Transcatheter Ablation for Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy: Long-term Results and Clinical Outcomes

Transcatheter Ablation for Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy: Long-term Results and Clinical Outcomes.

Running title: **Long-term results of atrial fibrillation transcatheter ablation in hypertrophic cardiomyopathy**

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Abstract

Introduction

Radiofrequency transcatheter ablation (RFCA) for atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy (HCM) has been proven feasible. However, the long-term results of RFCA and its impact on clinical course of HCM are unknown. The aim of this study was to analyse clinical outcomes and long-term efficacy of RFCA in a multicentre cohort of patients with HCM and concomitant AF.

Methods

Patients with HCM and AF consecutively undergoing RFCA were included. Ablation failure was defined as recurrence of AF, atrial tachycardia or flutter lasting more than 3 minutes and occurring after the blanking period.

Results

Overall, 116 patients with symptomatic AF refractory to antiarrhythmic drugs were included. Over a median follow-up of 6.0 years (IQR 3.0–8.9 years) recurrence rate after a single RFCA was 32.3 per 100 patient/years with 26% of patients free from AF relapses at six years follow-up. Among patients experiencing AF recurrence, 51 (66%) underwent at least one redo-procedure. The overall recurrence rate considering redo-procedures was 12.6 per 100 patients/years with 53% of patients free from AF relapses at six years. At last follow-up, with an average of 1.6 procedures, 67 (61%) patients were in sinus rhythm (SR). Patients remaining in SR showed better functional status compared with those experiencing arrhythmic recurrences (NYHA class 1.6±0.1 vs. 2.0±0.1, p=0.009).

Conclusions

RFCA of AF in HCM patients is an effective and safe strategy favoring long-term SR maintenance, reduction of atrial arrhythmic burden and improved functional status. However, most patients need repeat procedures and continuation of antiarrhythmic drugs.

Key words

Atrial fibrillation

Hypertrophic cardiomyopathy

Transcatheter ablation

Left atrium

Outcome

Introduction

Atrial fibrillation (AF) is the most common arrhythmic complication in the setting of hypertrophic cardiomyopathy (HCM) with approximately one patient out of five developing the arrhythmia during the clinical course of the disease (1,2,3). As compared with the general population, AF is more frequent and tends to occur at younger age in patients with HCM (2). Several factors including left ventricular outflow tract obstruction (LVOTO), mitral regurgitation and diastolic dysfunction may promote both electrical and structural remodeling and increase left atrial (LA) myocardium vulnerability (4,5,6,7). The occurrence of AF is usually poorly tolerated in patients with HCM because of loss of atrial contraction and reduced filling time worsening diastolic dysfunction (2). Besides the impact on functional capacity and quality of life, AF represents a critical turning point in the natural history of the disease as it increases the risk of dying for heart failure, stroke and worsens long-term prognosis (2,8,9,10). Therefore, when the arrhythmia occurs, particularly at a young age, restoration of sinus rhythm (SR) is highly desirable in patients with HCM. Unfortunately, available pharmacological options to maintain rhythm control are limited. Although disopyramide may be useful to mitigate LVOTO, its effects on SR maintenance have been poorly investigated in the context of HCM (11). In a small, double-blind crossover study, sotalol significantly suppressed supraventricular arrhythmias but its long-term safety and efficacy are unknown (12). Amiodarone can effectively maintain SR, reduce embolic episodes and electrical cardioversions (13) but frequent adverse effects and potential toxicities limit its long-term use especially in young individuals.

Radiofrequency transcatheter ablation (RFCA) of AF has been successfully introduced in clinical practice almost twenty years ago and has rapidly evolved into an effective treatment to prevent recurrent AF (14). In patients without underlying structural heart disease RFCA can be more effective than antiarrhythmic drugs showing similar complication rates (15,16). Although RFCA has been proved feasible also in patients with HCM, only data from small, single-center studies mainly focusing on short-term results are currently available (17,18,19,20,21). In contrast, little is

known regarding long-term results of RFCA and its impact on the clinical course of HCM. Therefore, aim of the present study was to analyze clinical outcomes and long-term efficacy of RFCA in a multicenter cohort of patients with HCM and concomitant AF.

Methods

Patient population

The study population included patients with HCM and AF consecutively undergoing RFCA from June 2001 to October 2015 in four high volume referral centers with experienced cardiac electrophysiology laboratories. All patients gave informed consent in accordance with the Helsinki declaration.

Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle (LV) [maximum wall thickness ≥15 mm], in the absence of any other cardiac or systemic disease capable of inducing the magnitude of evident hypertrophy (1,22,23).

Documentation of AF was based on electrocardiographic recordings obtained either after acute onset of symptoms or during routine examination. Patients were offered RFCA if they had symptomatic AF refractory to medical treatment, often in the context of disease progression and heart failure. All patients had been unsuccessfully treated with multiple antiarrhythmic drugs, including amiodarone. AF was defined as paroxysmal (episodes terminating spontaneously or with intervention within 7 days of onset), persistent (lasting >7 days), or long-standing persistent (lasting >1 year) in accordance with the 2016 ESC Guidelines for the management of AF (24).

All patients were anticoagulated either with Warfarin with a target international normalized ratio (INR) between 2-3 or with low molecular weight heparin (LMWH) at the time of ablation.

Echocardiography

Comprehensive two-dimensional and Doppler echocardiographic studies were performed using commercially available instruments. LV hypertrophy was assessed with two-dimensional echocardiography, both the site and the extent of maximal wall thickness were identified. Peak instantaneous LV outflow gradient due to mitral valve systolic anterior motion and mitral-septal contact was estimated with continuous wave Doppler under basal conditions (4). LA volume was measured at end-systole using the biplane area-length method (25).

