

1 **Title:** Long-term outcomes of the pentaspline pulsed field ablation catheter for the treatment of
2 paroxysmal atrial fibrillation: Results of the prospective, multicenter FARA-Freedom Study

3

4 **Running Head:** Primary Results of FARA-Freedom

5

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1 ABSTRACT

2 **Introduction/Objectives:** Pulmonary vein isolation (PVI) is well-established strategy for the treatment of
3 paroxysmal atrial fibrillation (PAF). Despite randomized controlled trials and real-world data showing the
4 promise of pulsed-field ablation (PFA) for this treatment, long term efficacy and safety data
5 demonstrating single procedure outcomes off antiarrhythmic drugs remain limited. The aim of the
6 FARA-Freedom Study was to evaluate long-term efficacy and safety of PFA using the pentaspline
7 catheter for PAF.

8 **Methods:** FARA-Freedom, a prospective, non-randomized, multicenter study, enrolled patients with PAF
9 undergoing *de novo* PVI with PFA, which were followed for 12 months with weekly transtelephonic
10 monitoring (TTMs) and 72-hr Holter ECG at 6 and 12 months. The primary safety endpoint was a
11 composite of device- or procedure-related serious adverse events out to 7 days post-ablation and PV
12 stenosis or atrioesophageal (AE) fistula out to 12 months. Treatment success is a composite of acute PVI
13 and chronic success; which includes freedom from any documented atrial tachyarrhythmia longer than
14 30s, use of antiarrhythmic drugs or cardioversion after a 3-month blanking period, or use of amiodarone
15 or repeat ablation at any time.

16 **Results:** The study enrolled 179 PAF patients (62 ± 10 yr, 39% female) at 13 centers. At index procedure,
17 all PVs were successfully isolated with the pentaspline PFA catheter. Procedure and left atrial dwell
18 times, with a 20 min waiting period, were 71.9 ± 17.6 and 41.0 ± 13.3 min, respectively. Fluoroscopy
19 time was 11.5 ± 7.4 min. Notably, monitoring compliance was high with 88.4% and 90.3% with weekly
20 event and 72-hour Holter monitors, respectively. Freedom from composite primary effectiveness
21 endpoint was 66.6%, 41 patients had atrial tachyarrhythmia recurrence: mostly recurrent atrial
22 fibrillation (31 patients). The composite safety endpoint occurred in 2 patients (1.1%), 1 tamponade and

1 1 TIA. There was no coronary spasm, PV stenosis, or AE fistula. There were 4 cases of transient phrenic
2 nerve palsy, but all resolved during index procedure.

3 **Conclusions:** In this prospective, non-randomized, multicenter study, PVI using a pentaspline PFA
4 catheter was effective in treating PAF patients despite rigorous endpoint definitions and high monitoring
5 compliance and demonstrated favorable safety.

6

7 INTRODUCTION

8 Pulmonary vein isolation (PVI) using radiofrequency ablation and cryoablation are well-established
9 treatment approaches for paroxysmal atrial fibrillation (PAF) ¹. Pulsed field ablation (PFA), though only
10 recently available as a modality for preferential cardiac ablation, has already been used on thousands of
11 patients in clinical trials and real-world registries ²⁻⁴. PFA uses high-voltage, microsecond electrical
12 pulses to permeabilize the cell membrane causing apoptosis where electrical fields reach sufficient
13 strength to cause irreversible damage. Cardiac cells are more susceptible to this damage allowing for
14 targeted ablation.

15 Clinical outcomes have been promising, with a favorably safety profile due to the non-thermal nature of
16 the PFA lesion as well as comparable efficacy compared to well established ablation techniques ^{2,4-}
17 ⁹[Refs]. Further, several large registries have demonstrated short learning curve and consistent
18 outcomes across centers and operators of various experience ^{4,7,8}.

