique. These findings are of interest, as HCM patients were excluded in the landmark trials evaluating cryoballoon AF ablation such as the FIRE and ICE trial [7].

In keeping with the previous literature [1], we found that left atrial diameter was negatively associated with long-term outcomes of AF ablation. Furthermore, we identified the presence of left ventricular apical aneurysm as an independent predictor of arrhythmia relapses in our multivariate model. However, this finding should be interpreted carefully given the limited sample size. HCM patients with apical aneurysms represent a subgroup at higher risk of adverse events, including arrhythmic sudden cardiac death, thromboembolism and heart failure [13]. Apical aneurysms are often but not exclusively associated with mid-ventricular obstruction [4], which might favour AF recurrences by promoting atrial stretching and subsequently shortening the atrial effective refractory period and increasing the dispersion of

repolarisation [1]. A genetic predisposition to apical aneurysm has been suggested [13], whether this genetic background might also predispose to a more aggressive substrate of AF is currently unknown.

Among the clinical scores tested, only the APPLE score (one point for age>65 years, persistent AF, glomerular filtration rate <60 ml/min/1.73 m^2, LA diameter ≥43 mm, left ventricular ejection fraction 50%) [3] demonstrated a discriminative capacity for relapses post ablation, however its performance was only low. Our study suggests that the APPLE score might help selecting the HCM patients who are more likely to benefit from AF ablation.

This is the first study to report outcomes of AF ablation in a cohort of genotyped HCM patient with a broad spectrum of gene mutations. Among the several genotypes causing HCM, mutations in the MYH7 and MYBPC3 genes are the most frequent [6]. Di Donna et al showed that efficacy of AF ablation was similar in a small group of genotype-negative individuals compared to 11 genotyped-positive patients, almost exclusively with mutation on the MYBPC3 gene [14]. Based on our larger sample, we were able to identify a trend of higher rate of relapses post AF ablation in subjects with either MYH7 or MYBPC3 mutation, or those who are genotype-negative, compared to those with other less common genotypes. It has been hypothesised that specific genotypes might be directly associated to atrial myopathy, resulting in a direct predisposition to AF [15]. Recent evidences suggest that subjects with pathogenic variation in the MYH7 gene may be at greater risk of AF [15]. Further studies are required to clarify the impact of specific genetic mutations in the pathogenesis of AF as well as in the outcomes of ablation.

Finally, we found a higher rate of major complications, in particular cardiac tamponade, compared to the rate observed in the general population in our centres [16]. Based on our experience, use of intraprocedural transoesophageal or intracardiac echocardiogram should be encouraged in HCM patients to minimise risks.

Limitations

Several limitations should be acknowledged. Arrhythmia burden has been recently suggested as a useful alternative endpoint for assessing AF ablation efficacy [20], however no data on arrhythmia burden pre and post ablation were available. Our cohort includes patients undergoing catheter ablation over a long timeframe, it is conceivable that the procedural outcomes especially in terms of safety might nowadays be improved given the growing experience and the development of new technology for AF ablation over the last decade.

Conclusion

Mid-term outcomes for AF ablation of HCM patients are poor, namely in patients with persistent AF. Left atrial size, left ventricular apical aneurism, genotype data, and use of the APPLE score might contribute to identify subjects at higher risk of relapse post-ablation. Cryoballoon ablation in HCM patients appears as safe and effective as radiofrequency ablation.

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Legend to Tables and Figures

Table 1. Baseline characteristics of the study population

Table 2. Procedure details and outcomes

Table 3. Univariate and multivariate analysis

Figure 1. Kaplan-Meier of atrial arrhythmia-free survival after index procedure for paroxysmal and persistent AF

Figure 2. Kaplan-Meier of atrial arrhythmia-free survival after index procedure based on APPLE score (A) and genotype (B)

Figure 3. Trend of periprocedural complications

Figure 4. Kaplan-Meier of atrial arrhythmia-free survival after index procedure based on HCM-risk SCD score (A) and ACC/AHA stratification model for SCD (B)

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Table 1. Baseline characteristics

