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Catheter ablation of atrial fibrillation in patients with heart failure with reduced ejection fraction: Real world experience from 6 European centers

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Abstract

Introduction: Catheter ablation of atrial fibrillation (AF) has been recently shown to have an impact on the outcome of patients with heart failure and reduced LV ejection fraction (LVEF). We aimed to assess patients with reduced LVEF referred to catheter ablation of AF, and the efficacy and safety of this procedure compared to healthier patients.

Methods: 2,083 consecutive procedures of catheter ablation of AF in 6 centers were divided in two groups based on LVEF (≤ vs. >35%) and comparisons were performed regarding procedural safety and efficacy.

Results: Only 51 (2.4%) of patients had low LVEF. Complication rate was comparable: 8.0% vs. 6.9% (P=0.760). Low LVEF patients are more frequently in persistent AF at the time of the procedure, have higher degree of left atrial dilation, and higher CHA_2DS_2VASc score. The rate of atrial arrhythmia relapse post-blanking

period in the first 12 months was higher in the low LVEF group: 58.0% vs. 37.6% (P<0.001). During a median follow-up of 14 months (IQR 5-24), after adjusting for all baseline differences, AF duration, paroxysmal AF, CHA_2DS_2VASc score, BMI, and indexed LA volume were independent predictors of relapse. LVEF and LVEF≤35% were not identified as predictors of relapse.

Conclusions: Patients with reduced LVEF account for only a minority of patients undergoing catheter ablation of AF. However, ablation appears to be as safe as for the general population, and albeit the efficacy seems lower, this appears to be driven by other comorbidities or features, which are more frequent in this population.

Keywords: heart failure; LV ejection fraction; vascular complications; sinus rhythm; mortality.

Background

Catheter ablation of atrial fibrillation (AF) has emerged as an effective treatment option, and now has a Class I indication in symptomatic patients with drug-refractory AF [1, 2]. The recent *Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation* (CASTLE-AF) publication has suggested that catheter ablation of AF in patients with heart failure (New York Heart Association class II, III, or IV) and reduced left ventricular ejection fraction (LVEF of 35% or less) was associated with significantly lower rate of death from any cause and hospitalization for worsening heart failure when compared with guideline-based medical therapy (50% relative risk reduction for both endpoints) [3]. However, it is unknown to the medical community whether this type of patients is being referred for catheter ablation in the real-world, and whether catheter ablation is as safe and effective in this group compared with other patients being referred for this

procedure. Addressing this knowledge gap would be of importance, as concerns over this procedure may be preventing these patients from being exposed to the beneficial prognostic effect of this procedure. Understanding of the efficacy and safety of this procedure, and providing reassurance to referring cardiovascular physicians, may be a way of addressing this matter.

Methods

Setting and patient population

Non-randomised, observational study in 6 European centers. We compared procedural and mid-term outcomes of patients who underwent catheter ablation of AF, based on their LVEF *levels* (using the ≤ vs. >35% cut-off coming from the inclusion criteria in the CASTLE-AF study [3]. LVEF was assessed as a potential independent predictor of AF/atrial tachycardia relapse.

All patients aged over 18 undergoing a left atrial ablation procedure during a 24 months' time interval, with AF refractory to at least one class I or class III anti-arrhythmic drug were included in this analysis. All patients provided written informed consent prior to the procedure. No patients were excluded from the study as a result of acute complications. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics committees.

Centers contributing to this paper were asked to provide data of all consecutive patients ablated during a minimum of 6 months, during 2014, and 2015. At that time, the following annual AF ablation volumes were observed: Toulouse 700, Frankfurt 700, Brussels 500, Barts 350, Grenoble 200, and Rouen 150 AF ablations-per-year.

Pre-Procedural Assessment

All variables at the time of the procedure were defined and categorized according to the literature or common practice. Information was collected regarding demographics, admission day anthropometric data, clinical comorbidities based on patients' notes and referral letters. Patients with a history suggestive of obstructive sleep apnea (OSA) were routinely referred for screening by local sleep specialists. Data from the referral transthoracic echocardiogram was analysed and a multislice computed tomography scan imaging of the left atrium was systematically collected whenever available.

Procedural details on ablation procedures

Procedures were performed under sedation or general anesthesia, according to each institution's protocol. Venous access was obtained via the femoral vein. A quadripolar or decapolar catheter was positioned in the coronary sinus in all patients as a reference and for pacing. 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 upon completion or before the transseptal puncture, according to each institution's protocol. The transseptal sheaths throughout were continuously flushed with heparinized saline.

