

One-year outcomes of Pulmonary Vein Isolation with a novel cryoballoon: Primary results of the FROZEN AF Trial

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Abstract

Introduction: Cryoablation therapy for pulmonary vein isolation (PVI) to treat paroxysmal atrial fibrillation (PAF) is well established. A novel 28 mm cryoballoon system designed to operate under low pressure to safely reach a lower nadir temperature and maintain constant balloon size during cooling has not been prospectively studied in a large patient population for safety and efficacy. The FROZEN AF (NCT04133168) trial was an international multi-center, open-label, prospective, single-arm study on the safety and performance of a novel cryoballoon system for treatment of PAF. **Methods and Results:** The study enrolled patients at 44 sites in 10 countries across North America, Europe, and Asia. Subjects were indicated for PVI treatment of PAF and had failed or were intolerant of 1 or more antiarrhythmic drugs. Procedural outcomes were defined based on the 2017 HRS consensus statement. Follow-up was performed at 7 days, 3, 6, and 12 months. Data are reported as mean±SD or Median (IQR). PVI was performed with a 28mm cryoballoon in 325 drug refractory PAF patients. Complete PVI was achieved in 95.7% of patients. In cryoablation lesions longer than 60s, 60.1% of PV isolations required only a single cryoballoon application. Procedure related complications included: phrenic nerve palsy [transient 4 (1.2%), persistent 0 (0.0%)], cardiac tamponade/perforation 2 (0.6%), and air embolism 1 (0.3%). Freedom from documented atrial arrhythmia recurrence at 12 months was 79.9% (AF 82.7%, AFL 96.5%, AT 98.1%), Antiarrhythmic drugs (AAD) were continued or re-initiated in 26.8% of patients after the 3-month blanking period. Additionally, an extension arm enrolled 50 pts for treatment with 28/31mm variable size cryoballoon. A single temporary PNP occurred in this group, which resolved prior to discharge. Freedom from documented recurrence at 12 months in these pts was 82.0%. **Conclusions:** This novel cryoballoon may facilitate PVI to treat PAF, providing more options to address the variety of anatomy present in patients with PAF. This cryoballoon system was safe and effective for treatment of patients with drug refractory or drug intolerant PAF.

Introduction:

Cryoablation to achieve pulmonary vein isolation (PVI) to treat paroxysmal atrial fibrillation (PAF) is well established.¹ Cryoballoon treatment has been available for PVI since the Arctic Front[™] (Medtronic, MN, USA) was launched over 15 years ago.² STOP-AF demonstrated first generation cryoballoon superiority to AADs,³ and later Fire and ICE demonstrated comparable efficacy of cryoballoon to RF ablation.⁴ FIRE and ICE showed comparable efficacy of radiofrequency and cryoballoon but cryoablation has a distinct safety profile compared to RF, shifting primary safety events from heat associated pericarditis/perforation to cold associated phrenic nerve impairment and PV stenosis.⁴ Despite over a decade of use the safety profile of cryoablation remains relatively unchanged.⁵⁻¹⁰

Recently a novel 28 mm cryoballoon system that operates under markedly lower pressure and maintains constant balloon size during cooling became available for clinical studies.¹¹ Additionally, a second generation of this novel cryoballoon that allows inflation and ablation at 2 sizes, 28mm or 31mm, has also become available.¹² At present there is limited long-term (1yr) outcome data on this novel cryoballoon, and little data available on the safety or effectiveness of the novel variable size cryoballoon.¹² While multiple studies have reported both acute procedural data,¹³⁻¹⁶ and chronic 1 year outcomes,¹⁷⁻¹⁹ only a few reports of large patient cohorts exist.^{13,14,18,20,21}

FROZEN AF is an international multi-center, open-label, prospective, single-arm study to determine the safety and performance of a novel cryoballoon system for treatment of PAF, and an extension arm which examined the safety and performance of a novel variable size cryoballoon.

Methods:

Design: FROZEN-AF is a prospective, non-randomized, multi-center, investigation conducted to establish the safety and effectiveness of the POLARx cryoablation system in subjects with symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation. The trial was registered at clinical trials.gov (NCT04133168). All patients provide written informed consent to participate in the trial and all centers obtained approval by their local IRB.

