Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success

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Aims
Long-term efficacy following cryoballoon (CB) ablation of atrial fibrillation (AF) remains unknown. This study describes 5 years follow-up results and predictors of success of CB ablation in patients with paroxysmal atrial fibrillation (PAF).

Methods and results
In total, 163 patients were enrolled with symptomatic, drug refractory PAF. Pulmonary vein isolation (PVI) with CB technique was performed. Primary endpoint of this consecutive single-centre study was first electrocardiogram-documented recurrence of AF, atrial tachycardia or atrial flutter (AFLAT). Five years success rate after single CB ablation was 53%. In 70% of the patients acute complete PVI was achieved with a single 28 mm balloon. The univariate predictors of AFLAT recurrence were (1) size of left atrium, with normalized left atrium (NLA) ≥ 10.25 [hazard ratios (HR) of 1.81, 95% confidence interval (CI): 1.28–2.56] when compared with NLA, 10.25 (35% vs. 53%, P = 0.0001) and (2) renal function, with impaired glomerular filtration rate (GFR), 80 ml/min (HR of 1.26, 95% CI: 1.02–1.57) when compared with GFR ≥ 80 ml/min (45% vs. 53%, P = 0.041). Normalized left atrium ≥ 10.25 was the sole independent predictor for outcome (HR 2.11; 95% CI: 1.34–3.31; P = 0.0001).

Conclusions
Sinus rhythm can be maintained in a substantial proportion of patients with PAF even 5 years after circumferential PVI using CB ablation. The rate of decline in freedom from AFLAT was highest within the first 12 months after the index procedure. The patients with enlarged left atrium and/or impaired renal function have lower outcome.

Keywords
Ablation • Arrhythmia • Cryoballoon • Catheter ablation • Tachyarrhythmias • Paroxysmal atrial fibrillation • Pulmonary vein isolation • Long-term follow-up

Introduction
Findings from several multicentre prospective clinical trials,¹–³ systematic reviews, and meta-analyses⁴–⁷ have consistently shown that catheter ablation of atrial fibrillation (AF) is more effective compared with antiarrhythmic drug (AAD) therapy for maintenance of sinus rhythm.⁸ Furthermore, successful catheter ablation of AF was associated with improved symptoms and quality of life.⁸–¹⁰

Cryoballoon (CB) ablation as an alternative technology for ablation of AF offers many potential advantages over radiofrequency (RF) energy.¹¹–¹⁷ Still, the best technique for pulmonary vein isolation (PVI) is unknown and long-term clinical outcomes are expected.⁸,¹⁸

The latest consensus on ablation of AF underlines the need for reporting long-term success, defined as ‘freedom from AF/AFL/AT recurrences following the 3 months blanking period through a minimum of 36 months follow-up from the date of the ablation procedure in the absence of Class I and III AAD therapy’, especially in ‘newer ablation technologies such as ‘balloon techniques’.¹⁹

Following the recommendations we present the long-term safety and efficacy outcomes of CB ablation of paroxysmal atrial fibrillation (PAF), additionally we discuss predictors of success.
Methods

Patients

Between 2005 and 2007, we enrolled 163 consecutive patients with symptomatic and drug refractory PAF. In all patients, AF was electrocardiogram (ECG) documented at least once within the last 3 months before ablation. Exclusion criteria were defined as advanced structural heart disease, including moderate-to-severe valvular stenosis or insufficiency; previous myocardial infarction, congenital heart disease, left ventricular ejection fraction <50%, coronary artery bypass graft surgery within the last 3 months, chronic obstructive pulmonary disease treated with beta-sympathomimetic drugs, severe respiratory insufficiency, known bleeding diathesis or intolerance of heparin or oral anticoagulation, attempted AF ablation in the past, left atrial (LA) thrombus, pregnancy, and severe co-morbidity.

Pre-ablation

Medical history was obtained during outpatient visits with a thorough review of the medical records including ECGs and Holter ECG recordings showing episodes of AF. The risk of ablation was discussed in detail and all the patients gave written informed consent before the procedure. The study was approved by the local institutional ethics committee. Three days before intervention, coumadin was stopped and replaced by subcutaneous low-molecular-weight heparin. All AADs were discontinued at least 3 days before ablation. Beta-blockers were allowed according to the protocol.