Electrophysiological study and radiofrequency catheter ablation

Transesophageal echocardiography was performed in all patients before RFCA to rule out atrial thrombi. Imaging integration with a pre-acquired contrast enhanced cardiac magnetic resonance (MR) or cardiac computed tomography (CT) of the LA was used in the majority of patients (n=91). The electrophysiological study was performed under local anesthesia with conscious sedation. Femoral venous accesses were used to introduce catheters into the hearth: (i) a deflectable decapolar catheter positioned within the coronary sinus; (ii) 10 pole, circumferential mapping catheter to guide pulmonary vein (PV) isolation introduced with the aid of a long sheath continuously perfused with heparinized saline; and (iii) a quadripolar ablation irrigated catheter. Surface ECG and intracardiac electrograms were recorded using EP-WorkMate (St. Jude Medical, Saint Paul, USA), LabSystem PRO (Bard, Boston Scientific, Marlborough, USA) or CardioLab (GE Healthcare, Chicago, USA) electrophysiological recording systems. Access to the LA was achieved through a patent foramen ovale, whenever present, or by a single transseptal puncture. Heparin was administered in boli immediately at the time of transseptal and throughout the procedure to maintain the activated clotting time to target. The circumferential mapping catheter was introduced into the LA via the transseptal sheath that was then withdrawn into the right atrium to facilitate passage of the ablation catheter into the LA through the same puncture point. In most of the cases (n=94), a three-dimensional shell representing the LA and PV ostia was constructed using an electroanatomic

mapping system (Carto, Biosense-Webster, Irvine, USA or EnSite NavX, St. Jude Medical, Saint Paul, USA) merged with the cardiac MR or CT reconstruction, while in the remaining cases catheter ablation was performed under fluoroscopic guidance (n=22). Radiofrequency was applied using an open irrigated-tip catheter (Navistar Thermocool, Thermocool-SF or Smartouch, Biosense-Webster, Irvine, USA; Coolpath, CoolpathDuo or Coolflex, St. Jude Medical, Saint Paul, USA) with power output up to 40 W close to the PV ostia and up to 45 W while creating the roof and the left mitral isthmus lines, using an irrigation rate of 20–30 ml/min or 8–15 ml/min, depending of the type of catheter used (0.9% saline) in order to maintain a tip temperature below 45°C.

Catheter ablation protocol and periprocedural management

The preferred ablation protocol among patients with paroxysmal AF consisted of a point-by-point PV electrical isolation carried out anatomically and confirmed electrophysiologically by complete elimination or dissociation of PV potentials determined with the circular mapping catheter positioned at the PV ostia. In patients with persistent or long-term persistent AF, in addition to PV electrical isolation, ablation protocol included linear lesions interconnecting the upper PV ostia (roof line) and the left inferior PV down to the mitral annulus (mitral isthmus line). Cavo-tricuspid isthmus line was performed in patients with history of isthmus dependent atrial flutter (AFl). Electrical block of the linear lesions was confirmed using pacing maneuvers. When conduction recovery was documented, additional lesions were performed at the gaps but no additional lines were carried out. In a subset of patients ablation of complex atrial fractionated electrograms (CAFE) in the LA was also performed. Following RFCA, the ECG was continuously monitored and LMWH and/or Warfarin therapy were reinstituted on the following day. A 3-months blanking period was considered for each patient following transcatheter ablation. After the blanking period, a repeat ablation procedure was undertaken in the event of a symptomatic recurrence of AF or atrial tachycardia (AT). During repeat procedures PV electrical isolation and completeness of linear lesions were assessed and further ablation delivered as necessary.

Follow-up and study end-points

After hospital discharge, patients were followed-up at 1, 3, 6 and 12 months with 12-lead ECG, transthoracic echocardiography and 24-hours Holter monitoring and every 12 months thereafter through telephone contact or outpatient clinic visits. In the event of new symptoms, patients were instructed to seek medical attention. Discontinuation or gradual tapering of antiarrhythmic therapy was considered in each patient taking into account medical history, coexistence of ventricular arrhythmias and the severity of underlying HCM after 3 months from the index procedure. Ablation failure was defined as recurrence of AF, AT, or AFl lasting ≥3 minutes and occurring after the blanking period. Arrhythmic events were documented with 12-lead ECG performed during symptoms relapses, Holter recordings or cardiac implantable electronic devices memory log. All-cause mortality, cardiovascular (CV) hospitalization and the composite of all-cause death, CV-hospitalization or heart transplantation were the main clinical endpoints of the study. The occurrence of cerebrovascular accidents (i.e. strokes and transient ischemic attacks [TIA]) and of peripheral embolisms was also investigated throughout follow-up.

Statistical methods

Student's t-test, X^2 and Fisher's exact test were used to assess significant differences in continuous variables (expressed as mean±SD) and categorical variables (expressed as counts and percentages). Kaplan–Meier analyses were used to determine median arrhythmia-free survival and presented as event curves. Cox proportional hazard models were used to assess the association between baseline covariates and AF/AFl relapses. Multivariable analyses adjusted for variables significantly associated with AF/AFl relapses at univariate analysis. All p-values were two-sided and considered significant when $p < 0.05$. Calculations were performed with STATA 14.0 software (StataCorp, LP, College Station, Texas, USA).

Results

Study population

The study group included 116 patients (71% male) with a mean age of 53.6±11.4 years at the time of index ablation. Baseline clinical characteristics of the study population are summarized in Table 1. All patients had AF refractory to antiarrhythmic medical therapy, including 43 patients (37%) with paroxysmal, 51 (44%) with persistent and 22 (19%) with long-standing persistent AF. Average time elapsed between the first clinical diagnosis of AF and RFCA was 5.0±5.6 years. Median value for LA volume was 168±41 mL, exceeding 150 mL in 55 patients (47%).

Index transcatheter atrial fibrillation ablation procedural details

At the time of hospital admission for the ablation procedure, 52 (45%) patients were in SR, while 56 (48%) patients had AF and 8 (7%) patients showed left AT or AFl (2 typical and 4 atypical AFl). Twenty patients (17%) had undergone ≥1 previous AF ablation procedure in other centers. The ablation scheme encompassed pulmonary vein isolation (PVI) alone in 22 patients (19%), PVI and the addition of ablation lines (roof and mitral isthmus lines) in 75 patients (65%), PVI and CAFE ablation were performed in 7 patients (6%) whereas in 12 patients (10%) the scheme included PVI, lines and CAFE ablation (Table 2). All patients had evidence of complete PVI and conduction block along ablation lines (if performed) at the end of the procedure. Cavo-tricuspid isthmus ablation was performed in 73 patients (68%). Among patients in whom the index ablation was performed during AF, SR was restored during radiofrequency delivery in 28 cases (24%) while 41 patients (35%) required electrical cardioversion to restore SR at the end of the procedure. Mean total procedural time was 148±59 minutes and mean total radiofrequency time was 65±25 minutes. There were no major periprocedural complications or deaths, mild pericardial effusion managed conservatively occurred in 10 patients (8%). Following the procedure, 71 patients (61%) were in NYHA functional

class I, whereas 45 (39%) were in class II or III. A total of 103 patients (89%) were in SR at hospital discharge.