Subjects: Subjects were indicated for PVI treatment of PAF and had failed or were intolerant of 1 or more antiarrhythmic drugs. To allow orientation to the new investigational system and minimize potential learning curve bias each ablating physician was required to treat one “roll-in” patient. Sixty-three total roll-in patients were treated, their data is not reported here. Briefly, patients were indicated for PVI to treat recurrent symptomatic AF and had failed at least one Class I or III antiarrhythmic drug (AAD) and had not been on amiodarone for at least 90 days. Patients were excluded if they had contraindications for AF ablation (or anticoagulants), continuous AF (longer than 7 days), a history of prior left atrial ablation for AF/AFL/AT, structural heart disease or implanted cardiac devices. For full inclusion and exclusion criteria, see supplement.

All subjects fitting the enrollment criteria, signing the consent and undergoing the index procedure with the study devices were followed for up to 12 months after the index procedure. FROZEN-AF was conducted as a post market study in those regions where the device was already approved, including Europe.

Site description : Investigators and sites were selected based on prior experience with cryoablation, ensuring that sites had adequate access to subject population, staff, and documentation practices. In total, 44 sites participated in the study, 30 in the United States, 6 in Europe, 4 in Canada, and 4 in Asia/ Pacific.

Patient Flow: In total, 404 subjects were enrolled across 44 centers (30 in the US, 6 in Europe, 4 in Canada, and 4 in Asia/ Pacific). Of these 385 subjects received treatment with the investigational device, 60 treatment subjects were classified as roll-In subjects and 325 as non-roll-in subjects. Fifteen treatment patients and 4 “roll-in” patients withdrew consent from the study, which was in line with the protocol assumed 10% attrition. Additionally, as part of an extension arm, 54 patients were enrolled to examine the safety and effectiveness of the novel variable size cryoballoon POLARx FIT[™] (Boston Scientific, MN, USA). Of these, there was 1 consent ineligible, 3 intent to treat, and 50 treatment patients.

Cryoballoon Ablation Procedure

Index Procedure: Procedural guidance (described here) was provided to inform use of the novel study device, but in general procedures were performed in accordance with local standard of care at physician discretion.

Dosing recommendation: Cryoapplications were recommended based on an algorithm measuring time to isolation (TTI), with a 180s application where TTI occurred in less than 60s and a 240s application where TTI occurred after 60s or was not detected, but the duration and number of cryoapplications was at physician discretion.

Esophageal management: Esophageal monitoring was required with a recommended cut-off temperature of 20°C.

Phrenic Monitoring: Phrenic nerve monitoring with the integrated DMS (Diaphragm Movement Sensor) was recommended, in conjunction with local standard of care monitoring. The integrated DMS allows the physician to monitor the amplitude of paced electromyogram like potential based movement recorded from an external sensor and visible as real time changes in amplitude on the cryoablation system, with an adjustable threshold and automatic recommendations to stop the cryoablation if the electrogram amplitude decreases by a pre-set percentage, see Supplement. In this study the DMS was recommended to be set at 65%. Phrenic nerve impairment was confirmed with a “sniff test” or radiography during the index procedure, discharge, and follow-up visits until resolved.

PVI Procedure: Procedural guidance (described here) was provided to inform use of the novel study device, but in general procedures were performed in accordance with local standard of care at physician discretion. Cardioversion was performed at operator discretion. Anti-coagulation was recommended to be uninterrupted or minimally interrupted prior to procedure. PVI procedures were conducted based on local standard of care and cryoablation system instruction for use. Acute success was confirmed by entrance and exit block, lack of confirmed or recorded block was reported as acute procedural failure.

Additional ablations: Additional ablation of non-PV foci that initiate AF (including locations in the left atria, right atrium, or superior vena cava), targeting complex fractionated electrograms or ganglionated plexi or performing LA mitral isthmus or roof lines was not allowed. Additional ablation of the cavo-tricuspid isthmus (CTI) with a market approved RF catheter was allowed in cases where typical atrial flutter was documented by patient history or occurred during the case (either spontaneously or inducible).

Redo Ablations: One repeat ablation was allowed during blanking, use of ‘non-study’ device for redo was considered a failure.

Follow-Up: Follow-up was performed at discharge, 7 days, 3 months, 6 months, and 12 months post index procedure. Trans telephonic monitoring (TTM) was collected by patients 2 times per month (either symptomatic or asymptomatic) from 3 to 12m post procedure. Only 43 subjects had monitoring related deviations. 24h Holter monitoring was provided at the 12m FU visit.

Study Endpoints

Endpoint definitions: Procedural outcomes were defined based on the 2017 HRS consensus statement. Full endpoint definitions are included in the Supplement.

