

**Long Term outcomes of percutaneous atrial fibrillation ablation in patients with continuous monitoring**

**Running Title: AF ablation outcomes using continuous monitoring**

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**Conflicts of Interest**

None

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## Abstract

### Introduction

There is limited data using continuous monitoring to assess outcomes of atrial fibrillation (AF) ablation. This study assessed long-term outcomes of AF ablation in patients with implantable cardiac devices.

### Methods:

207 patients (mean age  $68.1 \pm 9.5$ , 50.3% men) undergoing ablation for symptomatic AF were followed up for a mean period of  $924.5 \pm 636.7$  days. Techniques included The Pulmonary Vein Ablation Catheter (PVAC) (59.4%), cryoablation (17.4%), point by point (14.0%) and The Novel Irrigated Multipolar Radiofrequency Ablation Catheter (nMARQ) (9.2%).

### Results

130 (62.8%) patients had paroxysmal AF (PAF) and 77 (37.2%) persistent AF. First ablation and repeat ablation reduced AF burden significantly (relative risk 0.91, [95% CI 0.89 to 0.94];  $P < 0.0001$  and 0.90, [95% CI, 0.86–0.94];  $P < 0.0001$ ).

Median AF burden in PAF patients reduced from 1.05% (interquartile range [IQR], 0.1%-8.70%) to 0.10% ([IQR], 0%-2.28%) at one year and this was maintained out to four-years. Persistent AF burden reduced from 99.9% ([IQR], 51.53%-100%) to 0.30% ([IQR], 0%-77.25%) at one year increasing to 87.3% ([IQR], 4.25%-100%) after four

years. If a second ablation was required, point-by-point ablation achieved greater reduction in AF burden (relative risk, 0.77 [95% CI, 0.65–0.91];  $P < 0.01$ ).

## **Conclusion**

Ablation reduces AF burden both acutely and in the long-term. If a second ablation was required the point-by-point technique achieved greater reductions in AF burden than “single-shot” technologies. Persistent AF burden increased to near pre ablation levels by year 4 suggesting a different mechanism from PAF patients where this increase did not occur.

## **Key words**

Atrial fibrillation, ablation, cardiac implantable device, continuous monitoring

## **Introduction**

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of 2% in the general population.(1) Its prevalence is increasing year on year and it is associated with significant morbidity and mortality.(1,2) Over the past two decades ablation has become the preferred treatment option for patients with drug refractory AF.(3)

Most clinical studies reporting outcomes from AF ablation are limited to only one-year outcome. In addition, the majority rely on intermittent monitoring such as three to six monthly Holters to objectively determine outcomes which significantly overestimates the true success rate of catheter ablation. (4,5) Implantable devices such as pacemakers, implantable cardiac defibrillators and loop recorders are able to overcome these limitations and reflect the actual arrhythmia success rate of catheter ablation. (6)

The aim of this study is to evaluate the long-term success of percutaneous AF ablation in patients with continuous beat-to-beat monitoring.

## **Methods**

### **Study Design and population**

The study population consisted of 207 patients from The Eastbourne District General Hospital AF Ablation Registry. All patients with an implantable cardiac device (implantable cardiac defibrillator, cardiac resynchronisation therapy device, dual-chamber pacemaker or implantable loop recorder) with symptomatic paroxysmal or persistent AF despite pharmacological therapy, who had undergone ablation (radiofrequency or cryoballoon) in our institution (Eastbourne District General Hospital) between 2005 and 2018 were reviewed (Figure 1). All patients gave written informed consent before the procedure. The study was approved by the local ethics board and complies with the Declaration of Helsinki.

### **Percutaneous Ablation**

All procedures were performed under conscious sedation. All patients were therapeutically anticoagulated. This was continued during and after the procedure without interruption. No oesophageal temperature monitoring was used. In all cases a decapolar catheter was placed in the coronary sinus. After transseptal puncture a bolus of unfractionated Heparin (70 units per kg of body weight) was injected intravenously. Thereafter, unfractionated Heparin was administered to maintain the activated clotting time (ACT) above 300 seconds whilst the left atrium (LA) was instrumented. Immediately following removal of the left atrial catheter, 50 mg of Protamine was injected intravenously and sheaths were removed and haemostasis was achieved with manual pressure.