	Global Sample (n=137)
Age	55.0±13.4
Female Sex	29.1% (39)
AF type at index procedure	
Paroxysmal	57.5% (77)
Persistent	41.0% (55)
Longstanding Persistent	1.5% (2)
Baseline ECG in Sinus Rhythm – Index Procedure	58.2% (78)
AF Duration (time since diagnosis)	3.3±3.1
Previous Non-AF ablation	9.8% (13)
Previous Alcohol Septal Ablation	4.5% (6)
Previous Surgical Myectomy	10.4% (14)
LGE ≥ 15%*	30.4% (17)
LV Apical Aneurysm	1.5% (2)
Congestive HF	15.7% (21)
Hypertension	25.4% (34)
Diabetes	14.2% (19)
Stroke or TIA	10.4% (14)
Vascular Disease	9.7% (13)
Renal Disease	3.8% (5)
Obstructive Sleep Apnoea	6.7% (9)
EHRA Class	2.7±0.7
NYHA Class	1.8±0.7
CHA_2DS_2VASc	1.5±1.5
HAS-BLED	0.8±0.9
HCM-risk SCD	3.8%±3.3%
APPLE	1.7±1.1
Syncope	18.7% (25)
FH of SCD	23.1% (31)
NSVT	37.3% (50)
Sustained VT	8.2% (11)
Single or dual-chamber ICD	35.1% (47)
Permanent pacemaker	6.7% (9)
CRT-D	3.7% (5)
ILR	2.2% (3)
Amiodarone	46.6% (61)
Sotalol	12.2% (16)
Apical Hypertrophy	10.9% (14)
Moderate to Severe MR	12.2% (14)
Restrictive pattern	21.6% (29)
Max LVOT gradient (mm Hg)	14±24
Max LV Thickness (mm)	17±4
LA diameter (mm)	47±7
LA area (cm^2)	31±7
LV end-diastolic diameter (mm)	48±7
LVEF	58±9

Legend -
* Cardiac MRI data only available for 56 patients.

Table 2. Procedure details and outcomes

	Global Sample (n=137)
Number of Procedures*	1.7±1.0
Number of Ablation Procedures	1.6±1.0
Ablation approach / energy	
Use of point-by-point RF	58.2% (78)
Use of Cryoballoon	33.6% (45)
Other Single-shot techniques**	2.4% (2)
Surgical ablation	3.7% (5)
Pulmonary Vein Isolation	97.8% (131)
Roof line	31.3% (42)
Mitral Isthmus	26.1% (35)
Cavo-Tricuspid Isthmus Ablation	29.9% (40)
CFAE ablation	22.4% (30)
Efficacy Outcomes	
Freedom from AF/AT relapse at 12 months after a single procedure	44.6% (45)
Freedom from AF/AT relapse at 12 months after one or multiple procedures	54.5% (55)
Freedom from Paroxysmal AF / one procedure	63.3% (38)
Freedom from Paroxysmal AF / one or multiple procedures	71.7% (43)
Freedom from Persistent AF / one procedure	17.1% (7)
Freedom from Persistent AF / one or multiple procedures	29.3% (12)
All-cause mortality during Follow-up	5.2% (7)
Heart Transplant following ablation	3.0% (4)
Complications, % per patient (n) and % per procedure	
Cardiac Tamponade	6.6% (9) 4.0%
Stroke	0.7% (1) 0.4%
Vascular Access-Related***	2.2% (3) 1.3%
Pneumonia	0.7% (1) 0.4%
PV Stenosis	0.7% (1) 0.4%
Acute Pulmonary Oedema	2.2% (3) 1.3%
Complete AV Block	0.7% (1) 0.4%
Phrenic nerve palsy****	1.5% (2) 0.9%

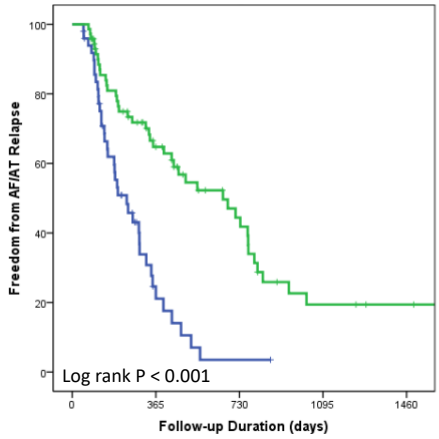
Note: * Including aborted procedures post-transseptal where no ablation was performed as a result of cardiac tamponed. ** CardioFocus (n=1), nMARQ (n=1). *** Haematoma with Hgb drop (n=1), pseudoaneurysm (n=1), Retroperitoneal haematoma (n=1). **** Transient, recovered at follow-up.