19 Recently, the ADVENT randomized controlled trial demonstrated non-inferiority of the pentaspline PFA
20 system to standard-of-care thermal ablation – radiofrequency and cryoballoon ablation.¹⁰ However,
21 long term efficacy and safety data on the effectiveness of single-procedure PVI with PFA at preventing

1 the need for AAD usage remain limited. The aim of the FARA-Freedom Study was to evaluate long-term
2 efficacy and safety outcome of PFA using the pentaspline catheter in patients with PAF.

3

4 **METHODS**

5 FARA Freedom (NCT05072964) was a prospective, non-randomized, single-arm, multicenter study. The
6 study protocol was approved by local institutional review boards at each center. Centers were recruited
7 based on prior PFA experience with the pentaspline catheter. The study was conducted in accordance
8 with the Declaration of Helsinki. All patients were over 18 years old and provided written informed
9 consent.

10 Thirteen centers across six countries in Europe participated in this study. Study recruitment took place
11 between Dec 2021 and August 2022. Centers enrolled 3 to 27 patients each, mean enrollment was of
12 13.2 ± 8.6 pts. With 2 sites trenching the 27 pt enrollment cap. Eligible patients were those with
13 symptomatic PAF who previously failed AAD treatment (Class I-IV) and were indicated for a PVI.
14 Indication for ablation followed current guidelines and expert consensus statements. Exclusion criteria
15 included non-paroxysmal AF, any contraindications for AF ablation, treatment with amiodarone within 3
16 months prior to ablation, any prior atrial ablation (accept right side STI/SVT), prior cardiac surgery within
17 6 months of ablation, recent CIED implant (<3 months), prior LAA closure or valve device implant, and
18 life expectancy of less than 1 year.

19 **Pre-ablation Protocol**

20 Anticoagulation was guided by the 2017 Heart Rhythm Society Expert Consensus Statement and the
21 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society Focused
22 Update^{11,12}. Subjects with a CHA2DS2-VASc score ≥ 2 (men) or ≥ 3 (women) received oral anticoagulants

1 throughout follow-up. Subjects not on anticoagulants received therapeutic anticoagulation for at least 3
2 weeks prior to the index procedure regardless of CHA₂DS₂-VASc score. Cardiac imaging using
3 transesophageal echocardiography or computed tomography (CT) was performed within 48 hours prior
4 to the index procedure to exclude left atrial thrombus. Alternatively, intracardiac echocardiography (ICE)
5 was used for this purpose intraprocedurally. All subjects without contraindications were maintained on
6 suitable anticoagulation for at least 2 months following the index procedure.

7 Sedation or general anesthesia was determined according to institutional standard of care. Femoral vein
8 access was obtained using the Seldinger technique with ultrasound guidance recommended. A bolus of
9 heparin was delivered prior to or immediately following transeptal puncture. Procedural activated
10 clotting times were maintained at a minimum of 300 seconds using intravenous heparin bolus and/or
11 continuous infusion.

12 **Pulsed Field Ablation – Index Procedure**

13 PVI was performed using the pentaspline PFA catheter (Farawave, Boston Scientific Inc), deflectable
14 sheath (Faradrive), and PFA generator (Farastar) optimized for left atrial ablation. The 12.8F over-the-
15 wire ablation catheter has 5 splines that can be deployed in the basket and flower configurations to
16 adapt to the anatomy of the pulmonary veins. For each application, the generator delivers ultra-rapid,
17 high-voltage electrical pulses causing irreversible electroporation of targeted cardiac tissue. The
18 recommended procedure was that each PV receive a total of 4 applications in the “basket” configuration
19 with a rotation after the first 2 applications, followed by a second set of 4 applications in the “flower”
20 configuration with a rotation after the first 2 applications. The workflow recommended a total of 8
21 applications per PV with additional applications allowed at the discretion of the operator. In 2 pts the
22 device was used for posterior wall isolation, and there were 20 pts with a common PV (19 LCPV, 1
23 RCPV); in these cases more than the recommended 8 applications per PV were applied.