### **Pulmonary vein ablation catheter (PVAC)**

After venous access was achieved, a deflectable trans-septal sheath was used to perform a single trans-septal puncture. Pulmonary vein (PV) anatomy was determined fluoroscopically using the PVAC catheter and guide wire, but without routine left atrial angiography. The PVAC catheter was used to perform PV ablation using the GENius generator Version 15.1. PV entrance and exit block was tested using the PVAC catheter. Inducibility of arrhythmia was tested with incremental atrial pacing and isoprenaline infusion. PV isolation was rechecked during isoprenaline infusion.

### **The Novel Irrigated Multipolar Radiofrequency Ablation Catheter (nMARQ)**

nMARQ irrigated ablation was performed in a similar manner to PVAC ablation. Differences included use of a CARTO® geometry created using the nMARQ catheter. The nMARQ ablation system displayed live data from Tissue Connect, an impedance-based tissue contact algorithm, on to the CARTO® generated geometry. All nMARQ ablations were performed prior to changes in energy settings and algorithms recommended by the manufacturers. The maximum bipolar power delivered was 25W. Otherwise, all other aspects of the procedure were similar to the PVAC ablation.

### **Point-by-point ablation**

Pulmonary vein isolation in this group was performed using an irrigated tip radiofrequency ablation catheter (Navistar Thermocool®, Biosense Webster, CA, USA) guided by CARTO® 3 electroanatomical mapping and fluoroscopy. Two transseptal punctures were performed to give access to the left atrium for the irrigated

tip ablation catheter and circular mapping catheter (Lasso 2515 Variable, Biosense-Webster). Wide area circumferential ablation was performed using irrigated radiofrequency ablation at a power of 25W to 35W. The procedure was stopped when all pulmonary veins had been electrically isolated as demonstrated by pulmonary vein entrance and exit block.

### **Cryoablation**

LA access was achieved directly using a steerable 15F sheath (FlexCath Advance, Medtronic, Minneapolis, MN, USA) or using the modified Brockenbrough technique and a 8.5F transseptal sheath (SL1, St Jude Medical, St Paul, MN, USA) which was then exchanged over the wire for the 15F Flexcath Advance.

An Amplatz Super Stiff Guidewire (Boston Scientific Corporation, Boston, MA, USA) was used in the inner lumen of the FlexCath and was advanced into each pulmonary vein. A 28-mm Arctic Front Advance cryoballoon (Medtronic, Minneapolis, MN, USA) was positioned in each pulmonary vein ostium and inflated. Complete vessel occlusion was demonstrated by contrast injection with no reflux of contrast into the LA. Each ablation was performed with a single 3-minute freeze for each vein.

A second freeze using a different balloon angulation was performed if there was contrast backflow into the LA or a temperature of -40C was not reached within 60 seconds.

Prior to ablation of right-sided pulmonary veins, the decapolar catheter was placed in the right subclavian vein or superior vena cava to pace the right phrenic nerve (10–20

mA at 1.0–2.0 msec pulse width at a cycle length of 1000 msec). Ablation was immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction.

### **Follow up and device interrogation**

Patients were followed up three months post AF ablation and thereafter on an annual basis. Anti-arrhythmic medication was continued for at least three months post intervention and stopped at three months. Continuation and reintroduction of anti-arrhythmic medication in patients with recurrence was dependent upon physician direction and discretion.

In patients with pacemakers or defibrillators, all stored high atrial rate EGM's (> 180 bpm) were analysed, and the AF burden calculated by the device algorithm was obtained. In patients with implantable loop recorders episodes of AF lasting more than 2 minutes were analysed and the AF burden obtained for each duration of follow up.

### **Definitions and Outcomes**

AF was classified as paroxysmal if episodes lasted less than seven days or persistent if lasting more than seven days as per ESC guidelines.(2)

The primary efficacy outcome measure was AF burden defined as the overall percentage of AF relative to the duration of the monitoring period. Secondary outcomes included examining the effect of ablation on AF burden over time, examining the impact of co-morbidities on AF burden post ablation and examining the effect of

ablation technique and subsequent repeat ablation on AF burden.