Details of the AF ablation technique and periprocedural management at our institutions have been published previously [4-6]. Basically, pulmonary vein isolation 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 organised into an atrial tachycardia this was mapped and ablated. In patients undergoing cryoballoon

ablation, or other single-shot ablation techniques, 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. In patients undergoing radiofrequency ablation of persistent AF and not cardioverting to sinus rhythm, or not organising to atrial tachycardia during ablation, we mapped and ablated areas of complex fractionated atrial electrograms in both atria and the coronary sinus and subsequently DC cardioverted the patient if AF persisted.

If patients organized into atrial tachycardia while having their ablation performed, the tachycardia was mapped and ablated.

Follow-up

A systematic transthoracic echocardiography was performed before discharge. Patients were also evaluated at 3, 6, and 12 months after the procedure. Information collected during follow-up included a 12-lead electrocardiogram and 24-hour Holter monitoring at each visit. Additional patient visits and further testing were allowed in case of symptoms. After the first year, follow-up was performed on an annual basis. Antiarrhythmic drugs were prescribed at discharge only for specific indications (i.e. relapse during the admission, need for cardioversion, longstanding persistent AF, etc) and at the operator's discretion. In those instances, antiarrhythmic drugs were stopped after the first 3 months in the absence of recurrence. The first 3 months post-procedure were considered blanking period.

Endpoints and safety concerns

Recurrence was defined as any symptomatic or asymptomatic atrial arrhythmia lasting >30 seconds following the 3 months blanking period after catheter ablation. Patients

with relapse during the blanking period with no response to pharmacologic or electrical cardioversion were also classified as having a relapse.

The main efficacy endpoint was freedom from atrial arrhythmias following a blanking period of 3 months. AF or atrial tachycardia relapse during the initial 3-month blanking period was also documented.

With regard to safety, information on the following complications was systematically collected: vascular complications (if requiring intervention or prolongation of admission), thromboembolism (transient ischemic attack, stroke and/or systemic embolism happening during or in the first month after the procedure), phrenic nerve palsy post-procedure, pericardial effusion (if causing haemodynamic instability and/or requiring pericardiocentesis or prolonged monitoring), esophageal fistula, and procedure-related death. Other complications were reported at the discretion of the operator.

Statistical analysis

Comparisons were performed across the two pre-specified LVEF categories. 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 favor of the absence of normal distribution. Results with $P < 0.05$ were regarded as significant.

Kaplan-Meier curves were traced for illustrating freedom from AF or atrial tachycardia among patients in the different LVEF groups, and the log rank P test was used for assessing existing differences. Independent predictors of sinus rhythm

maintenance after a single ablation procedure were assessed through Cox regression (Method: Forward Likelihood Ration, Probability for Stepwise 0.05).

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis.

Results

Study Population

During the study inclusion period, 2,083 patients underwent catheter ablation procedures. Only 51 (2.4%) of patients had low LVEF. The majority of procedures were performed in patients with LVEF >55% (n=1,921). The aetiology of heart failure in the low LVEF group was valvular heart disease in 5.9%, ischaemic cardiomyopathy in 23.5%, and all other patients had a non-ischaemic aetiology.

Women accounted for a minority of patients (28.3%, n=589), and the mean age of the sample was 61.3±10.0 years. Mean CHA_2DS_2VASc score was 1.6±1.4 and the number of procedures was 1.2±0.5 per patient. Most patients (53.8%) had paroxysmal AF at baseline. Cryoballoon ablation was used in more than a third of patients and distributed evenly between the two groups (Table 1).

Prior to the procedure 5% of patients were not on antiarrhythmic drugs, 10.7% were on class Ic agents, 32.4% on beta-blockers, 3.1% on class III (sotalol, amiodarone or dronedarone), 4.9% on calcium channel blockers, 11.3% treated with an association of two anti-arrhythmic agents other than amiodarone (e.g. beta-blockers and class Ic), and 32.6% were on amiodarone and another antiarrhythmic drug (e.g. beta-blockers and amiodarone). No significant differences in the use of anti-arrhythmic drugs were observed when comparing patients according to LVEF categories. However, no

patients in the low LVEF group were treated with calcium channel blockers, dronedarone, or sotalol, and only one patient in that group was treated with flecainide.