Primary Efficacy Endpoint: Failure free rate at 12 months post procedure, with failure defined as occurrence of any of the following events; acute procedural failure, surgical treatment for AF/AFL/AT, use of non-study catheter for AF targets, more than 1 repeat during blanking, repeat or surgical treatment after blanking, documented recurrence of AF, AFL, or AT after blanking; electrical or pharmacological cardioversion after blanking, use of Class I/III AADs or any other AADs for control of AF/AFL/AT, any use of amiodarone (pre or post blanking).

Primary Safety Endpoint: Primary safety event free rate at 12 months post procedure. Event free rate

was defined as a composite of the following acute and chronic procedure-related and device-related adverse events: Acute primary safety endpoint events, events occurring up to 7 days post index or hospital discharge, whichever is later, include: Death; myocardial infarction (MI); transient ischemic attack (TIA); stroke/cerebrovascular accident (CVA); vascular access complications; mitral or tricuspid valvular damage; thromboembolism/ air embolism (leading to a life-threatening event such as a ventricular arrhythmia, stroke, pulmonary embolism, or myocardial infarction and, thromboembolic events that result in permanent injury, require intervention for treatment, or prolongs/requires hospitalization for more than 48 hours); gastroparesis/injury to vagal nerve; pneumothorax; pulmonary edema/heart failure; atrioventricular block; cardiac tamponade/perforation (occurring up to 30 days post index procedure). chronic primary safety endpoint events, events occurring through 12 months post procedure, include: atrial esophageal fistula; severe PV stenosis ([?] 70% reduction in the diameter of the PV or PV branch from baseline); persistent phrenic nerve palsy. Safety events, including but not limited to the predefined safety endpoint, were reviewed by an independent Clinical Events Committee.

Stenosis Sub-study: Fifty treatment patients were assessed for stenosis associated with cryoablation. Patients PVs were imaged by CT/MRI at baselines and 3 to 6 months post procedure. The degree of narrowing (mild <50%, moderate 50-70%, severe [?]70%) from the 3 to 6 months follow-up scan compared to baseline was assessed by a central lab.

FIT Extension: In addition to the primary study arm, an extension arm to FROZEN AF treated 50 pts to assess safety of novel variable size balloon that allows inflation and ablation at both 28mm and 31mm. Patients received at least one PV cryoablation with the 31mm sized cryoballoon, otherwise pts treatment and design were similar to the larger cohort.

Statistical Analysis: The primary arm of this study was designed around an expected event-free rates of 94% (Safety) 60% (Effectiveness), targeting 90% power to compare to performance goals of 89% (Safety) and 50% (Effectiveness) with a 95% one-sides confidence limit. The FIT extension arm was designed with a primary safety endpoint based on 3-month follow-up and acute success, with the same performance goal as the parent study (89% freedom from safety events), while the effectiveness endpoint did not have a designated acceptance criteria. For ease of comparison, the pre-defined primary effectiveness endpoint of the initial study was also calculated for the 50 patient FIT extension arm. Secondary analysis reported here include survival analysis to efficacy component events. Analyses were performed with SAS version 9.4 (SAS Institute Software Company). Data are reported as mean +- standard deviation, median (IQR, or N (%) as appropriate.

Results:

Patient Disposition : The study enrolled 404 patients, of which 5 were consent ineligible, 63 were ‘roll-in’ pts, and 336 non roll-in. Of the non roll-in pts there were 10 intention to treat (enrolled after study met treatment goals), 1 attempt to treat, and 325 treatment subjects (Supplemental Figure 1). A PV stenosis sub-study enrolled 55 pts, of which 50 contributed to the PV stenosis analysis. These patients underwent MRI or CTA to measure pulmonary veins size pre procedure and then a repeat study 3 months after ablation. Additionally, an extension arm enrolled 54 pts to examine the performance of the variable size POLARx FIT catheter, Of these 1 was consent ineligible, 3 were Intention to treat, and 50 received treatment with the 31mm inflation size in at least one PV.

Patient Demographics: Characterization of patient demographics is provided in Table 1. Briefly, patients in the primary cohort were 62 +- 11 yrs old on average, 38.2% (124/325) were females, average BMI was 29. Patients had an average CHADS₂-VA₂SC score of 1.7 +- 1.3, LVEF of 58.6% +- 5.8%. Patients were enrolled an average of 3.0 yrs post initial diagnosis, and an average of 87 days since their most recent episode. Similar demographics were seen in the FIT extension arm, though patients had a shorter time since AF diagnosis (Mean 1.6yrs; Median 0.4, IQR 0.2, 1.0) and higher CHADS₂-VA₂SC scores (2.2).