### **Statistical analysis**

Continuous variables are presented as mean +/- SD or median (IQR), as appropriate. Categorical variables are presented as absolute number and percentage. Continuous variables between groups were analysed using Student's t-test or Mann-Whitney U test. Categorical variables between groups were analysed using the chi square test.

Generalised mixed models were used to examine the effects of ablation on  $\log_e$  AF burden (included in the model as  $\log_e(1+\text{AF burden})$ ). Models were parameterised to examine the effects of first, second or third ablation, and type of ablation, through fitting main effects and interactions. Random intercept terms were included for patients, and the denominator degrees of freedom were specified on the basis of the number of patients. Fitted models were compared using Akaike's Information Criterion. Time to atrial arrhythmia (> 30 seconds) was plotted using the Kaplan-Meier estimator. The log-rank test was used to compare freedom from arrhythmia between groups. Models were fitted in Proc Glimmix (SAS, SAS Institute, Cary NC) version 9.4.

## Results

### Baseline characteristics

207 patients with a cardiac implantable device underwent ablation for AF. 123 (59.4%) patients underwent PVAC ablation, 36 (17.4%) cryoablation, 29 (14.0%) point-by-point, 19 (9.2%) nMARQ ablation. Of the 207 patients, 130 (62.8%) had paroxysmal AF and 77 (37.2%) had persistent AF at the time of index procedure.

77 patients with PAF underwent PVAC ablation, 10 PAF patients underwent cryoablation, 27 PAF patients underwent point by point ablation and 16 PAF patients underwent nMARQ ablation. 46 patients with persistent AF underwent PVAC ablation, 26 persistent AF patients underwent cryoablation, 2 persistent AF patients underwent point by point ablation and 3 persistent AF patients underwent nMARQ ablation.

The mean age of patients was  $68.1 \pm 9.5$  and 104 (50.3) were male (Table 1). Patients who had persistent AF were significantly older ( $71.4 \pm 7.5$  vs  $66.1 \pm 10.0$ ,  $p < 0.001$ ), were significantly more likely to have congestive cardiac failure (7 (10.1%) vs 2 (1.5),  $p$  value = 0.009) and had a significantly higher HATCH score ( $1.96 \pm 1.5$  vs  $1.43 \pm 1.3$ ,  $p = 0.009$ ).

The mean follow up for the whole group was  $924.5 \pm 636.7$  days and the median follow up was 823 days (interquartile range [IQR], 433-1181).

## Clinical outcomes

At baseline the median AF burden in PAF patients was 1.05% ([IQR], 0.1%-8.70%). This reduced to 0.10% ([IQR], 0%-2.28%) at one year, 0.05 % ([IQR], 0%-1.20%) at two years, 0.10% [IQR], 0%-4.50%) at three years and 0.10 % ([IQR], 0%-2.00%) at four years follow up. (Figure 2)

At baseline the median AF burden in persistent AF patients was 99.9% ([IQR], 51.53%-100%). This reduced to 0.30% ([IQR], 0%-77.25%) at one year and then increased to 14% ([IQR], 0%-98.43%) at two years, 59.7% ([IQR], 1%-100%) at three years and 87.3% ([IQR], 4.25%-100%) at four years follow up. (Figure 3)

During overall study follow up, there was a significant 1.4% annual increase in AF burden in the overall population (95% CI 0.4% to 2.4%; p=0.008).

A documented recurrence of an atrial arrhythmia lasting longer than 30 seconds occurred in 163 of 207 (78.7%) patients. Arrhythmia recurrence occurred in 96 of 130 (73.8%) PAF and 67 of 77 (87.0%) persistent AF patients (Figure 4). There was no significant difference in arrhythmia recurrence between the two groups. (p =0.383)

During the follow up period, 23 (11.1%) patients were started on a class 1 or 3 antiarrhythmic medication. 9 (7.8%) PVAC, 7 (35.0%) nMARQ, 3 (10.3%) point-by-point and 4 (11.1%) cryoablation patients were restarted an antiarrhythmic drug during the follow up period.