1 Electroanatomical mapping was used at operator discretion. Esophageal temperature monitoring or
2 deviation were not recommended. After the last PV application, electrical isolation was confirmed
3 following a minimum 20-minute wait with the optional use of adenosine for final assessment. The status
4 of the phrenic nerve was evaluated at the end of the index procedure. No phrenic nerve pacing was
5 performed during ablation of the right sided PVs.

6 **Endpoints**

7 The primary safety endpoint was a composite of predefined device- or procedure-related serious
8 adverse events with an onset within 7 days of the index procedure and PV stenosis or AE fistula
9 occurring at any time during the 12-month follow-up.

10 The primary efficacy endpoint of treatment success was defined as a composite of acute procedure
11 success and chronic success which included freedom from documented recurrence of AF, atrial flutter
12 (AFL), or atrial tachycardia (AT) $\geq 30s$, use of Class I or III AAD, or cardioversion after the blanking period,
13 or re-ablation for AF, AFL or AT or (due in part to its long half-life) the use of amiodarone at any time.

14 **Follow-up**

15 Patients were followed for 12 months. Phone call assessments were completed at 7, 30, and 60 days
16 post index procedure. At 60 days, the patient was instructed to discontinue any AADs. In person visits
17 were performed at 3-, 6-, and 12-months post index procedure with 72-hour Holter ECG monitors
18 performed at 6 and 12 months. Event monitors were used for weekly scheduled monitoring along with
19 any symptomatic events starting after the blanking period (3 months) and continued to the end of the
20 12-month follow-up.

21

22

1 **Statistics**

2 Continuous variables are reported as mean \pm standard deviation or median (IQR). Categorical variables
3 were summarized as count and percentage. Freedom from event survival analyses were calculated with
4 Kaplan-Meier to determine protocol defined endpoints and lower confidence limits and relevant event
5 data. Odds ratios of relevant procedural characteristics and recurrence were calculated. All analysis
6 was conducted with SAS Version 9.4 (SAS Institute Software Company). A p-value < 0.05 was considered
7 significant.

8 9 **Results**

10 In total, 180 patients were enrolled in the study. However, one patient was excluded from this analysis
11 due to a persistent AF diagnosis. The remaining 179 patients with PAF underwent PVI with the
12 pentaspline PFA catheter. The mean age was 62.3 ± 10.1 years (38.5% female) with a mean BMI of 27.3
13 ± 4.0 and CHADS-VASc of 1.8 ± 1.4 , additional demographics are shown in **Table 1**.

14 **Acute Procedural Results**

15 Procedural characteristics are provided in **Table 2**. Procedure duration and LA dwell time were $71.9 \pm$
16 17.6 and 41.0 ± 13.3 minutes, respectively, inclusive of a protocol-mandated 20-minute waiting period.
17 The mean fluoroscopy time was 11.5 ± 7.4 minutes All PV but 1 RIPV were performed at 2.0kV, the
18 single RIPV was ablated at 1.9kV. All PVs were acutely isolated with PFA using a mean of 9.5 applications
19 per PV.

20 **Rhythm Monitoring Compliance**

21 Rhythm monitoring compliance was notably high during follow-up. Patients were given event monitors
22 to record weekly EKGs and as needed for symptoms starting after the 3-month blanking period. Event

1 monitor compliance was 88.4% for the scheduled weekly transmissions. Additional rhythm monitoring
2 compliance details can be found in **Table 3**. For the 72-hour Holter monitor, compliance was 92.1% and
3 88.5% at 6- and 12-month follow-up, respectively.

4 **Safety**

5 The composite safety endpoint occurred in two patients (1.1%; **Figure 1**), one cardiac tamponade and
6 one transient ischemia attack. The tamponade was suspected to be caused by LA perforation due to the
7 guidewire and was stabilized during the procedure. The TIA occurred two days after the ablation
8 procedure in a patient with a clotting disorder. Imaging studies were performed with no abnormalities
9 observed. The TIA resolved without further sequelae. There were no instances of clinically apparent
10 coronary spasm, PV stenosis, or AE fistula. Phrenic nerve function was assessed during the index
11 procedure. There were 4 instances of transient phrenic nerve palsy, but all cases had documented
12 resolution during the procedure.