Supraventricular arrhythmic events during long-term follow-up

Over a median follow-up of 6.0 years (IQR 3.0–8.9 years, mean 6.1±3.5 years) 6 patients (5%) were lost to follow-up and were excluded from the analysis since only incomplete information regarding arrhythmic events and survival were retrieved. Of the 110 remaining patients, 33 (30%) remained in stable SR after a single procedure. Conversely, 77 (70%) had AF/AT recurrences within a median of 10.7 months (IQR 3.1–30.9 months) from the index RFCA procedure (Figure 1). The recurrence rate after a single ablation procedure was 32.3 per 100 patients/years (95% CI 25.8–40.4) with 48%, 32%, 26% of patients free from AF/AT relapses at one, three and six years of follow-up respectively (Figure 2A). Amongst patients experiencing AF/AT recurrence, 51 (66%) underwent at least one redo procedure (Figure 1). In all patients, conduction recovery of one or more PV or a conduction gap along the ablation lines was documented. At last follow-up, with an average of 1.6 procedures per patient, 67 patients (61%) were in stable SR. Conversely, in the remaining 43 patients (39%), RFCA was deemed unsuccessful due to AF/AT recurrences after one (n=25, 58%) or more procedures (n=18, 42%). The average number of procedures performed in this group did not differ significantly from the number of procedures performed in patients with successful RFCA (1.7±1.1 vs. 2.0±1.4; p=0.25). The subtype of arrhythmic recurrence was paroxysmal AF in 9 patients (21%), persistent or long-term persistent AF or atypical AFl in 11 patients (26%) and permanent AF in 23 patients (53%). Among patients with successful RFCA, 33 (49%) underwent a single procedure, whereas 34 (51%) required repeat procedures. The overall RFCA recurrence rate including redo-procedures was 12.6 per 100 patients/years (CI 95% 9.3–17.0) at last follow-up with 68%, 59%, 53% of patients free from AF/AT relapses at one, three and six years of follow-up respectively (Figure 2B). At the time of last follow-up, the vast majority (61 out of 67 patients, 91%) of patients remaining in SR was on antiarrhythmic treatment. Eighty-eight patients (80%)

were on anticoagulation therapy (78 on Warfarin, 9 on new oral anticoagulants and 1 on LWMH). Amongst those not receiving anticoagulants 12 patients (11%) were on aspirin and 10 (9%) were off both anticoagulant and aspirin. The main reasons for being off anticoagulant therapy were poor patient compliance and/or decision of the referring physician based on past medical history (e.g. labile INR, previous hemorrhagic events). Pharmacological and non-pharmacological treatments at long-term follow up are shown in the supplementary Table A.1.

At final evaluation, 49 patients (45%) were in NYHA class I, 44 (40%) were in class II, whereas 17 (15%) were in class III. There was no significant difference in average NYHA at baseline vs. last follow-up (1.8±0.1 vs. 1.7±0.1, p=0.59). This lack of difference was confirmed both for patients in SR and those experiencing arrhythmic recurrences. However, patients remaining in SR at long-term follow-up showed a better functional status as compared with patients showing arrhythmic recurrences (NYHA class 1.6±0.1 vs. 2.0±0.1, p=0.009).

As compared with baseline, the supraventricular arrhythmic burden of the study population significantly improved at long-term follow-up (Figure 3). More in detail, the number of patients suffering paroxysmal AF went from 41 (35.3%) to 9 (7.8%). Similarly, at last follow-up, less patients with persistent and long-standing persistent AF/AT were observed compared with baseline (8 [7.3%] vs. 48 [43.6%] for persistent AF/AT and 3 [2.7%] vs. 32 [29.1%] for long-standing persistent AF/AT). Nevertheless, in 23 patients (18%), after failure of ≥1 RFCA, rhythm control strategy was abandoned opting for rate control in the context of permanent AF.

Predictors of arrhythmic recurrences after RFCA

The predictors of RFCA outcome after the index procedure and at last follow-up were analyzed separately. At univariate analysis, predictors of recurrence after single procedure were presence of thyroid disease (Hazard Ratio, HR 1.77, 95% CI 1.07–2.94, p=0.026), all types of persistent AF (HR 1.81, 95% CI 1.11–2.95, p=0.018), LA volume (HR per 10 ml increase 1.14, 95% CI 1.08–1.20, p<0.001) and moderate to severe mitral regurgitation (HR 2.85, 95% CI 1.77–4.57, p<0.001).

At multivariable analysis, the only significant factor associated with AF/AT recurrence after the index RFCA was LA volume (HR per 10 ml increase 1.10, 95% CI 1.02–1.18, p=0.014) [Table 3A].

Considering multiple procedures, long-term follow-up predictors of AF/AT recurrence at univariate analysis were NYHA class II/III (HR 3.01, 95% CI 1.39–6.49, p=0.005), all types of persistent AF (HR 2.11, 95% CI 1.06–4.21, p=0.033) and LA volume (HR per 10 ml increase 1.08, 95% CI 1.01–1.15, p=0.023). At multivariable analysis no significant predictors of very late arrhythmic recurrence were found. A trend for an association between LA volume and NYHA class II/III and AF/AT relapses at long-term follow-up was observed (Table 3B).