### **Effect of repeat ablation on AF burden**

During the study period 49 (23.7%) patients underwent a second ablation; 22 PVAC, 14 nMARQ, 10 point by point and 3 surgical ablation. 8 patients underwent a third ablation; 3 nMARQ, 2 point-by-point and 3 PVAC. 7 patients underwent a third ablation; 4 nMARQ, 2 point-by-point and 1 PVAC (Table 2). After first ablation there was a significant decrease in AF burden (0.91[95% CI 0.87 to 0.94],  $P < 0.0001$ ). After second ablation, there was also a significant decrease in AF burden over time (0.90 [95% CI 0.86 to 0.94],  $P < 0.0001$ ). After the third ablation, there was a non-significant decrease in AF burden (0.96 [95% CI 0.83 to 1.10],  $P = 0.55$ ). (Figure 5)

### **Effect of ablation technique on AF burden**

At first ablation, cryoablation had the greatest effect upon AF burden (0.70 [95% CI 0.64 to 0.75],  $P < 0.0001$ ) when compared to PVAC (0.94 [95% CI 0.90 to 0.98],  $P = 0.005$ ), nMARQ (0.93 [95% CI 0.87 to 0.99],  $P = 0.25$ ) and point by point (0.92 [95% CI 0.86 to 0.98],  $P = 0.14$ ). If a second ablation was required, the point-by-point technique had the greatest significant effect on decreasing AF burden (0.77 [95% CI, 0.65–0.91];  $P < 0.01$ ). At second ablation nMARQ had the least effect on AF burden (0.93 [95% CI, 0.84–1.03],  $p = 0.62$ ).

### **Effect of Comorbidities**

The presence of heart failure and stroke were the only co-morbidities associated with a significantly increased AF burden post ablation (relative risk, 1.26 [95% CI, 1.01–

1.42],  $p = 0.002$  and 1.40 [95% CI, 1.17–1.62,  $p = 0.001$ ]). (Figure 6)

## Discussion

The major study findings were

- 1) Median AF burden decreased in PAF patients up to four year follow up.  
Persistent AF patients also had a decrease in AF burden however after two years AF burden increased suggesting a different mechanism for this arrhythmia.
- 2) Point by point ablation resulted in the greatest reduction in AF burden after second ablation
- 3) The presence of heart failure and previous stroke were associated with worse outcomes post catheter ablation

In this study the majority of patients had a arrhythmia recurrence. There is a greater recurrence rate reported in this study as the majority of previous studies of AF catheter ablation report outcomes based on discontinuous monitoring such as 12 lead electrocardiograms, short term patch monitoring or Holter monitors which may lead to an overestimation of clinical and technical success.(7) A reduction in AF burden rather than recurrence of atrial arrhythmia is a better indicator of improved clinical outcomes in these patients. Using continuous monitoring, patients with paroxysmal AF were more likely to have a lower AF burden than patients with persistent AF which is to be expected given that greater left atrial dilatation, fibrosis and arrhythmogenic substrate is commonly seen in patients with persistent AF. (8)

Median AF burden in PAF patients at baseline was 1.05%, which is similar to previous studies (9,10) and showed a large decrease following ablation that persisted during long-term follow up. This contrasts with persistent AF patients who also had a large decrease in AF burden after one year but suffered a regular increase in AF burden thereafter. There was an overall significant increase in AF burden over time in all patients but this was largely driven by the persistent AF cohort. It is highly suggestive that the two types of AF have differing mechanisms. Paroxysmal AF seems suppressible by pulmonary vein isolation techniques implying a pulmonary vein trigger as the aetiology, however the increase in AF burden from two years in persistent AF patients suggests that non pulmonary vein substrates (which are less susceptible to ablation techniques) are the mechanistic cause.(11)

The outcome of ablation in patients with persistent AF has been shown to be consistently poorer than that of PAF patients.(12) This may be related to the presence of non-pulmonary vein substrate or the lack of durable lesions when ablating.(12) It may be the case that newer advanced ablation technologies or techniques may improve the outcomes in these patients. Techniques such as using ablation index guided ablation or vein of Marshall ethanol infusion may improve the long-term results seen in this cohort. (13,14)

During the follow up period the introduction of antiarrhythmic medication and management of AF episodes were dependent upon physician discretion. Overall only a small proportion of patients in the study were restarted on an antiarrhythmic drug, thus the effect of antiarrhythmic therapy upon AF burden is likely to be low. A higher

proportion of nMARQ patients restarted an antiarrhythmic drug during the follow up period which should be taken into account when comparing the different technologies. Additionally, the increased AF burden seen beyond three years in the persistent AF group may be related to the acceptance of a rate control strategy in the majority of these patients, given the higher average age of this cohort of patients.