13 **Efficacy**

14 At 12-month follow-up, freedom from composite primary effectiveness endpoint was 66.6% (**Figure 2**).
15 The primary failure modes are shown in **Table 4**. The most common mode of primary treatment failure
16 was recurrent atrial tachyarrhythmia, with AF being the most common (31 patients) followed by AT (7
17 patients). Twelve patients had failure due to Class I/III AADs being used after the blanking period (day
18 90). Of those 12 subjects, 5 discontinued their AAD medication between days 92-95.
19 Early recurrence of AF (ERAF), defined as recurrence of AF during the 3-month blanking period, occurred
20 in 14 patients (8.1%), 9 of which also had recurrent AF during the post-blanking period. Thirteen of these
21 14 patients met the definition of treatment failure (7 for arrhythmia recurrence, 3 for AAD, 1 for
22 reablation, 2 for amiodarone).

1 Patient quality of life scores were captured at baseline and at 12-months follow-up using the AFEQT and
2 EQ-5D-3L, which both significantly improved with an average increase of 23.8 and 6.4 in the scores,
3 respectively.

4 **Repeat Ablations**

5 Out of 179 patients, 11 (6.1%) returned for repeat ablation at a mean follow-up of 7.3 ± 2.7 months. One
6 patient had a repeat ablation performed during the blanking period, with the remaining 10 patients
7 having repeat ablation post-blanking. These 11 patients had a mean age of 64 years, a BMI of 28.9 ± 3.9 ,
8 and a CHADS-VASc score of 2.4 ± 1.2 . At repeat ablation, 65% (26/40 PVs) of the PVs were durably
9 isolated, and 2 patients (18.2%) had all treated PVs durably isolated. Eight patients out of these 11
10 patients (72.8%) needed ablation beyond the PVs; including, 5 LA roof, 2 LA floor, 2 mitral isthmus, 2
11 posterior wall, 1 focal in LA. The most common reconnection was the RSPV (6/11 PVs; **Table 5**).
12 Interestingly, there were significantly more repeat ablations in patients with a left common pulmonary
13 vein (LCPV). Of 19 patients with LCPVs included in the study, 5 (26.3%) returned for repeat ablation
14 versus 6 in the remaining patient cohort (3.8%; $p=0.002$), although 3/5 LCPVs (60%) remained durably
15 isolated. There was no PV-stenosis in repeat ablation patients.

17 **Discussion**

18 The FARA Freedom study provides long-term, single procedure outcomes in PAF patients
19 treated with the pentaspline PFA catheter. Despite a rigorous definition of treatment success, e.g. not
20 allowing membrane active AADs or reablation, 12-month efficacy was comparable to thermal ablation
21 outcomes and other PFA technologies. In this study, there was high rhythm monitoring compliance
22 contributing to the rigor of the clinical assessment. These results also demonstrate an excellent safety
23 profile for patients undergoing PVI using this PFA technology.

1 **Safety**

2 PFA continues to demonstrate favorable safety outcomes, eliminating the thermal complications seen
3 with radiofrequency and cryoballoon ablation such as phrenic nerve paralysis, PV stenosis, and AE
4 fistula. In this study, there were only two reported composite safety events, one of which was a TIA in a
5 patient with a clotting disorder and predisposition for embolic complications. In good agreement with
6 reports of near zero risk of long-term phrenic nerve damage^{4,6,7}, here there were only intraprocedural
7 phrenic nerve impairments, all of which resolved during the procedure. Additionally, it is notable that
8 though there is recent interest in coronary artery spasms as a result of vascular muscle stimulation by
9 the PFA electrical field,¹³ this study saw no instances of clinically manifest coronary spasm. PV stenosis
10 continues to be a rare event regardless of ablation modality, but a recent publication on the ADVENT
11 RCT reports that sub-clinical PV narrowing in patients with available imaging data.¹⁴ While no clinical PV
12 stenosis occurred, they found that more PV narrowing is more likely to be present following thermal
13 ablation.¹⁴ Similarly, the present study had no incidents of PV stenosis. There are recent reports of
14 acute kidney damage associated with extensive ablation sets.¹⁵ While a recent study demonstrates that
15 these effects can be completely prevented by post-ablation hydration,¹⁶ the present study saw no acute
16 kidney damage, though it should be noted that this study used ablation sets for PVI-alone which did not
17 approach the high numbers associated with kidney damage,¹⁶ though subclinical effects of minor
18 hemolysis may have gone undetected. Overall, there were no complications leading to permanent
19 sequelae in any patient.