Baseline Differences Across LVEF classes

The lower LVEF group was composed mostly of men. These patients more frequently had persistent AF, albeit with shorter time since AF diagnosis (both $P<0.05$; Table 1). The CHA_2DS_2VASc score in the low LVEF group was higher, likely driven by the significantly higher incidence of congestive heart failure and vascular disease. Also, a more pronounced degree of left atrial dilation was observed in the low LVEF group. No other relevant differences were observed at baseline.

Safety Outcomes

The incidence of periprocedural complications was similar in both groups: low LVEF group 8.0%, n=4, vs. 6.9%, n=140, in the remaining patients (P=0.760) (Table 2). Comparable complications rates were also observed in patients undergoing only one ablation procedure: low LVEF group 5.0%, n=2; vs. 7.1%, n=140; (P=0.612).

The incidence of cardiac tamponade, other bleeds, major vascular complications, transient phrenic nerve palsy, and stroke or systemic embolism was very low and comparable. However, healthier patients had a slightly higher incidence of transient ischemic attack. On the other hand, one case of peri-procedural pulmonary oedema was observed in the low LVEF group (Table 2).

Other rare complications, like atrioesophageal fistula, gastroparesis, esophageal ulcer, bradyarrhythmic complications, anaphylaxis, myocardial stunning, PV stenosis and air embolism, were only observed in the higher LVEF group of patients.

On multivariate analysis, age (HR = 1.04 per year 95%, CI 1.01-1.06, P=0.002), was the only independent predictor of occurrence of complications (Supplementary material - Table S-1).

A patient with normal LVEF who underwent redo radiofrequency ablation for persistent AF died 15 days following the procedure, as the result of bronchial haemorrhage, which started in the same day of the procedure.

Procedural and Midterm Efficacy Outcomes

There was a trend for slightly longer procedure duration, by an extra 20 minutes, in patients with more severe cardiomyopathy. Use of the cryoballoon was comparable in both groups. The rate of pulmonary vein isolation at the end of the procedure was comparable in both groups. Ablation of complex fractionated atrial electrograms (CFAE) was performed in 17.2% (n=358), additional LA lines in 30.2% (n=629), and a cavotricuspid isthmus in 26.1% (543). CFAE ablation and additional LA lines were more frequent in the low LVEF group of patients (Table 2), but when performing a sub-analysis of persistent AF patients numbers were comparable. Ablation of CFAE: 35.7%(n=329) vs. 37.5% (n=15), P=0.814; and LA lines: 54.2%(n=500) vs. 52.5%(n=21), P=0.830.

Relapse during blanking occurred more frequently in patients with LVEF ≤35%. At 12 months, there was a trend for higher relapse rate after a single procedure in the low LVEF group (60.8% vs. 48.2%; P=0.08). After one or more procedures, documented atrial arrhythmia relapse was more frequent in individuals with LVEF ≤35% (58.0% vs. 37.6%, P<0.001) (Table 1).

During a median follow-up of 14 months (IQR 5-24) a significantly higher relapse rate was observed for patients with persistent AF with lower LVEF. The curves show a similar separation for paroxysmal AF, but the low patient numbers with low LVEF and paroxysmal AF, and hence lack of statistical power, does not allow crossing of the significance threshold (Figure 1).

Assessment of independent predictors of AF or arrhythmia relapse is illustrated in table 3. On multivariate Cox regression, total AF duration in years, paroxysmal AF, CHA_2DS_2VASc score, BMI and indexed left atrial volume were independent predictors of relapse (Table 3). Cryoballoon ablation and additional substrate ablation were not predictors of a successful midterm outcome, even though CFAE ablation and additional lines to the left atrium were associated with higher relapse rate on univariate analysis. Similarly, variables like obstructive sleep apnea, congestive heart failure and low LVEF, were predictors on univariate analysis, but, after adjustment, were not included in the multivariate analysis model.

Discussion

Our multicentre data show that, prior to the publication of the CASTLE-HF study, patients with LVEF ≤35% corresponded to a minority of patients having catheter ablation of AF in our centres. Even though our data suggest that the success rate of the procedure may be lower, as measured by freedom from atrial arrhythmia relapse after the blanking period, the complication rate seems to be comparable. Data from CASTLE-AF show that these patients experience a significant reduction in AF burden [3]. Therefore, we believe that patients with low LVEF should not be denied a catheter ablation procedure over safety concerns.