Very few studies have used continuous monitoring to report long-term outcomes post catheter ablation. Martinek et al were the first to report in a small study of 14 patients significant reductions in AF burden using continuous monitoring post ablation.(15) More recently Choudhury et al and Wechselberger et al also reported significant reductions in AF burden using cryoablation and radiofrequency ablation respectively. (16,17) Similarly to other trials, we also report significant reductions in AF burden post ablation however, whereas previous studies have reported and analysed absolute reductions in AF burden we also assessed relative change in AF burden which may be more clinically relevant.

Previous investigations have shown that 20-40% of patients undergo a repeat ablation. (18) In this study we also report a similar number of patients undergoing repeat ablation. We also report significant reductions in AF burden after the second ablation. Only a small proportion of patients underwent a 3<sup>rd</sup> ablation (8 of 207 patients) and there was a non-significant decrease in AF burden in this group. The non-significant reduction may be due to the fact these patients likely had increased non pulmonary vein substrate for atrial fibrillation. However the small sample size of this group precludes any firm conclusions.

The majority of first ablations in this study were performed using “single shot” technologies. There was a similar decline in AF burden using the PVAC catheter, nMARQ and point-by point-technique, however there was a greater AF burden reduction using cryoablation. The majority of patients undergoing cryoablation had persistent AF thus this reduction would be expected.

At second ablation, only point-by-point ablation resulted in significant reductions in AF burden. This may be due to the more extensive ablation these patients underwent including additional linear ablation and/or complex fractionated electrogram ablation in addition to pulmonary vein re-isolation whereas the majority of patients undergoing second ablation with “one-shot” technologies only had pulmonary vein re-isolation.

The presence of heart failure resulted in increased residual AF burden post catheter ablation in this study. This may appear to be in contrast to the recently published CASTLE-AF study, which showed a reduction in AF burden at baseline from  $51\% \pm 47\%$  to  $27\% \pm 42\%$  at 60 months. (19) The differing results seen may be due to the different methodologies used in assessing differences in AF burden. The CASTLE AF study reports differences in AF burden covering the period from the last follow-up to the previous regular follow up whereas in this study we assessed relative change in AF burden over the whole time period from 3 months after ablation to final follow-up. (19) In addition our investigation did not include a control group and simply compares heart failure patients undergoing AF ablation to the population undergoing AF ablation without this co morbidity. Thus the AF burden in patients with heart failure may still have been decreased to a greater extent than those patients with heart failure who were treated medically.

## **Study Limitations**

Half the patients in this cohort had an implantable loop recorder inserted (Medtronic Reveal XT) only capable of detecting AF episodes of more than 2 minutes duration. Although some short duration AF episodes may have been missed, in the long term this is unlikely to have affected the AF burden significantly as it is rare for patients to have multiple short duration AF recurrences that would be undetected by this device. (17)

It is possible that other factors and treatments including weight loss, improved aerobic fitness levels, hypertension control, management of sleep disordered breathing and anti-arrhythmic medications may have affected and contributed to the reduction in AF burden seen in the study.

Additionally patients were not randomised to different treatment options in this study thus there may be selection bias, which may account for some of the differences observed.

## **Conclusions**

Whilst the vast majority of studies of AF ablation outcomes quote either clinical or very intermittent ECG monitored endpoints, this study with long-term beat-to-beat continuous monitoring shows catheter ablation results in significant reductions in AF burden over the long-term in PAF patients. There was a significant year on year increase in AF burden largely driven by the persistent AF cohort whose AF burden

deteriorated to near baseline levels in the long term, contrasting with the PAF group which showed a prolonged decrease in AF burden following ablation. This may confirm a different underlying mechanism for persistent AF compared to paroxysmal AF.

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### **Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## **Figure Legends**

Figure 1: Study patient numbers and type of cardiac implantable devices

Figure 2: Change in AF burden in paroxysmal AF patients post ablation

Figure 3: Change in AF burden in persistent AF patients post ablation

Figure 4: Kaplan–Meier estimation of the time to atrial arrhythmia recurrence

Figure 5: Effect of each ablation on AF burden

Figure 6: Effect of comorbidities on AF burden post ablation