Clinical endpoints at long-term follow-up

During long-term follow-up, 12 patients (10.9%) died and 4 patients (3.6%) underwent heart transplantation. Causes of death and main clinical events are detailed in the supplementary Table A.2. A total of 41 patients (37%) required hospitalization for cardiovascular (CV) reasons (Figure 4A) at a rate of 7.0 per 100 patients/years (95% CI 5.1–9.4). CV-hospitalizations occurred mainly in the context of end-stage progression and overt LV systolic dysfunction, heart transplantation, stroke or transient ischemic attack (TIA). No clear correlation with AF/AT recurrences was observed. Incidence of the composite end-point (CV hospitalization, all-cause death or heart transplantation) was 8 per 100 patients/years (95% CI 5.9–10.5) (Figure 4B). At last follow-up 6 patients (5.5%) reported a TIA, 6 patients (5.5%) suffered a stroke (including one hemorrhagic, fatal stroke) while 4 patients (3.4%) experienced peripheral embolism (2 fatal mesenteric embolisms). Of all thromboembolic events, 9 (4 strokes, 3 TIA, 2 peripheral embolisms) occurred during suboptimal INR therapeutic range or temporary Warfarin discontinuation. One patients taking Dabigatran for prior documentation of labile INR levels had an ischemic stroke whereas two patients had a fatal mesenteric embolism while on Warfarin and with INR in therapeutic range.

Discussion

This longitudinal study demonstrated the long-term efficacy of transcatheter ablation for AF in patients with HCM and confirmed its overall safety if performed in high volume centers by experienced operators. More in detail, effective rhythm control was achieved in more than half (61%) of patients over a very long follow-up with no major periprocedural complications. By including a relatively large population followed-up for a median of six years, this is the largest study with the longest available follow-up reported so far. Its main findings highlight the potential durability of a rhythm control strategy pursued by means of RFCA associated with antiarrhythmic drugs in patients with HCM. Of note, patients who were in SR at last follow-up showed a significant improvement in NYHA functional class compared with patients experiencing arrhythmic recurrences. However, it should be noted that these results were achieved with an average of 1.6 RFCA per patient since almost half (46%) of the study population required at least one repeat procedure. Whether the lower success rate of single RFCA was due to disease specific characteristics of the atrial tissue (e.g. primary atrial myopathy and hypertrophy of the muscle sleeves responsible for pulmonary vein trigger conduction to LA) or simply to the significant atrial remodeling observed in patients with HCM, remains to be determined. Indeed, the efficacy of RFCA in HCM patients is jeopardized by the peculiar features of the LA characterized by high degree of fibrosis (6) and severe dilatation (26) secondary to chronic diastolic dysfunction, mitral regurgitation due to anterior systolic motion of the mitral valve and structural abnormalities caused by sarcomere protein gene mutations (2,27). Moreover, recurrent ischemia due to severe coronary microvascular dysfunction, which may lead to abrupt worsening of LV function (mainly diastolic), likely contributes to these detrimental pathophysiological mechanisms (28).

Another important finding from the present study was the need to continue antiarrhythmic drug therapy despite successful RFCA in the vast majority of cases. Discontinuation of antiarrhythmic drugs was possible only in 9% of patients, a three-fold lower percentage as compared with a previous report from our group (29) probably explained by the significantly longer follow-up. The

main reason for antiarrhythmic drug continuation was rhythm control (i.e. hybrid therapy). However, many patients also required antiarrhythmic medications to prevent ventricular arrhythmias or minimize the likelihood of appropriate defibrillator shocks. Indeed, taking into account the arrhythmogenic nature of HCM and the advanced stage of the disease of many patients included in this study, it would have been unrealistic to expect a large prevalence of antiarrhythmic drugs discontinuation following RFCA.

A recent meta-analysis of previous studies has shown that RFCA for severely symptomatic AF is both a feasible and safe approach in patients with HCM (30). Reported success rate ranged from 41% to 92% depending on the duration of follow-up and the percentage of repeat procedures (varying between 39% and 72%). The short- and medium-term results of RFCA observed in the present study are consistent with such experiences. Discrepancy with the higher success rate (92%) reported by Klicaslan et al. (18) should be interpreted with caution considering the shorter duration of follow-up (mean of 341 days). The high failure rate after a single RFCA observed in the present study as well as in previous series underscores the need for accurate counselling of candidate patients, including full disclosure of the likelihood for repeat procedures. With this regard, the concept of offering a therapeutic strategy rather than a one-stop procedure should be privileged.

Previously reported predictors of successful transcatheter ablation included baseline paroxysmal AF, young age (< 50 years), LA volume below 130 mL, low NYHA class and performance of linear ablation lesions (19,29,31). In the present study, the only factor significantly associated with arrhythmic recurrences following the index ablation was LA dilation with an additional 10% risk per 10 ml volume increase. In contrast, heart failure symptoms and LA volume only showed a borderline association with arrhythmic recurrences occurring after last RFCA at long-term follow-up. This lack of significance may be partially explained by the progression of the severity of baseline disease over several years with many confounding factors adding up to known predictors of AF recurrence.

When long-term SR maintenance is not achievable, a more realistic endpoint of RFCA in the context of structural cardiomyopathy is represented by a reduction in atrial arrhythmic burden. In the current study, compared with baseline evaluation, significantly less patients experienced paroxysmal or persistent relapses at long-term follow-up. However, not surprisingly, almost one patient out of five progressed to permanent AF and the overall progression rate was 6.4 per 100-patient years. Such rate is much higher than that observed in patients with lone AF undergoing RFCA, but consistent with what observed in the context of other structural heart diseases (32,33). A relatively high number of fatal and nonfatal events was observed in the present study with an overall mortality (including heart transplantation) of 2.7% per year and frequent cardiovascular hospitalizations (6.8% per year). These outcomes are worse as compared with those reported in contemporary cohorts of patients suffering AF and undergoing transcatheter ablation (34) but in line with previous studies that specifically investigated the prognostic implication of AF in patients with HCM (2,3). Notably, the occurrence of stroke, transient ischemic attack and peripheral embolism was frequent, with 9% of patients experiencing such events, in two cases despite satisfactory anticoagulation levels. Nevertheless, it should be noted that the majority of thromboembolic events occurred during suboptimal drug administration or temporary withdrawal. This underscores the considerable thromboembolic risk of patients with HCM and concomitant AF and indicates that the threshold for life-long anticoagulation initiation in this clinical scenario should be low. In addition, compliance to treatment regimen as well as its efficacy should be regularly reassessed.

Some limitations of the present study should be acknowledged. First, the observational data reported originate from high volume centers with specific expertise in AF and HCM management and may be difficult to extend these findings to other realities. Second, although this is the largest study investigating the role of RFCA in patients with HCM conducted so far, its sample size is still relatively limited, compared with studies addressing AF management in the general population. Third, information regarding arrhythmic relapses were collected with intermittent ECG or Holter monitoring, unavoidably at risk for under detection. Nevertheless, silent AF is uncommon in HCM

due to the significant symptoms commonly associated with the arrhythmia. Lastly, we acknowledge the fact that the high prevalence of antiarrhythmic drug therapy may represent a confounder when assessing the efficacy of AF ablation in patients with HCM.