20 **Efficacy**

21 The present study had an overall 66.6% composite effectiveness, driven by recurrence of AF, I/III AAD
22 usage, reablation, and amiodarone usage. This rate is similar to reports on other PFA devices, where
23 Verma and colleagues reported a 66.2% effectiveness in the PAF patients in the PULSED-AF¹⁷ study and

1 Duystschaever and colleagues reported a 70.9% rate in the INSPIRE study¹⁸. Though it is notable that
2 these studies allowed AAD usage, thus may have apparent ‘higher’ effectiveness than studies like the
3 present where usage of AADs post-blanking was defined as treatment failure. The present findings are
4 also comparable to recent studies with the pentaspline catheter, for instance the MANIFEST and
5 EUPORIA registries reported effectiveness of 73% and 78%, respectively;^{4,7} and the ADVENT randomized
6 clinical trial reported an overall effectiveness of 73%². It should be noted that the large registries
7 MANIFEST and EUPORIA do not have the stringent endpoint and follow-up criteria of the present study.
8^{4,7} Efficacy is also comparable to legacy data from radiofrequency and cryoablation catheters, where
9 efficacy ranges from 64% to 75%;^{19,20} in line with recent data from ADVENT where thermal ablation was
10 71% effective.² Additionally, repeat ablation in this study are similar to a recent report on mapping data
11 from 25 of 360 patients that returned for reablation following PVI with the pentaspline catheter.²¹
12 Tohoku and colleagues reported that PV reconnection was low in these patients and that the most
13 common reason for reablation was macro-reentrant AT. The reported AT recurrence rate (4.4%,
14 16/325) is similar to the present findings (3.9%, 7/179).²¹ It seems likely that continued workflow
15 optimization with this still novel pentaspline catheter is likely to further reduce AT recurrence.
16 The range of reported effectiveness from different studies may result from multiple factors, such as
17 patient compliance, monitoring strategies, and endpoint definitions. Across studies there is a
18 relationship between patient compliance (i.e. rates of rhythm monitoring) and effectiveness (per
19 protocol, or documented recurrence). When compliance is high, effectiveness can appear lower. For
20 instance, historical RF trials DIAMONDAF and SMART AF had intersecting compliance and effectiveness
21 rates.^{22,23} DIAMONDAF had low compliance (61%) and high effectiveness (79%);²² while SMART AF had
22 high compliance (84%) and relatively lower effectiveness (72.5%, documented recurrence).²³ Thus the
23 present approximately 90% compliance rate should be factored into interpretation of endpoint data.
24 Differences in trial design, conduct, and monitoring protocols can also make comparing outcomes

1 challenging. From the studies published to date, it is clear that with more consistent and rigorous
2 monitoring, more arrhythmia recurrences will be captured and reflected as reduction in long-term
3 effectiveness. For instance, it should be expected that more rigorous TTM (such as weekly vs monthly)
4 would detect more asymptomatic AF episodes resulting in a higher documented recurrence rate.²⁴
5 Similarly, length of Holter monitoring may be expected to drive outcomes, with a longer monitoring
6 period (the present 72hrs, for instance) detecting more recurrence than the standard 24hr Holter
7 monitoring. Further discrepancies arise in defining what should be a clinically meaningful endpoint for
8 effectiveness. Trials often use the first recurrent 30s atrial tachyarrhythmia episode as treatment
9 failure.^{10,19,20} However, recent data suggest that in some treatment populations there may be a 'peak' in
10 recurrence post-blanking that does not reflect long-term effectiveness.²⁵ It is also important to
11 emphasize that, even though some operators may still be in their learning curve with PFA, the novel
12 pentaspline catheter achieves similar efficacy to well-established thermal technologies that have been
13 used for many years.¹⁰