Table 3. Univariate and multivariate analysis

	Univariate		Multivariate	
	HR 95%CI	P	HR 95%CI	P
Age	1.01 0.99-1.03	0.279	-	-
Female Sex	1.06 0.64-1.76	0.825	-	-
Paroxysmal AF	0.33 0.20-0.53	<0.001	0.37 0.21-0.64	<0.001
AF/AT on baseline ECG	2.90 1.81-4.65	<0.001	-	-
Number of Ablation procedures	1.35 1.12-1.63	0.002	-	-
AF duration (years since diagnosis)	1.03 0.96-1.12	0.388	-	-
Congestive HF	1.00 0.51-1.95	0.999	-	-
Hypertension	0.85 0.51-1.43	0.549	-	-
Diabetes mellitus	0.90 0.49-1.66	0.732	-	-
Stroke or TIA	1.04 0.50-2.16	0.924	-	-
CHA2DS2VASc	1.00 0.85-1.17	0.982	-	-
HAS-BLED	0.94 0.75-1.19	0.622	-	-
Obstructive Sleep Apnoea	0.79 0.36-1.72	0.549	-	-
EHRA class	0.78 0.56-1.07	0.120	-	-
NYHA class	0.85 0.62-1.18	0.328	-	-
Syncope	0.99 0.56-1.77	0.983	-	-
NSVT	1.26 0.81-1.97	0.312	-	-
VT	1.20 0.58-2.50	0.627	-	-
Family history of SCD	0.77 0.44-1.34	0.352	-	-
On Amidoarone at the time of ablation	1.03 0.66-1.60	0.906	-	-
On Sotalol at the time of ablation	1.14 0.61-2.11	0.683	-	-
HCM SCD-risk score	1.03 0.97-1.10	0.275	-	-
Max LV thickness	0.98 0.92-1.03	0.394	-	-
LA diameter	1.06 1.03-1.09	<0.001	1.05 1.02-1.09	0.003
LA area	1.06 1.03-1.10	<0.001	-	-
LV end-diastolic diameter	1.01 0.98-1.04	0.689	-	-
LVEF	1.01 0.98-1.03	0.624	-	-
Max LVOT gradient	0.99 0.98-1.01	0.336	-	-
LV apical aneurysm	12.07 2.72-53.51	0.001	30.78 6.39-148.25	<0.001
Mitral regurgitation III-IV	1.33 0.69-2.53	0.393	-	-
Restrictive pattern	1.61 0.96-2.70	0.074	-	-

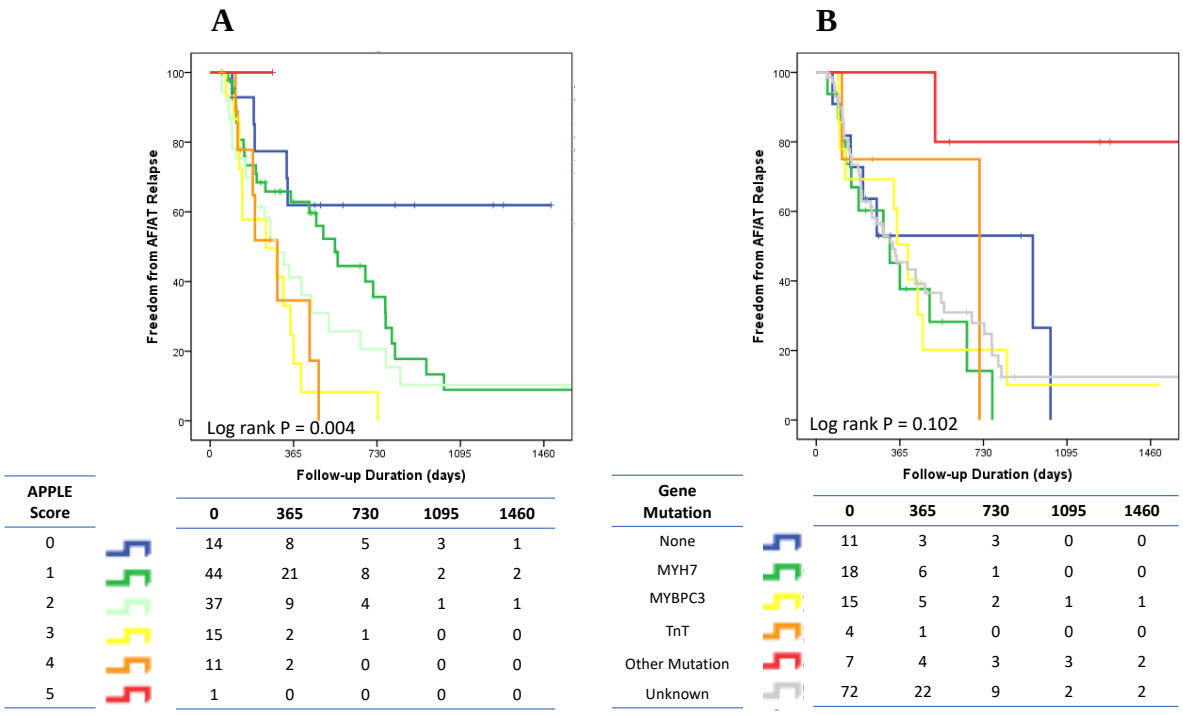
Previous Ethanol ablation	1.52 0.55-4.19	0.416	-	-
Previous Myectomy	1.26 0.68-2.33	0.469	-	-
CTI	1.11 0.48-2.58	0.808	-	-
CFAE	2.39 1.06-5.38	0.035	-	-
Mitral isthmus line	2.33 1.06-5.09	0.035	-	-
Roof line	1.65 0.70-3.85	0.250	-	-