Our findings are of importance, as this class of patients appears to be the one with more pronounced prognostic benefit based on results of the CASTLE-HF study [3], and a trial published by *Di Biase* and colleagues [7]. In fact, a systematic review recently published by our group confirms the prognostic benefit regarding mortality reduction of this intervention with a very low heterogeneity across trials, and <10 patients needed to be ablated to save a life in this population [8]. In spite of this, the *American Heart Association, American College of Cardiology and Heart Rhythm Society 2019 Focused update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation* [9] still provides a Class IIb indication to catheter ablation of AF in the heart failure population (with level of evidence B-Randomized). This occurs even after the publication of CASTLE-AF, which is discussed in that guideline, and the fact that another positive trial in this population (the AATAC) [7] is also cited. The document states that *"both studies have limitations, including relatively small and highly selected patient populations. Further, larger studies are needed to validate these findings"*. Also, the guideline failed to cite two meta-analysis which suggest mortality reduction for the heart failure population [8, 10], and makes no mention to the Swedish nationwide registry which shows a mortality reduction benefit with catheter ablation [11]. Finally, the all-cause mortality increase observed with most anti-arrhythmic agents in trials and meta-analysis (Dronedarone [12, 13], Sotalol [14, 15], Quinidine [14], Disopyramide [14], and Amidoarone [15]), should also be taken into account when deciding rhythm control strategies.

The group of patients with AF and LVEF ≤35% constitutes therefore a special class of patients, where catheter ablation may need to be considered due to its prognostic benefit. Imaging studies, using cardiac MRI [16] and echocardiography [17] show

that restoring sinus rhythm and reducing the AF burden in patients with heart failure leads to reverse remodeling and LVEF recovery which can explain this prognostic benefit. Recently, *Kadhim* and colleagues [18] suggested several other explanations for this added benefit in heart failure patients. These include the reduction in exposure to the toxicity of anti-arrhythmic drugs, improvement in heart rate variability and reverse remodelling of atrial cardiomyopathy (with reduction of left atrial size, restoration of the atrial kick, and AV synchronization), improvement in haemodynamic parameters, restoration of autonomic balance and more favourable myocardial supply/demand conditions, leading to a reduced risk of ventricular arrhythmias, reduced thromboembolic risk, and reduction of myocardial ischaemia and in the risk of falls [18].

In our institutions, the low LVEF population composed only a very small percentage of patients being treated with AF ablation in the years before the publication of CASTLE-AF. We believe that concern over patients' low LVEF and risk of complications or lack of procedure tolerance in these patients may have played a role: that centres may have been more reluctant to perform cases in patients with low LVEF. On a similar level, we also believe that referring physicians may also have been more reluctant to refer their sickest patients. The publication of the CASTLE-AF trial and the perception that, even though AF eradication may be difficult in this population, reduction of AF burden may by itself lead to a better outcome may contribute for a wider usage of this procedure in the heart failure population.

Finally, additional substrate ablation was not a predictor of a more successful midterm outcome, confirming that successful pulmonary vein isolation should be the main acute procedural endpoint in all patients [19]. As acute pulmonary oedema or heart

failure aggravation may be a possible issue in this patient group, shorter procedure times may be advisable to reduce that risk. Radiofrequency in the hands of highly experienced and quick operators, or a single-shot device may be the best approach in this scenario. However, this hypothesis lacks confirmation by a large trial with enough statistical power to show statistical differences in this infrequent complication, which was observed in 2% of the low LVEF group.

We acknowledge a few limitations in our work. First, this is a multicenter study including experienced centers performing several hundreds of cases annually, and may not represent the type of ablation activity performed in other centers with lower caseloads. Even though number of patients with low LVEF in our sample is small, our sample was larger than the small number of low LVEF individuals receiving ablation in the CABANA trial [20]. Furthermore, no sub-analyses of the CABANA trial based on LVEF levels have been published so far. As we had no access to the total number of AF patients with low LVEF who were potential ablation candidates, we cannot conclude whether or not under-referral was a cause for the low number of low LVEF individuals. Lastly, systematic monitoring using an implantable loop recorder or intracardiac devices might have documented higher rate of asymptomatic recurrence. This may have been the case in patients with low LVEF, who more frequently had intracardiac devices. Even though routine use of implantable loop recorders could have given us a better information of AF burden in the whole cohort, this practice would be hard to justify in the real world, outside the context of a trial.

Conclusion

Patients with heart failure and reduced LVEF constitute only a small minority of patients receiving catheter ablation of AF in the real world. Catheter ablation in this

population appears to be as safe as for the general population. Albeit the efficacy, measured as freedom from AF/AT relapse, appears to be lower, this appears to be driven by other comorbidities or features (left atrial dilation, and CHA_2DS_2VASc score), which are more frequent in this population, and by the higher frequency of persistent AF at the time of the procedure. Earlier referral of these individuals may prevent some of these adverse conditions from developing and may lead to higher success rates.