Assessment of left atrial size

The LA size was assessed at admission echocardiography by measurement of short and long axis in the apical four-chamber view.\(^\text{20}\) As a parameter, characterizing left atrial size, we used normalized left atrial area (NLA), previously described.\(^\text{21}\)

Intervention

All procedures were performed under conscious sedation and analgesia with appropriate doses of midazolam and piritramide. During the procedure, an infusion of heparin was maintained to achieve an activated clotting time >300 s. Measurements were performed every 30 min throughout the procedure.

A diagnostic quadrupolar catheter (Biosense Webster Inc., Diamond Bar, CA, USA) was positioned in the coronary sinus for the procedure. The risk of ablation was discussed in detail and all the patients gave written informed consent before the procedure. The study was approved by the local institutional ethics committee. Three days before intervention, coumadin was stopped and replaced by subcutaneous low-molecular-weight heparin. All AADs were discontinued at least 3 days before ablation. Beta-blockers were allowed according to the protocol.

Cryoballoon positioning and ablation was performed as previously described.\(^\text{22}\) Cryoballoon application time was between 240 and 360 s per freeze. During CB ablation of the antrum of the right-sided PVs, unaffected phrenic movement was monitored by either continuous phrenic nerve stimulation (n = 127) via a right atrial stimulation catheter or by continuous phrenic nerve movement (n = 36) monitoring of spontaneous breathing. Stimulation was maintained during the whole application of cryoenergy. An observation period after initial isolation to check for recurrence of PV conduction was 30 min. If a PV could not be reached with a CB or isolation could not be confirmed after five applications with any balloon, an 8 mm tip cryoablation catheter (FreezorMAX\(^\text{TM}\), MedtronicCryocath) was used to complete PVI signal controlled by Lasso\(^\text{TM}\) catheter.

Post-ablation management

After PVI intravenous heparin was continued to achieve a partial thromboplastin time of 60–80 s, followed by oral anticoagulation with Coumadin, targeting an international normalized ratio of 2.0 to 3.0 for at least 3 months. Before hospital discharge, all patients underwent transthoracic echocardiography to exclude pericardial effusion and chest X-ray in case of periprocedural phrenic nerve palsy (PNP) to document phrenic movement.

After ablation antiarrhythmic treatment was stopped. In case of AF relapse, AAD treatment was restarted during the blanking period.

Follow-up

Our strict follow-up protocol fulfills the latest recommendations.\(^\text{39}\) After discharge from the hospital, the patients were scheduled for quarterly follow-up visits. Late follow-up (>1 year post-intervention) was performed once a year. Seven-day Holter ECG recordings were obtained at each follow-up visit. Each patient, in case of any palpitations, was instructed to have ECG performed for confirming or excluding AF.

At least one magnetic resonance imaging (MRI) scan was performed to assess PV diameters and to exclude PV stenosis.

Statistical analysis

The study was designed as an observational cohort study. The endpoint was the first documented recurrence of AF, atrial tachycardia, and flutter (AFLAT) exceeding 30 s after a blanking period of 3 months.

Kaplan–Meier univariate analysis was used to estimate AFLAT-free survival and to define predictors among discrete variables. The association of continuous variables with outcome was analysed with the ROC-curve approach. Furthermore, variables being revealed in ROC-curve analysis were dichotomized at the optimal cut-off point by maximum sum of specificity and sensitivity. To avoid a potential model over fitting, only parameters revealed in univariate analysis to be significantly associated with outcome were included in the multivariate Cox regression model performed using the step-down procedure. Furthermore, among parameters univariately associated with outcome but being in strong relationship between them only variable showing strongest univariate association with outcome was included in multivariate analysis. Continuous data were described as median, lowest (inter-quartile range, IQR 25), and highest (IQR 75) quartiles. The discrete variables were given in number and percentage. The
impact of discrete variables on the outcome was described with positive and negative prediction accuracy and hazard ratio. The statistical analysis was performed using IBM SPSS Statistics v19.0.0. The differences were considered significant to be error probability $P < .05$.

**Results**

**Patients**
In total, 163 consecutive patients were treated with circumferential antral (28 mm CB) or ostial (23 mm CB) PVI using a CB catheter. The clinical characteristics are given in Table 1.