In conclusion, transcatheter ablation of AF in patients with HCM is an effective and safe therapeutic strategy favoring long-term SR maintenance, reduction of atrial arrhythmic burden and improved functional status. The need for repeat procedures and the likelihood of antiarrhythmic drug continuation despite successful transcatheter intervention should be openly discussed with patients. Long-term thromboembolic risk is high and requires life-long anticoagulation even after successful ablation procedures.

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Figure Legends

Figure1. Management of atrial fibrillation in the overall study population with details regarding procedural results, arrhythmic recurrences, repeat procedures and antiarrhythmic drugs use throughout follow-up. AAD = antiarrhythmic drug, AF = atrial fibrillation, RFCA = radiofrequency transcatheter ablation.

Figure 2. Kaplan-Meier survival curves for long-term arrhythmia-free survival. Long-term arrhythmia free survival following a single procedure (2A). Long-term arrhythmia free survival following the last procedure (2B). AF = atrial fibrillation, AT = atrial tachycardia.

Figure 3. Changes in supraventricular arrhythmic burden between baseline and long-term follow-up in the overall study population.

Figure 4. Kaplan-Meier hazard curves for the occurrence of clinical endpoints during long-term follow-up. Occurrence of hospitalization for cardiovascular reasons (4A). Occurrence of the composite endpoint of hospitalization for cardiovascular reasons or all-cause death or heart transplantation (4B).

Table 1. Baseline characteristics of the 116 HCM patients

Variable	Total Population N = 116
Age at the enrollment (years)	53.6 ± 11.4
Number of patients ≤50 years	42 (36%)
Female	34 (29%)
Hypertension	40 (34%)
Diabetes	6 (5%)
Dyslipidemia	27 (23%)
Thyroid disease	
Hypothyroidism	14 (12%)
Hyperthyroidism	13 (11%)
History of coronary artery disease	5 (4%)
Years since first diagnosis of HCM	13.8 ± 9.4
Family history of HCM	39 (34%)
Obstructive HCM	25 (22%)
Prior septal myectomy	13 (11%)
Prior alcohol septal ablation	9 (8%)
NYHA Class	
I	40 (34%)
II	60 (52%)
III	16 (14%)
Atrial fibrillation subtype	
Paroxysmal	43 (37%)
Persistent	51 (44%)
Long-standing persistent	22 (19%)
Years since first diagnosis of AF	5.0 ± 5.6
Echocardiographic parameters	
Septal LV thickness (mm)	21 ± 5
Posterior wall LV thickness (mm)	13 ± 3
Left atrial volume (ml)	168 ± 41
Basal LV outflow tract gradient (mmHg)	21 ± 24
LV ejection fraction (%)	57 ± 6
Systolic anterior motion of mitral valve	16 (16%)
Mitral regurgitation	
None	16 (14%)
Mild	65 (56%)
Moderate	34 (29%)
Severe	1 (1%)

Medical and nonpharmacological treatment	
Beta-blockers	65 (56%)
Non-dihydropyridine Ca^{2+} channel blockers	14 (12%)
Disopyramide	3 (3%)
Sotalol	31 (27%)
Amiodarone	73 (63%)
Other antiarrhythmic drugs	33 (28%)
Antiplatelet agents	5 (4%)
Anticoagulant agents	116 (100%)
ACE-I	20 (17%)
ARB	16 (14%)
MRA	7 (6%)
Loop diuretics	18 (16%)
Implantable cardioverter defibrillator	31 (27%)
Cardiac resynchronization therapy defibrillator	4 (3%)

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HCM = hypertrophic cardiomyopathy; MRA = mineralcorticoid receptor antagonist; NYHA = New York Heart Association; LV = left ventricle.

Table 2. Index transcatheter atrial fibrillation ablation procedural details

Variable	Total Population N = 116
Rhythm at hospital admission	
Sinus rhythm	52 (45%)
Atrial fibrillation	56 (48%)
Atrial flutter / ectopic atrial tachycardia	8 (7%)
Transcatheter ablation scheme	
PVI	22 (19%)
PVI + LA LINES	75 (65%)
PVI + CAFE	7 (6%)
PVI + LA LINES + CAFE	12 (10%)
Cavo-tricuspid isthmus ablation	73 (68%)
Sinus rhythm restoration	
During RFCA	28 (24%)
After electrical cardioversion	41 (35%)
Mean procedure time (min)	148 ± 59
Mean radiofrequency time (min)	65 ± 25
Rhythm at hospital discharge	
Sinus rhythm	103 (89%)
Atrial fibrillation	12 (10%)
Atrial flutter / ectopic atrial tachycardia	1 (1%)

Abbreviations: CAFE = complex atrial fractionated electrograms; LA = left atrium; PVI = pulmonary vein isolation; RFCA = radiofrequency transcatheter ablation.

Table 3A. Factors associated with arrhythmic recurrences after the index transcatheter ablation

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)
Thyroid disease	1.77 (1.07 – 2.94), p=0.026	1.42 (0.71 – 2.84), p=0.32
Persistent AF (including long-standing)	1.81 (1.11 – 2.95), p=0.018	1.10 (0.60 – 2.03), p=0.76
LA volume (ml) per 10 ml increase	1.14 (1.08 – 1.20), p<0.001	1.10 (1.02 – 1.18), p=0.014
Moderate-severe mitral regurgitation	2.85 (1.77 – 4.57), p< 0.001	1.57 (0.79 – 3.13), p=0.20

Table 3B. Factors associated with arrhythmic recurrences after last transcatheter ablation at long-term follow-up

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)
NYHA class II/III	3.01 (1.39 – 6.49), p=0.005	2.20 (0.90 – 5.34), p=0.08
Persistent AF (including long-standing)	2.11 (1.06 – 4.21), p=0.033	1.21 (0.54 – 2.70), p=0.65
LA volume (ml) per 10 ml increase	1.08 (1.01 – 1.15), p=0.023	1.06 (0.99 – 1.14), p=0.08

Abbreviations: AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; LA = left atrium; NYHA = New York Heart Association.