Procedural performance: Recommended dosing strategy was based on TTI timing (See Supplement), strategy was not followed in 206/325 pts. General anesthesia was used in a majority of pts (255/325),

conscious sedation was used in (70/325), esophageal temperature monitoring was used in 311/325 cases. 3D mapping was used in 184/325 cases. Average procedure, LA dwell, and Fluoroscopy times were 91, 59, and 13 minutes, respectively. Acute success was achieved in 311 cases (95.7%). Fourteen subjects (14) were acute procedural failures due to not achieving entrance block and/or exit block in one or more pulmonary veins, usage of a non-study catheter or not performing the entrance and exit block testing. In the FIT extension arm general anesthesia was used in all patients, 3D mapping had higher utilization (98%), and fluoroscopy time was shorter (7 min). The 31 mm balloon size was used in approximately 64% of ablations. Additionally, in the FIT arm acute success was achieved in all 50 patients for a rate of 100% with a 92.9% lower confidence interval.

Biophysical data: Biophysics data is reported in Table 2. Complete PVI, confirmed with exit and entrance block, was achieved in 95.7% of patients. On average PVs received 1.8 ± 1.3 ablations (IQR 1-2), with a total duration of 4.46 ± 2.7 min (IQR 3-5 min) per PV. Occlusion score of 3 or 4 was reported in 95.9% of PVs. Overall single shot success was achieved in 55.9% of PVs (726/1299), in cryoablations longer than 60s the single-shot rate was 60.1%. The mean nadir temperature for ablations was 56.4 ± 6.9 degC. TTI was available from 1044 ablations and averaged 45.1 ± 25.3 s. Biophysical and performance data by PV are reported in Table 2. Biophysical data from the 50 patient FIT extension arm are also reported in Table 2, however as usage of the larger 31mm balloon configuration was at operator discretion, it is challenging to directly compare data. Though, it is notable that nadir temperatures, and time-to-isolation appear relatively similar. See Figure 1 for visual comparison aggregate freeze curves from all ‘first ablation’ uses of the 28mm and 31mm balloon sizes.

Safety: The primary safety endpoint was a composite of multiple acute and chronic safety events. Safety events occurred in 4.0% of patients, resulting in a KM freedom from occurrence rate of 96.0%, which met the study safety goal of 89.0% (Figure 2). One death occurred in a treatment patient during the course of the study at approximately 6 months post ablation due to a non-healing foot wound but was adjudicated to be unrelated to the study device or the procedure. Primary safety events included: 5 vascular access complications, 3 gastroparesis, 2 tamponade, 1 air embolism, 1 pulmonary edema, and 1 myocardial infarction. In addition to prespecified endpoints, 4 patients had phrenic nerve palsy (temporary phrenic nerve impairment present at the end of procedure), all of which resolved by the end of the study. See Figure 1 for list of study safety endpoint events.

PV Stenosis Sub study: A subset of 50 patients in the primary cohort enrolled in an MRI sub-study to examine occurrence of PV stenosis. Core lab analysis of 3 and 6 month MRI (1.5 or 3T) images revealed mild stenosis in the LIPV of 2 patients, and no instances of moderate or severe stenosis.

Effectiveness:

Effectiveness endpoint, which incorporated atrial arrhythmia recurrence, AAD usage, acute procedural failure, cardioversion, repeat procedures, was met in 59.9% of patients (Figure 3), this met the study performance goal of 50%, which was based on similar prior trials. Examination of individual components revealed that the primary endpoint contributors were AAD usage and documented recurrence. Overall freedom from recurrence of atrial arrhythmia was confirmed in 79.9% of patients. Documented recurrence of atrial arrhythmias occurred in 20.1% of patient as of 12m follow-up, with recurrence of AF in 17.3%, AFL 3.5%, and AT 1.9%, Figure 3. Kaplan Meier analysis of AAD usage revealed a sharp drop in freedom from AADs shortly following blanking, which was partly attributable to relatively high AAD usage. Notably, 38 of the 46 patients that had treatment failure only due to AAD usage, i.e., with no documented recurrence or other events, received AADs at the same dose or lower than baseline. Examination of AAD usage across follow-up, suggests a marked decrease in AAD usage over the course of the trial, from 60.1% of patients on Class I/III AADs (typical for control of AF) pre-discharge to only 10.1% on Class I/III AADs at 12m follow-up, 13 pts on Class I (11 flecainide, 2 propafenone, 18 pts on Class III (6 amiodarone, 2 dofetilide, 3 dronedarone, 7 sotalolol), Figure 3C.