**Procedural characteristics**
The procedural characteristics are displayed in Table 2. In most of the patients (70%), PVI of all veins was achieved with a 28 mm balloon. A combination of both 23 and 28 mm cryoballoons was used in 33 (20%) patients. Owing to critical angulation in 13 patients (8%), occlusion and isolation of PV’s were impossible with CB and additional touch up ablations with FreezorMAX™ were necessary to achieve PVI (mostly right inferior pulmonary vein).

Atypical PV anatomy was found in 34 (21%) patients as following: additional PVs in 26 (16%) patients, common PV ostium in 6 (4%) patients, and both additional PVs and common ostium in 2 (1%) patients. Consequently, almost in all cases isolation of all PVs was achieved, using different balloon sizes and FreezorMax™, if needed. Eventually, using this strategy, 665 of 672 (98.9%) PVs were isolated.

**Complications**
Peri-procedural pericardial tamponades in two patients (1%) and pericardial effusion in three (2%) were treated with pericardial

### Table 1 Baseline characteristics ($n = 163$)

| Demographic variables                  | Median (IQR) | Male sex, $n$ (%) |
|----------------------------------------|--------------|-------------------|
| Median age at inclusion, years (IQR)   | 58 (50; 64)  | 101 (61.9)        |
| Medical history                         |              |                   |
| History of AF, years (IQR)             | 5.41 (2; 10) |                   |
| Structural heart disease               |              |                   |
| Ischaemic heart disease, $n$ (%)       | 12 (7.4)     |                   |
| Echocardiography                       |              |                   |
| Left ventricular ejection fraction, % (IQR) | 62 (57; 65) |                   |
| Left atrium short axis diameter in four-chamber view (mm) | 38 (36; 40) |                   |
| Left atrium long axis diameter in four-chamber view (mm) | 52 (48; 55) |                   |
| Left atrium area, cm² (IQR)            | 19.68 (17.4; 22.5) |                   |
| NLA (IQR)                              | 9.67 (8.6; 11) |                   |
| Risk factors for thromboembolism:      |              |                   |
| Hypertension, $n$ (%)                   | 101 (62)     |                   |
| Diabetes, $n$ (%)                       | 6 (3.7)      |                   |
| BMI, kg/m² (IQR)                       | 27.17 (24.6; 30) |                   |
| BSA, m² (IQR)                          | 2.07 (1.9; 2.2) |                   |
| Medical treatment at inclusion          |              |                   |
| Failed class I antiarrhythmic drugs, $n$ (%) | 95 (58.3) |                   |
| Failed class III antiarrhythmic drugs, $n$ (%) | 47 (28.8) |                   |
| Failed amiodarone therapy, $n$ (%)      | 25 (15.3)    |                   |
| Laboratory data                        |              |                   |
| Creatinine, mg/dL (IQR)                | 0.86 (78; 99) |                   |
| eGFR, mL/min (IQR)                     | 88.45 (78; 99) |                   |

BMI, body mass index; BSA, body surface area.

### Table 2 Procedural characteristics ($n = 163$)

| Basic data                      | Fluoroscopy time, minutes (IQR) | 50.2 (34.9; 65) |
|---------------------------------|---------------------------------|-----------------|
| Intra-procedural cardioversion, $n$ (%) | 11 (6.8)          |                   |
| Type of cryoballoon and/or FreezorMAX™ used, $n$ (%) | 17 (10.4)          |                   |
| Patients treated with Cryoballoon 23 mm | 113 (69.3)       |                   |
| Patients treated with Cryoballoon 28 mm | 33 (20.2)         |                   |
| Cumulative time of cryoballoon applications, minutes (IQR) | 12 (10; 17) |                   |
| Cumulative time of cryoballoon applications per patient, minutes (IQR) | 12 (10; 17) |                   |

RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein.
PVI with CB. In this prospective study, we included 163 patients who underwent CB ablation procedure in patients with PAF.

Follow-up
In this prospective study, we included 163 patients who underwent PVI with CB.

Twenty eight patients (17%) needed AAD after the blanking period as a result of AF relapse. Nevertheless, only six of them remained with sinus rhythm. In the other 22 cases, AAD were not efficient.

The 5 years success rate after single CB ablation procedure was 53% (Figure 1). Among 77 patients reached endpoints, 10 patients had LAT.