Figure 1.

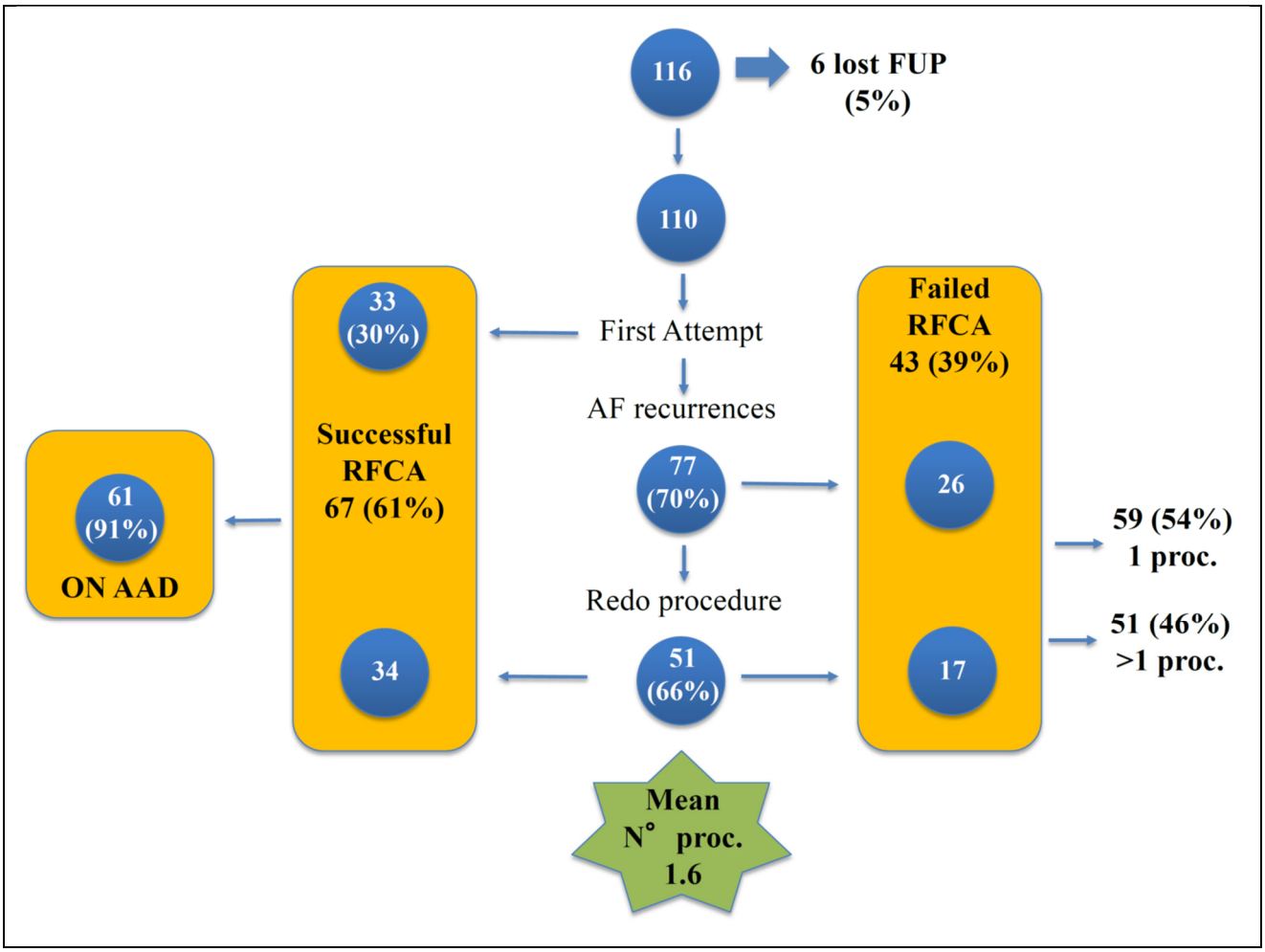
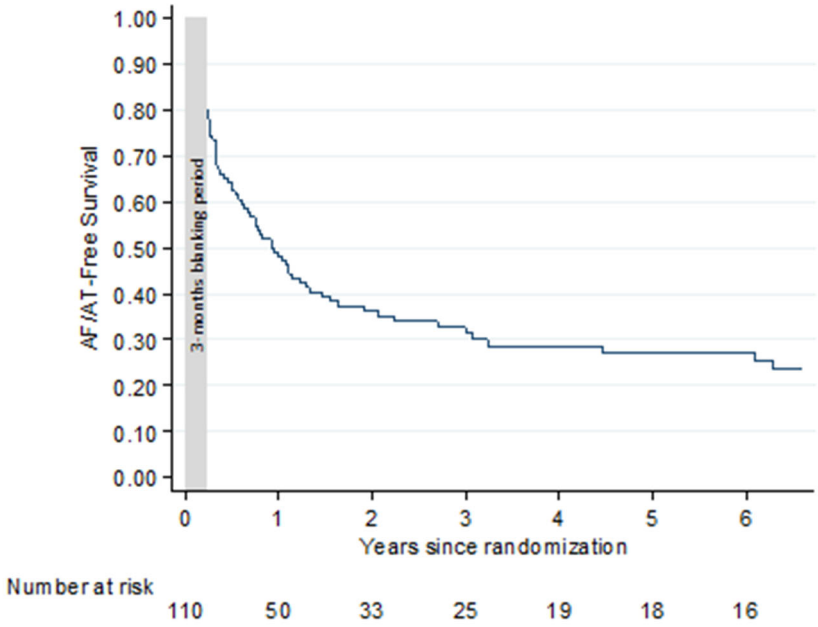

116
6 lost FUP
(5%)
110
First Attempt
33
(30%)
Successful
RFCA
67 (61%)
61
(91%)
ON AAD
34
AF recurrences
77
(70%)
Redo procedure
51
(66%)
Failed
RFCA
43 (39%)
26
17
59 (54%)
1 proc.
51 (46%)
>1 proc.
Mean
N° proc.
1.6

Figure 2.