14 **Limitations**

15 FARA Freedom was designed as a post market clinical follow-up study assessing single procedure success
16 based on standard of care in 6 countries and at 13 centers. This was a single arm study with 12-month
17 follow-up. The patient rhythm monitoring compliance was notably high in this study, this combined with
18 72-hour Holter monitor, and strict treatment success definitions make direct comparisons to other study
19 outcomes challenging.

20 **Conclusion**

21 In this prospective, non-randomized, multicenter study, PVI using the pentaspline PFA catheter was
22 effective in treating PAF patients despite rigorous endpoint definitions and high monitoring compliance
23 and demonstrated favorable safety.

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 3 been possible.

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5 **Data Availability:** The data from this clinical trial may be made available to other researchers in
 6 accordance with Boston Scientific's Data Sharing Policy (<http://www.bostonscientific.com/en-US/data-sharing-requests.html>).
 7

8

9 **Table 1. Patient Demographics**

Baseline Demographics	N = 179
Age (years)	62.3 ± 10.1
Female	69 (38.5)
BMI	27.3 ± 4.0
CHADS-VASc	1.8 ± 1.4
LVEF (%)	60.9 ± 5.7 (n = 175)
LA Diameter (cm)	4.0 ± 0.5 (n = 175)
Comorbidities	
Dyslipidemia	70 (39.1)
Diabetes	11 (6.1)

Hypertension	98 (54.7)
Medical Hx	
Cardiac Ablation	7 (3.9)
Non-AF Cardiac Arrhythmia	
Atrial Flutter	20 (11.2)
Bradycardia	10 (5.6)
Sick Sinus Syndrome	1 (0.06)
Cardiac Surgery or Intervention	9 (5.0)
Structural Heart Disease	
Stroke / TIA	11 (6.1)

1

2 **Table 2. Procedural Characteristics**

Procedural Characteristics	N = 179
Procedure Time (min)	71.9 ± 17.6
LA Dwell Time (min)	41.0 ± 13.3
Total Ablation Time (min)	17.8 ± 10.1
Fluoroscopy Time (n = 178) (min)	11.5 ± 7.4
Trans Esophageal Echo	67% (120)

Intra cardiac Echo	29.6% (53)
Acute Vein Isolation	100% (702 / 702 PVs)
First Pass Vein Isolation	98.6% (692 / 702 PVs)
Applications per PV	9.5 ± 3.0
CTI Ablation Performed	14/179 (7.8%)
Documented BDB	13/14 (92.9%)
Duration of CTI Ablation (min)	17.0 ± 17.4

1

2 **Table 3. Rhythm Monitoring Compliance**

Rhythm Monitoring Compliance		N = 179
Event Monitor (EM) Weekly Compliance		
Number of scheduled EM records		5184
Number of unscheduled EM records		9217
Number of EM records per subject		81.4
Mean EM weekly compliance		88.4% (5184 / 5866)
Holter Monitor Compliance		
Holter Monitor at 6 months		92.1% (163 / 177)
Holter Monitor at 12 months		88.5% (154 / 174)

3

1 **Table 4. Primary Efficacy Failure Mode**

First Primary Effectiveness Failure Mode	
Any Primary Effectiveness Failure Mode	59
Acute Procedural failure	0
PVI performed with non-PFA device	0
Post-blanking Detectable AF/AFL/AF/SVT	41
Post-blanking Detectable AF	31
Post-blanking Detectable AFL	0
Post-blanking Detectable AT	7
Post-blanking Detectable SVT	3
Post-blanking cardioversion for AF/AFL/AT	0
Post-blanking use of Type I/III AAD	12
Any re-ablation for AF/AFL/AT	3
Any non-procedural use of amiodarone	3