Figure 1. Kaplan-Meyer of arrhythmia-free survival after index procedure for paroxysmal and persistent AF



	0	365	730	1095	1460
Persistent	58	7	1	0	0
Paroxysmal	79	36	17	6	4

Figure 2. Kaplan-Meyer of arrhythmia-free survival after index procedure based on APPLE score (A) and genotype (B).



APPLE Score	0	365	730	1095	1460
0	14	8	5	3	1
1	44	21	8	2	2
2	37	9	4	1	1
3	15	2	1	0	0
4	11	2	0	0	0
5	1	0	0	0	0

Gene Mutation	0	365	730	1095	1460
None	11	3	3	0	0
MYH7	18	6	1	0	0
MYBPC3	15	5	2	1	1
TnT	4	1	0	0	0
Other Mutation	7	4	3	3	2
Unknown	72	22	9	2	2

Figure 3. Trend of periprocedural complications

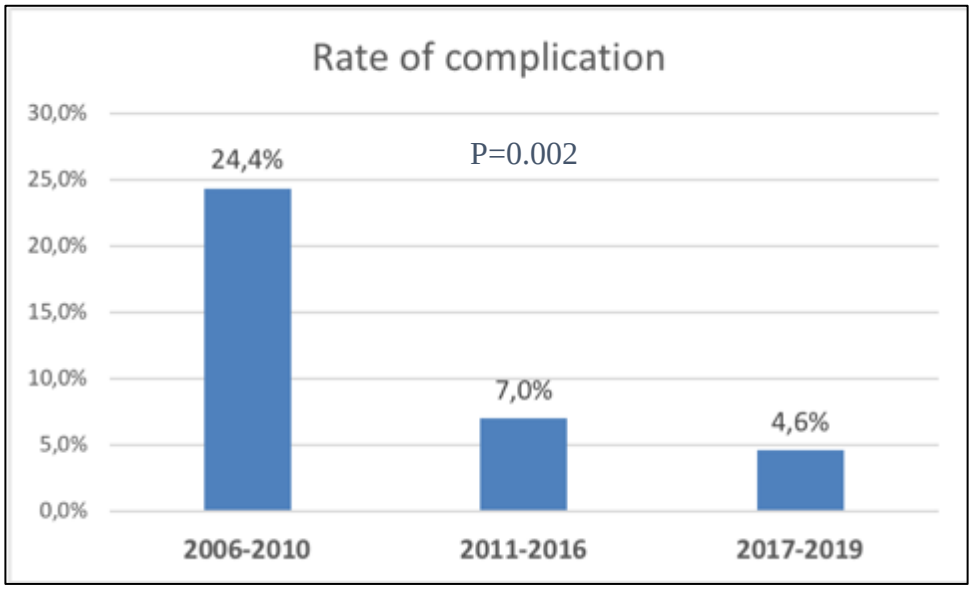
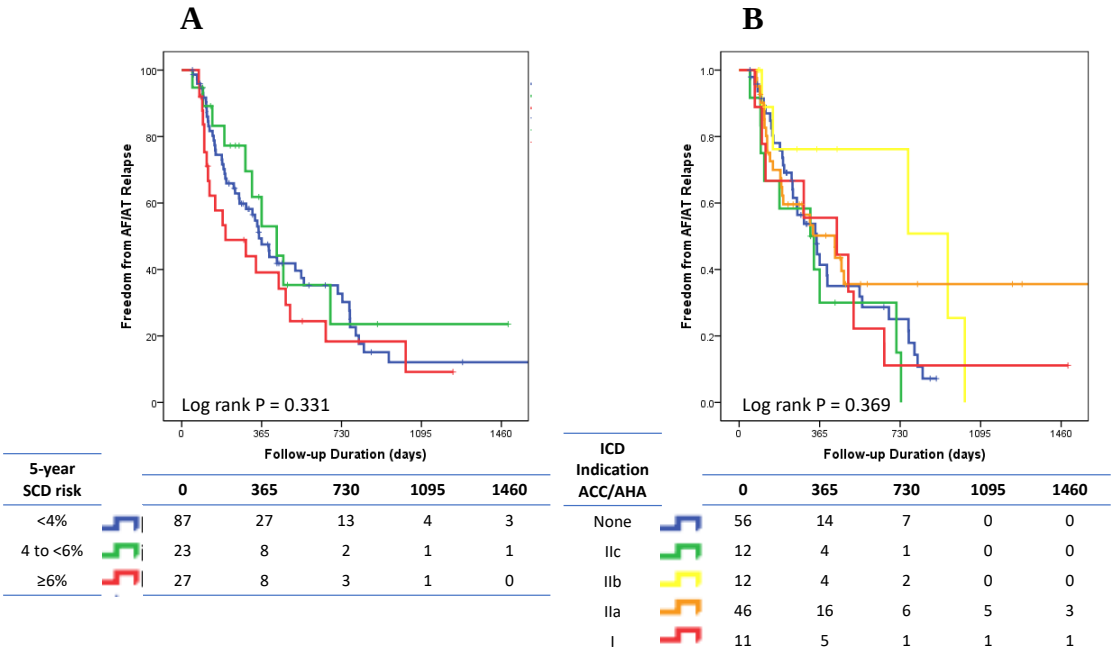