A


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
AF/AT-Free Survival
3-months blanking period
0
1
2
3
4
5
6
Years since randomization
Number at risk
110
50
33
25
19
18
16

B

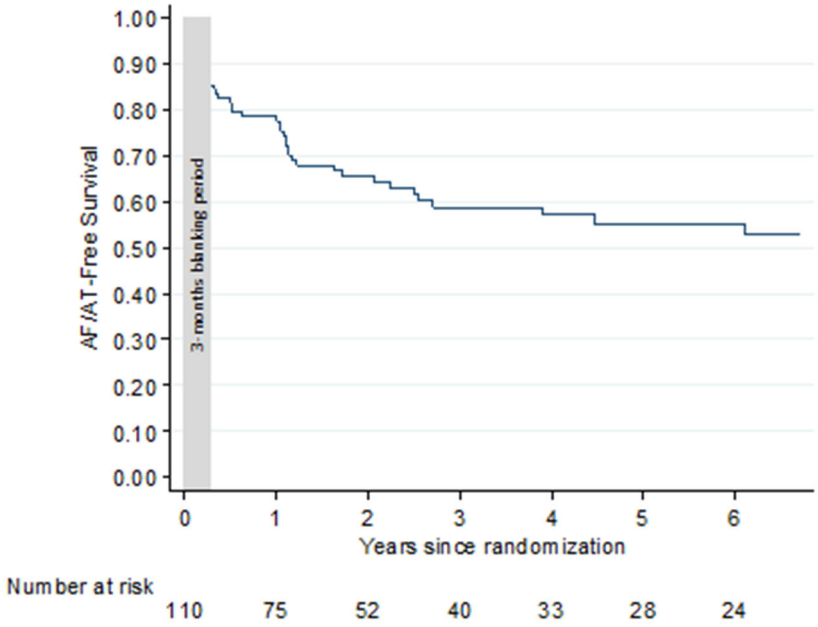

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
AF/AT-Free Survival
3-months blanking period
0
1
2
3
4
5
6
Years since randomization
Number at risk
110
75
52
40
33
28
24

Figure 3.

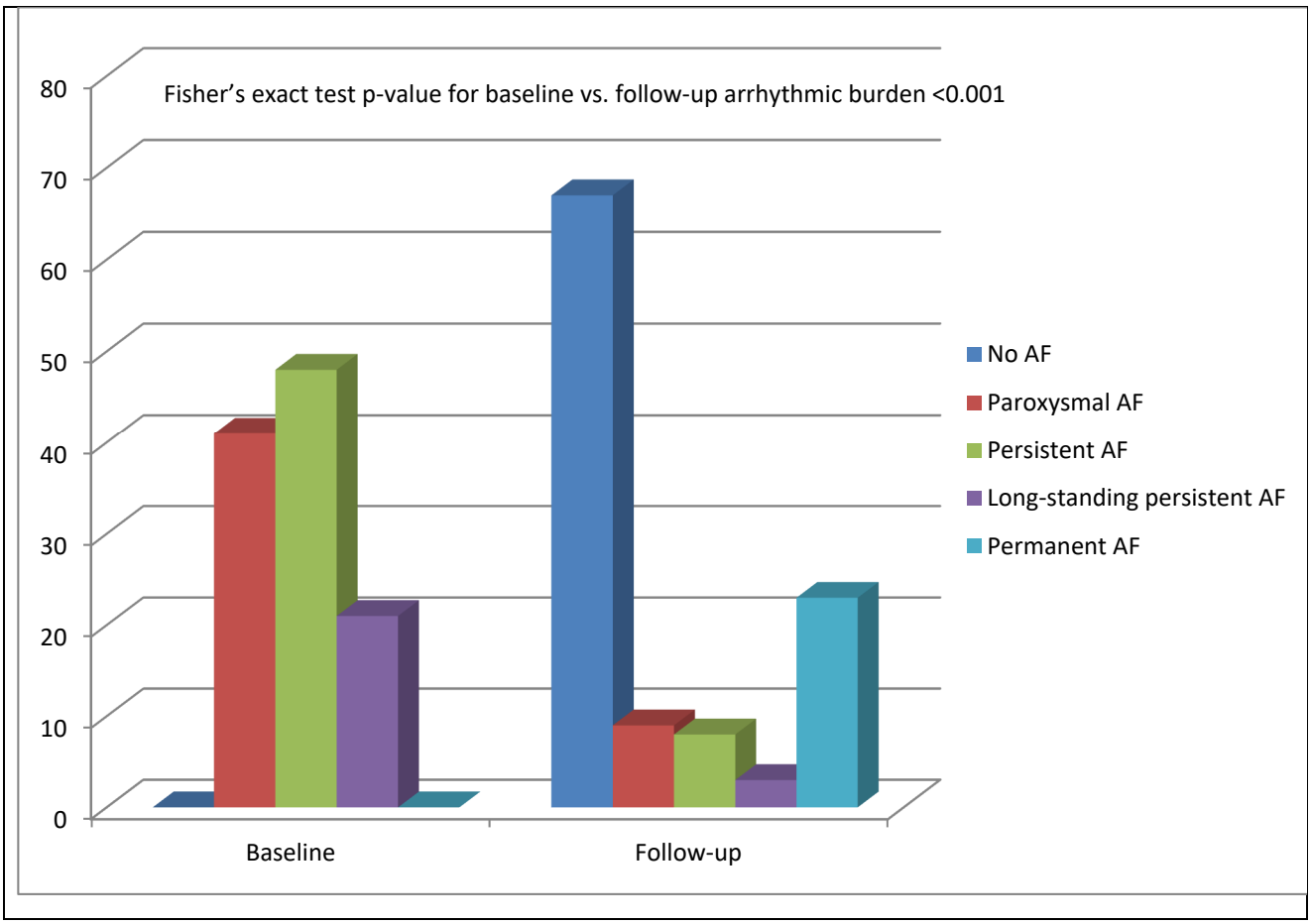
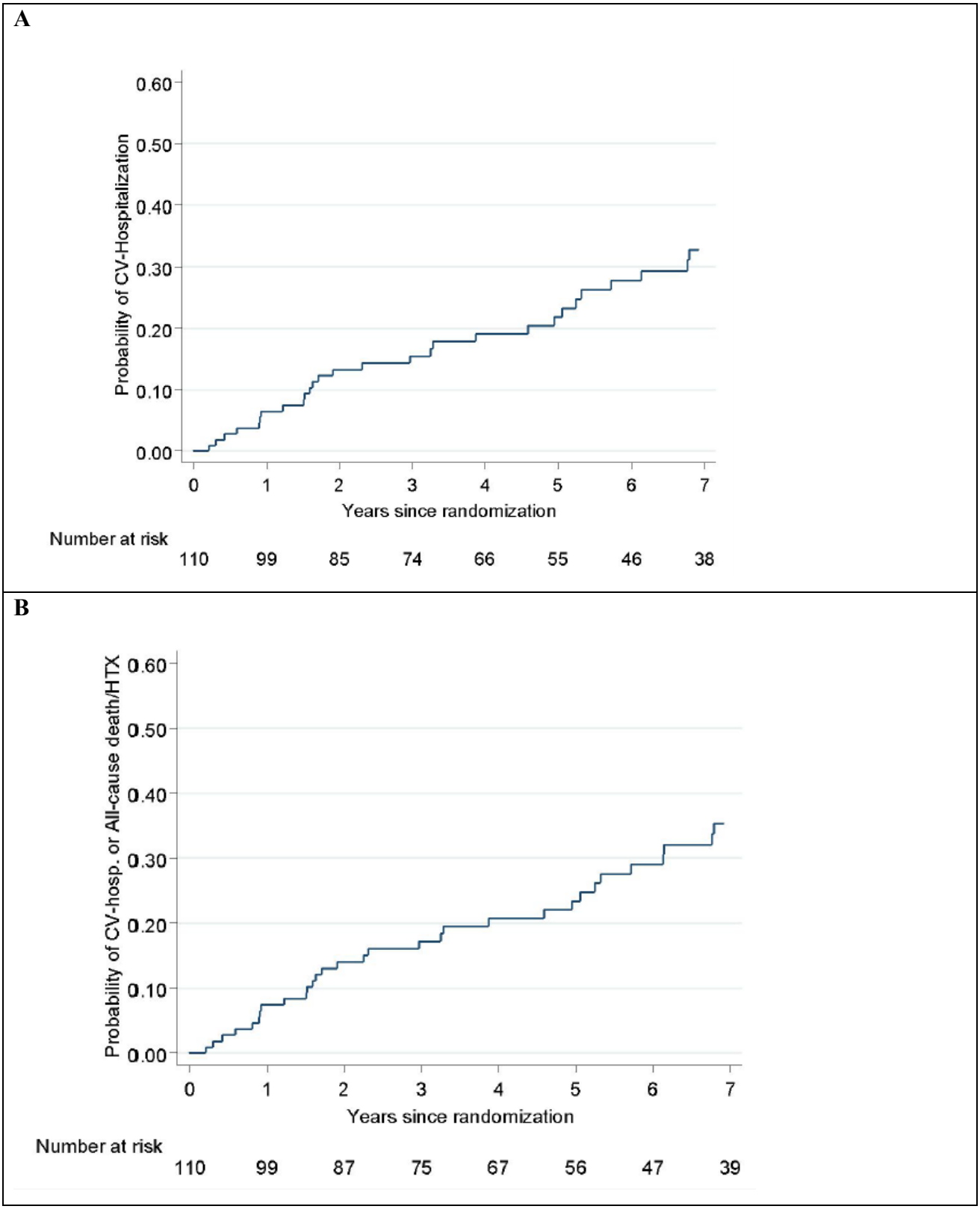