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1 **Table 5. Repeat Ablation**

Parameter	% (n/N)
Recurrent AF	45.5% (5/11)
Recurrent CTI-mediated AFL	0.0% (0/11)
Atypical flutter (LA)	18.2% (2/11)
Atypical atrial flutter (RA)	0.0% (0/11)
Atypical flutter (bi-atrial)	0.0% (0/11)
Atrial tachycardia (RA)	0.0% (0/11)
Atrial tachycardia (LA)	18.2% (2/11)
AVRT / Accessory Pathway	0.0% (0/11)
AVNRT / slow pathway modification	0.0% (0/11)
PVCs	0.0% (0/11)
Ventricular tachycardia	0.0% (0/11)
Note 1: Some subjects had multiple ablation indications.	

2

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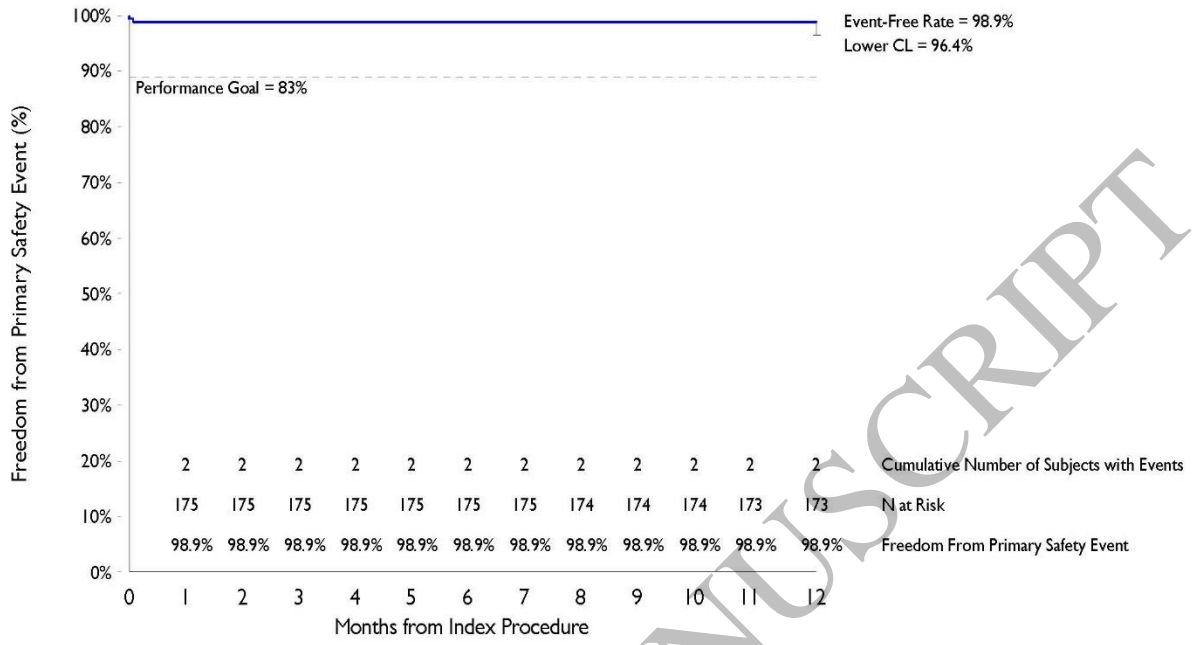


Figure 1
171x144 mm (x DPI)