The cut-off values of 10.25 for NLA and of 80 ml/min for glomerular filtration rate (GFR) were calculated from ROC-curve analysis. After a single CB procedure, the univariate predictors of AFLAT recurrence were (Table 3):

- size of LA, with NLA ≥ 10.25 associated with HR of 1.81, 95% CI: 1.28–2.56, when compared with NLA < 10.25 (35% vs. 64%, P = 0.0001; Figure 2); among all parameters describing size of LA (i.e. LA short- and long-axis diameter in four chamber view, left atrium area, NLA) NLA showed to be the strongest predictor and was only used in further analysis
- renal function, with GFR < 80 ml/min associated with HR of 1.26, 95% CI: 1.02–1.57, when compared with GFR ≥ 80 ml/min (45% vs. 56%, P = 0.041; Figure 3).

In multivariate Cox-regression model we found NLA ≥ 10.25 to be the sole independent predictor for outcome (HR 2.11; 95% CI: 1.34–3.31; P = 0.0001).

Discussion
The emerging need for reporting long-term success of catheter ablation for AF with novel technologies has been emphasized in the latest expert consensus statement.19 The combination of a theoretically safer cryothermal energy source with the ease of use associated with balloon-based catheter ablation systems have positioned CB catheter technique at the forefront of alternative technologies. Herein, we report the longest follow-up to date of CB ablation of AF. After a single procedure, circumferential PVI with the CB technique is associated with maintenance of sinus rhythm in 53% of patients with PAF during long-term follow-up. As the sole independent predictor of outcome, size of left atrium could be identified.

Efficacy: comparison with previous studies
Acute procedural success, i.e. isolation of 98.9% of targeted veins, is comparable with reported by others.23,24 The 1 year success rate in our study is consistent with prior reports with a 3 months blanking period of ~70% at 1 year for PAF.22,25–28 Over time, we observed a gradual decrease in arrhythmia-free survival. We noted that the rate of decline in freedom from AFLAT stabilized after the initial 12 months, although it did not entirely plateau.

Studies with longer follow-up after CB ablation have not been published so far. We are able to compare our long-term results with outcomes after RF procedures. Gaita et al.29 followed 204 patients for 3 years and reported freedom from AFLAT after a single procedure in 29% of patients with PAF, treated with PVI only and in 53% of PAF, treated with PVI plus left linear lesions, respectively. In 4 years follow-up of a group of 110 patients with PAF, drainage, both resolved without the need for surgery. We observed five patients (2.5%) with groin haematoma, no patients with retroperitoneal bleeding, two patients (1%) with femoral arterial pseudoaneurysm, and one patient (0.5%) with femoral arterio-venous fistula. All these cases with vascular complications were managed conservatively.

In 18 (11%) patients, right PNP was observed during cryoablation of the right superior pulmonary vein. PNP was resolved in 5 of the 18 cases during the procedure. An early termination of cryoenergy application during right phrenic pacing did not prevent the subsequent occurrence of PNP. In all patients, full recovery of right phrenic function was observed during follow-up of <14 months. We observed higher occurrence of PNP in patients treated with the 23 mm balloon as compared with 28 mm: 12 vs. 6 patients, respectively.

One patient developed transient ischaemic attack, but he was discharged without any persisting neurological defect. Transient air embolism occurred in two patients. Both of them imposed with ST segment elevation in the inferior leads and typical chest pain for some seconds. The clinical symptoms and ECG changes self-resolved without further consequences.

The median (IQR 25/75) diameters of the left superior pulmonary vein, left inferior pulmonary vein, right superior pulmonary vein, and right inferior pulmonary vein were 19 (17–22), 17 (15–18), 21 (17–22), and 19 (17–21) mm in the large axis of PV. During follow-up, PV measurements of 151 patients were available. No stenosis or diameter reduction was observed.

No fatal complications like atrio-esophageal fistula, stroke, or death occurred.

Figure 1 Five years outcome in patients with paroxysmal atrial fibrillation – Kaplan–Meier event-free survival curve after a single CB ablation procedure in patients with PAF.