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Figure

Figure 1 – Freedom from atrial arrhythmia relapse for all AF patients

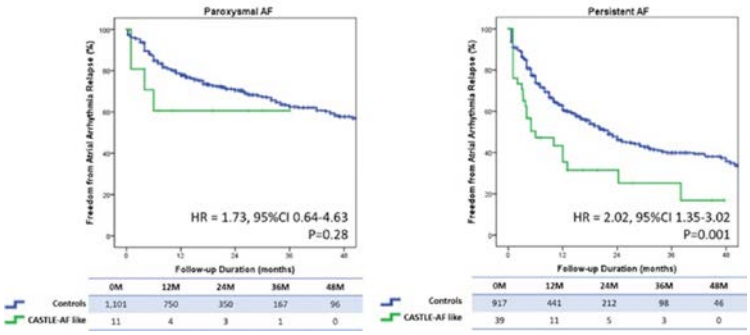

Table 1 - Baseline characteristics of the study population

Variable	Total sample (n=2,083)	CASTLE-AF like (n=51)	Controls (n=2,032)	Overall P
Age (years)	61.3±10.0	61.3±8.4	61.3±10.0	0.981
Female gender	28.3% (589)	13.7% (7)	28.6% (582)	<0.001
BMI (Kg/m^2)	27.9±8.0	29.4±4.8	27.8±8.1	0.165
AF duration (years)	5.0±5.5	3.8±3.5	5.1±5.5	0.142
Paroxysmal AF	53.8% (1,121)	21.6% (11)	54.6% (1,110)	<0.001
Persistent AF	46.2% (962)	78.4% (40)	45.4% (922)	
Mean n of Procedures	1.2±0.5	1.3±0.5	1.2±0.5	0.657
CHA_2DS_2-VASc	1.6±1.4	2.6±1.2	1.6±1.4	<0.001
Congestive heart failure	9.3% (194)	100% (51)	7.1% (145)	<0.001

Hypertension	45.5% (947)	54.9% (28)	45.2% (919)	0.171
Diabetes mellitus	9.2% (191)	13.7% (7)	9.1% (184)	0.254
Stroke or TIA	8.3% (173)	11.8% (6)	8.2% (167)	0.365
Vascular disease	10.1% (210)	23.5% (12)	9.7% (112)	0.001
Obstructive Sleep apnea	7.9% (164)	7.8% (4)	7.9% (160)	0.994
eGFR (ml/min)	75.1±18.4	69.4±21.7	75.1±18.4	0.212
Indexed LA volume (mL/m^2)	45.0±16.4	60.3±13.7	44.8±16.3	<0.001
LVEF (%)	62±9	31±4	62±8	<0.001
Cryoballoon ablation	35.3% (735)	31.4% (16)	35.4% (719)	0.554
Procedure Duration (min)	133±58	153±76	132±57	0.061
Fluoroscopy Duration (min)	24±13	21±14	24±13	0.155
CFAE ablation	17.2% (358)	29.4% (15)	16.9% (343)	0.019
Additional LA lines	30.2% (629)	49.0% (25)	29.7% (604)	0.003
Cavotricuspid isthmus ablation	26/1% (543)	21.6% (11)	26.2% (532)	0.459
Class I or III AADs on discharge	26.1% (540)	34.0% (17)	25.9% (523)	0.198

Legend: Values are given as mean ± SD or number and (%). AF - atrial fibrillation; CHA_2DS_2-VASc - cardiac failure or dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled] - vascular disease, age 65–74 years, sex category [female]; TIA - transitory ischemic attack; LA - left atrium; LVEF - left ventricular

ejection fraction; CFAE – complex fractioned atrial electrograms; AAD – anti-arrhythmic drugs; SD - standard deviation.