1
2
3

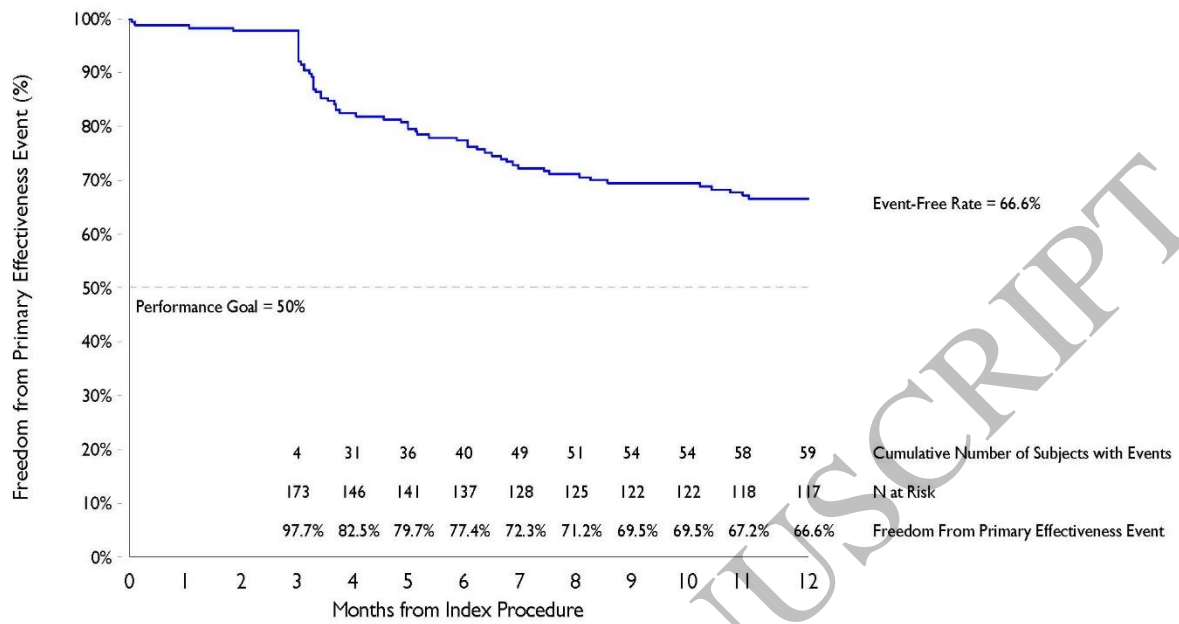


Figure 2
169x139 mm (x DPI)

1
2
3

FARA Freedom

Acute Safety

1.1% major complications
(0.6% Tamponade, 0.6% TIA)

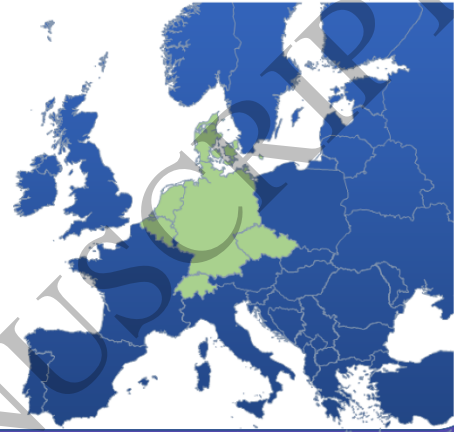
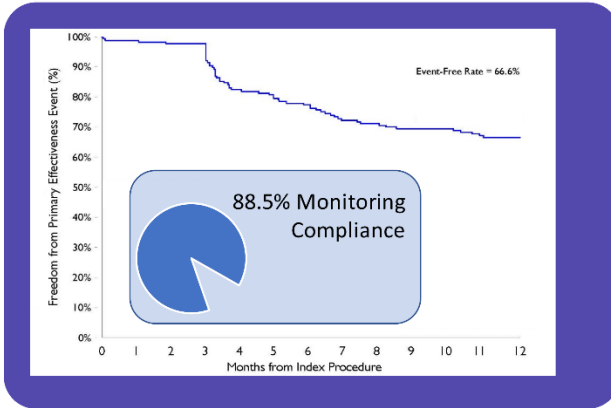
Acute Efficacy

100% Acute Isolation
71.9 min procedure time*
* [w/20m wait]

6 Countries

13 Centers

179 AF patients
treated with PFA



1
2
3

Graphical Abstract
339x190 mm (x DPI)