Number at risk: 163 113 101 98 94 91

Table 3

| dv                  | Total | Events | Censored |
|---------------------|-------|--------|----------|
| N                   | 163   | 77     | 86       |
| %                   |       | 47.1%  | 52.9%    |

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Table 3 Predictors of outcome after single cryoballoon ablation procedure

(a) Continuous variables (ROC analysis)

| Predictor                                      | AUC  | 95% Confidence interval | P       |
|------------------------------------------------|------|-------------------------|---------|
| History of AF                                  | 0.53 | 0.42 0.63               | 0.592   |
| Age                                            | 0.50 | 0.40 0.61               | 0.948   |
| BMI                                            | 0.52 | 0.42 0.62               | 0.711   |
| BSA                                            | 0.50 | 0.40 0.61               | 0.971   |
| Left atrium short axis diameter in four-chamber view | 0.66 | 0.56 0.76 | 0.003 |
| Left atrium long axis diameter in four-chamber view | 0.64 | 0.55 0.74 | 0.006 |
| Left atrium area                               | 0.68 | 0.59 0.78               | 0.001   |
| NLA                                            | 0.69 | 0.60 0.79               | 0.000   |
| Creatinine                                     | 0.55 | 0.49 0.64               | 0.118   |
| Glomerular filtration rate                     | 0.56 | 0.51 0.65               | 0.041   |
| Left ventricle ejection fraction               | 0.53 | 0.44 0.62               | 0.469   |

(b) Discrete variables

| Predictor                                      | Hazard ratio | 95% Confidence interval | P       |
|------------------------------------------------|--------------|-------------------------|---------|
| Gender                                         | 0.96         | 0.78 1.18               | 0.707   |
| Hypertension                                   | 1.36         | 0.93 1.98               | 0.116   |
| Diabetes mellitus                              | 1.06         | 0.13 8.55               | 0.956   |
| Ischaemic heart disease                        | 0.87         | 0.52 1.46               | 0.688   |
| NLA > 10.25                                    | 1.81         | 1.28 2.56               | 0.001   |
| GFR > 80 mL/min                                 | 1.26         | 1.03 1.53               | 0.041   |
| Common ostium (n = 10)                         | 0.53         | 1.06 2.12               | 0.864   |
| Abnormal anatomy (Akz PV and common ostium), n = 34 patients | 1.00         | 0.44 2.26               | 0.991   |

(c) Multivariate Cox regression model

| Predictor                                      | Hazard ratio | 95% Confidence interval | P       |
|------------------------------------------------|--------------|-------------------------|---------|
| NLA > 10.25                                    | 2.11         | 1.34 3.31               | 0.0001  |
| GFR < 80 mL/min                                 | 1.76         | 0.83 2.11               | 0.247   |

Figure 2: Size of left atrium and 5 years outcome – Kaplan–Meier event-free survival curve after a single CB ablation procedure in patients with PAF. The cut-off value of 10.25 for NLA was calculated from the ROC-curve analysis.

Figure 3: Renal function and 5 years outcome – Kaplan–Meier event-free survival curve after a single CB ablation procedure in patients with PAF. The cut-off value of 80 mL/min for GFR was calculated from the ROC-curve analysis.
Predictors of very late recurrence after cryoballoon ablation of atrial fibrillation

Many factors have been proposed as predictors of lower outcome after PVI.19 The most consistent predictor of very late recurrence was type of AF followed by LA size.19 We studied only patients with PAF and found that the independent predictors of very late recurrence of PAF after single CB ablation was size of LA, while impaired renal function was associated with the outcome in univariate analysis only. We did not study sleep apnoea, and left ventricular ejection fraction below 50% was defined as exclusion criteria in our protocol.

The identified predictors are associated with deep remodelling in LA structure. Pulmonary vein antrum isolation, by eliminating focal triggers, may reverse electrical remodelling but it cannot be expected to stop or reverse structural remodelling. Firstly, it is possible that some late recurrences of AF result from non-PV arrhythmogenic foci that were not targeted during CB procedure. Secondly, it is possible that ongoing electrical and structural remodelling of the atria leads to progressive atrial electrical instability.19 This raises a question for early intervention13 in PAF and possible role of ‘upstream therapy’ in slowing the progression of AF after PVI.8,20

None of the procedure-related factors were correlated with the clinical outcome during long-term follow-up.