Fisher's exact test p-value for baseline vs. follow-up arrhythmic burden <0.001
80
70
60
50
40
30
20
10
0
Baseline
Follow-up
No AF
Paroxysmal AF
Persistent AF
Long-standing persistent AF
Permanent AF

Figure 4.


A
Probability of CV-Hospitalization
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0 1 2 3 4 5 6 7
Years since randomization
Number at risk
110 99 85 74 66 55 46 38
B
Probability of CV-hosp. or All-cause death/HTX
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0 1 2 3 4 5 6 7
Years since randomization
Number at risk
110 99 87 75 67 56 47 39

Appendix

Table A.1 Pharmacological therapy during follow-up

Drug or device	Total Population N = 110
Beta-blockers	67 (61%)
Non-dihydropyridine calcium channel blockers - Verapamil - Diltiazem	 5 (5%) 3 (3%)
Disopyramide	1 (1%)
Sotalol	16 (14%)
Amiodarone	34 (31%)
Other antiarrhythmic drugs	10 (9%)
Antiplatelet agents	12 (11%)
Anticoagulant agents	88 (80%)
ACE-I	29 (26%)
ARB	27 (25%)
MRA	19 (17%)
Loop diuretics	40 (36%)
Implantable cardioverter defibrillator	37 (34%)
Cardiac resynchronization therapy defibrillator	5 (5%)

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralcorticoid receptor antagonist.

Table A.2 Causes of death at long-term follow-up

N	Age	CV Cause	Duration of follow-up (yrs)	Cause	Rhythm	AAD	OAT
1	70	No	9.8	Cancer	SR	No	No
2	84	Yes	2.0	Mesenteric embolism	SR	No	Unknown
3	67	Yes	6.2	SCD	Permanent AF	Amiodarone	Yes
4	72	Yes	5.3	Mesenteric embolism	SR	Amiodarone	Yes
5	74	No	7.8	Cancer	Permanent AF	Amiodarone Beta-blockers	Yes
6	83	No	8.9	Pneumonia	Permanent AF	Atenolol	Yes
7	70	Yes	5.4	SCD	SR	No	Yes
8	61	Yes	0.5	Ischemic Stroke	SR	Amiodarone	Yes
9	46	Yes	2.3	Hemorrhagic Stroke	SR	Beta-blockers	Yes
10	44	Yes	1.2	SCD	SR	Amiodarone	Yes
11	47	Yes	1.5	SCD	Permanent AF	Amiodarone Beta-blockers	Yes
12	58	No	1.3	Cancer	SR	Amiodarone Beta-blockers	Yes

Abbreviations: AAD = antiarrhythmic drugs; AF = atrial fibrillation; CV = cardiovascular; OAT = oral anticoagulation therapy; SCD = sudden cardiac death; SR = sinus rhythm.