Table 2 – Efficacy and Safety Endpoints

	Variable	Total sample (n=2,083)	CASTLE-AF like (n=51)	Controls (n=2,032)	Overall P
Efficacy	**Pulmonary Vein Isolation**	99.0% (2,064)	100% (51)	99.1% (2,013)	0.488
	Relapse during blanking	25.2% (505)	44.0% (22)	24.7% (483)	0.002
	Relapse during first 12 months after ≥ 1 procedure	38.1% (787)	58.0% (29)	37.6% (758)	<0.001
Safety	**Per-procedural complications**	6.9% (144)	8.0% (4)	6.9% (140)	0.760
	Cardiac tamponade	0.8% (17)	0% (0)	0.8% (17)	0.512
	TIA	0.2% (4)	0.1% (3)	2.0% (1)	0.003
	Stroke	0.3% (6)	0% (0)	0.3% (6)	0.698
	Transient phrenic nerve palsy	1.5% (37)	2.0% (1)	1.5% (30)	0.778
	Major vascular complications	3.1% (64)	2.0% (1)	3.1% (63)	0.641
	Procedure-related death*	0.1% (1)	0% (0)	0.1% (1)	0.874
	Other complication	0.8% (21)	2.0% (1)	1.0% (20)	0.491
Other Complications	**Esophageal fistula**	0.1% (2)	0% (0)	0.1% (2)	0.823
	Gastroparesis	0.1% (2)	0% (0)	0.1% (2)	0.823

Esophageal ulcer	0.1% (1)	0% (0)	0.1% (1)	0.874
Non-Access related bleeds	0.3% (6)	0.3% (6)	0% (0)	0.698
Bradyarrhythmic complications	0.2% (5)	0% (0)	0.2% (5)	0.723
Anaphylaxis	0.1% (1)	0% (0)	0.1% (1)	0.874
Transient myocardial stunning	0.1% (1)	0% (0)	0.1% (1)	0.874
PV stenosis	0.1% (1)	0% (0)	0.1% (1)	0.874
Air embolism	0.1% (1)	0% (0)	0.1% (1)	0.874
Acute pulmonary edema	0.1% (1)	2.0% (1)	0% (0)	<0.001

Legend: Values are given as number and (%), and incidence and (95%CI). Legend: TIA – transient ischaemic attack; CI – confidence interval. * death occurred as a result of diffuse lung bleed without identifiable source.

Table 3 –Predictors of Post-blanking atrial arrhythmia relapse after an ablation procedure

Variable	**Univariate Cox Regression**			**Multivariate Cox Regression**		
	HR	**95%CI**	**P**	**HR**	**95%CI**	**P**
Age (per year)	1.01	1.00-1.02	0.026	-	-	-
Female gender	1.07	0.91-1.24	0.414	-	-	-
AF duration (per year)	**1.02**	**1.01-1.03**	**<0.001**	**1.02**	**1.01-1.04**	**<0.001**
Paroxysmal AF	**0.49**	**0.43-0.57**	**<0.001**	**0.55**	**0.46-0.65**	**<0.001**
Congestive heart failure	1.76	1.43-2.16	<0.001	-	-	-

Hypertension	1.22	1.06-1.40	0.006	-	-	-
Diabetes mellitus	1.42	1.14-1.77	0.002	-	-	-
Stroke or TIA	1.32	1.05-1.67	0.019	-	-	-
Vascular disease	1.32	1.06-1.64	0.012	-	-	-
Obstructive Sleep apnea	1.38	1.09-1.75	0.007	-	-	-
CHA_2DS_2-VASc	**1.13**	**1.08-1.19**	**<0.001**	**1.10**	**1.04-1.17**	**0.001**
BMI (per Kg/m^2)	**1.04**	**1.03-1.06**	**<0.001**	**1.04**	**1.02-1.06**	**<0.001**
eGFR (per ml/min)	1.00	0.99-1.00	0.149	-	-	-
Indexed LA volume (per mL/m^2)	**1.01**	**1.01-1.02**	**<0.001**	**1.01**	**1.00-1.01**	**0.003**
LVEF (per %)	0.99	0.98-0.99	0.002	-	-	-
LVEF ≤35%	2.39	1.65-3.47	<0.001	-	-	-
Cryoballoon ablation	0.94	0.81-1.08	0.374	-	-	-
CFAE Ablation	2.06	1.76-2.40	<0.001	-	-	-
Additional lines to the LA	2.06	1.79-2.37	<0.001	-	-	-
Cavotricuspid isthmus ablation	1.00	0.85-1.16	0.956	-	-	-

Legend: HR – hazard ratio; CI – confidence interval; AF - atrial fibrillation; TIA - transitory ischemic attack; CHA_2DS_2-VASc - cardiac failure or dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled] - vascular disease, age 65–74 years, sex category [female]; BMI - body mass index; LA - left atrium; LVEF - left ventricular ejection fraction; AAD – anti-arrhythmic drugs; CFAE – complex fractionated atrial electrograms.