Safety

The most frequent peri-procedural complication was transient PNP, observed in 11% of cases, i.e. higher than reported nowadays.24 despite preventive high-output phrenic nerve pacing in a superior vena cava during ablation of right-sided PVs. In none of the patients PNP persisted beyond 14 months after procedure. In our opinion, the complication rate was highly related to ‘early experience’ of the operators’ learning curves and initially available catheters and sheaths. With recently developed techniques and mapping catheters the rate of PNP’s seems to be halved.24 However, PNP was one of the CB-related complications to be learned at the beginning of PVI with CB.

In our study, no stenosis or diameter reduction was observed. This observation is consistent with others.22–26,28 However, Packer et al.27 described a relevant rate of PV stenosis, even with the cryoballoon technique. This observation might be explained with a mechanical trauma by inflation of the balloon inside the PV, which we have strictly avoided.

All other observed complications and rate of complications are comparable with PVI with the RF technique.

No late or unexpected complications were detected at 5 year follow-up.

Study limitations

This study has the following potential limitations: (1) this is a single-centre, non-randomized, prospective report with the inherent limitations of this study design. However, there was no selection bias for study inclusion since all consecutive patients undergoing CB ablation for paroxysmal AF at our institution were included for analysis. (2) The results reported in our study have to be seen in the light of the early stage in the development of CB technology: without a steerable sheath (up to the end of 2005). Achieve™ catheter, or Arctic Front Advance™ catheter. The long fluoroscopy times do not represent the actual fluoroscopy times today and might be a result of adoption of a new technology.

(3) The results of this study are further limited by a potential variability of operator experiences.23 (4) According to the latest Consensus Report,8 the follow-up results in our study are presented without consideration of recurrences during the blanking period. This could lead to an overestimation of a true success rate. (5) The latest data,34,35 unknown at the time of our study, show that intermittent rhythm monitoring is significantly inferior to continuous monitoring with implanted devices. Our follow-up was based on clinical evaluation and 7 days Holter ECG recordings. Although the vast majority of patients presented with sustained forms of AFLAT, some asymptomatic non-sustained episodes may have been missed. (6) No patients developed an atrio-esophageal fistula. Since the estimated incidence of atrio-oesophageal fistula after RF ablation of AF has been reported to be <0.25%,8 the number of patients in our study is too small to definitely exclude this possible complication following CB ablation. (7) MRI was not routinely performed after 3 years clinical follow-up to detect asymptomatic PV stenosis; however, patients were specifically questioned regarding clinical symptoms, and imaging was performed to rule out a suspected diagnosis.

Clinical implications

Clinical implications of these results are substantial with regard to the care of patients with AF and after CB ablation. Firstly, empirical long-term follow-up data should be presented to patients to inform about the decision-making process and provide reasonable expectations. Patients at early stages of PAF and NLA ≤ 10.25 are first-line candidates for CB procedures. Secondly, ongoing surveillance is warranted, even if CB ablation was deemed initially successful. Incidence of late recurrence may be related to the extent of ECG monitoring and earlier recurrence may be missed in selected patients with no or minimal symptoms. Clinical evaluation should be performed on a regular basis and any complaint of ‘heart palpitations’34 or suspected silent AF should be addressed. Thirdly, attention to control patient-related AF risk factors remains an integral part of AF management after the ablation procedure.19

Fiala et al.30 reported that 56% of them were free from arrhythmia after a single RF procedure, without AAD. Similar results were presented by Bertaglia et al.,31 in PAF and NPAF patients after PVI plus mitral isthmus lesion, with 58% of patients free from AFLAT after 4 years. Still almost 19% of those patients were on continuous treatment with AADs. Ouyang et al.,32 who used 3-D electro-anatomical mapping, described the single-procedure success rate of 46.6% in 5 years follow-up. Our data show that freedom from AFLAT recurrence after a single CB ablation without AAD was 53% for patients with PAF during 5 years follow-up. We demonstrate better,29,30,32 or at least not inferior,31 CB outcome in patients with PAF, than recently published RF results. These results must be confirmed in randomized trials.
Conclusions

Sinus rhythm can be maintained in a substantial proportion of patients with PAF even 5 years after circumferential PVI using CB ablation. The rate of decline in freedom from AFLAT was highest within the first 12 months after the index procedure. The patients with enlarged left atrium and/or impaired renal function have lower outcome.

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