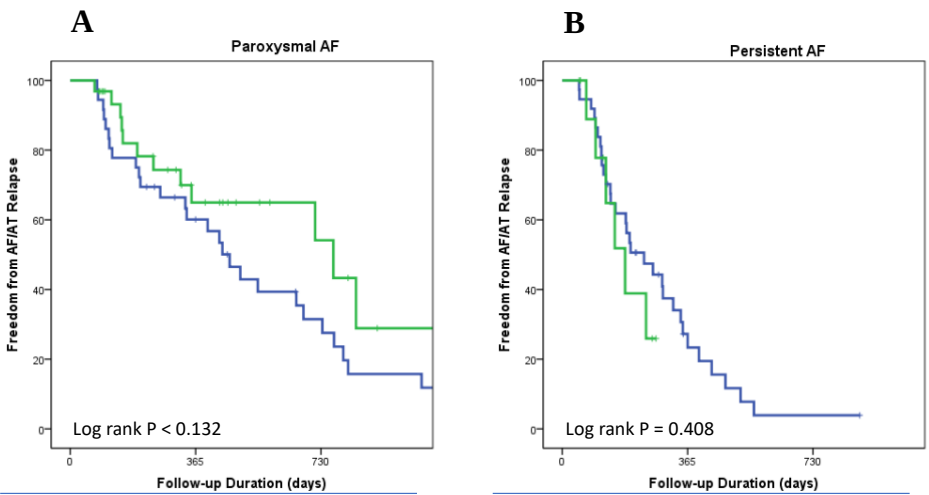
Figure 4. Kaplan-Meyer of arrhythmia-free survival after index procedure based on HCM-risk SCD score (A) and ACC/AHA stratification model for SCD (B).



5-year SCD risk	0	365	730	1095	1460
<4%	87	27	13	4	3
4 to <6%	23	8	2	1	1
≥6%	27	8	3	1	0

ICD Indication ACC/AHA	0	365	730	1095	1460
None	56	14	7	0	0
IIc	12	4	1	0	0
IIb	12	4	2	0	0
IIa	46	16	6	5	3
I	11	5	1	1	1

Supplementary Figure 1. Kaplan-Meyer of arrhythmia-free survival after index procedure based on ablation technique (radiofrequency vs. cryoballoon) for paroxysmal (A) and persistent AF (B).



	0	365	730
RF	36	19	7
Cryo	32	13	5

	0	365	730
	37	7	1
	11	0	0