FIT Extension ARM:

Safety: In the FIT extension arm, as of 3-month FU, there were no primary safety events resulting in a 100% (LCL 92.9%) freedom from occurrence rate, meeting the safety goal of 89% (Figure 4). There was a single transient PNI which resolved prior to discharge.

Effectiveness: In the FIT extension arm, analysis based on the per protocol endpoint resulted in a freedom from event rate of 78% (66.5% LCL), which meets the study performance goal, Figure 4. Eleven subjects in this extension arm had failures for documented recurrence (9), AAD use (5), and repeat procedures (3), in total, with some subjects contributing multiple categories. Additional analysis showed an 84% freedom from recurrence of AF, 94% freedom from AFL, and 100% freedom from AT. Though AAD usage was considerably lower in the extension arm a pattern similar to the larger study was apparent with AAD usage for atrial arrhythmia reducing from 60% at baseline to only 8.2% at 12m FU, with only a single pt on Class 1 and 2pts on Class 3 AADs. Electroanatomic mapping data was available from only a sub-set of patients across both study arms. Figure 5 presents two representative cases, one of a patient where the 28mm balloon size was used in all PVs and one of a different patient from the FIT extension where the 31mm balloon size was used in all PVs. Fractional antral scar is calculated to facilitate comparison of lesion extent in these two representative patient cases.

Repeat Procedures: Repeat ablation procedures were performed in a total of 26 patients, 11 were performed during the blanking period, and 15 (4.6%) were performed post-blanking. In the FIT extension arm there were 4 total repeat procedures 3 (6%) of which were performed post blanking.

Discussion:

The FROZEN AF study demonstrates the safety and effectiveness of the POLARx cryoballoon, the trial met effectiveness and safety endpoints in patients with drug-refractory paroxysmal atrial fibrillation, with a high 1-year recurrence free rate of 79.9% and 0% phrenic nerve palsy. Additionally, the FIT extension arm demonstrates the promise of the variable size cryoballoon, with 84% freedom from AF recurrence and a promising safety profile.

Safety

The present study reports a safety event free rate of 96% in the primary cohort, and 100% in the extension arm. The landscape of adverse events associated with cardiac ablation procedures has consistently improved from radiofrequency ablation, to irrigated RF, cryoablation, and pulsed field ablation. Early, landmark cryoablation trials demonstrated that though RF and cryoablation have similar overall adverse event rates, the primary adverse events in cryoablation were PV stenosis and phrenic nerve impairment, but more serious extremely rare events, like atriopharyngeal fistula, could occur.^{3,4} Technical and procedural advancements have reduced PV stenosis to negligible levels and use of esophageal temperature monitoring has significantly reduced esophageal damage (as well as AE fistula). Phrenic nerve impairment remains at an incidence of 2-4%,⁵ varying based on definition (transient, temporary, chronic, or permanent), with permanent phrenic nerve palsy thought to occur in less than 1% of patients.⁵ The present study saw zero permanent phrenic nerve palsy, with all patients recovering, and a lower rate of temporary phrenic nerve impairment in the FIT extension arm. This observation may be attributable to multiple factors. One, DMS was recommended in this study, the integrated DMS sensor may allow better detection of early transient PNI during ablation, resulting in lower overall rates of PNP. Two, the lower pressure and controlled pressure during ablation of this cryoablation system may allow better contact to PV tissue avoiding seating of the balloon deep into the PVs. Three, the 31mm configuration in particular may allow a more antral positioning and thus further from the phrenic nerve.

Efficacy

The 79.9% recurrence rate reported here is higher than reports from recent meta-analysis of treatment success for PAF, cryoablation (28% recurrence) AADs (45% recurrence).²² Additionally, the current data are promising in light of historic studies of the effectiveness of cryoablation.¹ Though it used different endpoints, FIRE and ICE reported cryoballoon effectiveness of 65%, with 87/376 pts (23%) having documented

recurrence of atrial arrhythmia.²³ STOP AF reported a 69% overall effectiveness of cryoablation³ though that study allowed continued treatment with the same dose of previously ineffective AADs but used a first generation cryoballoon. Cryo-First reported similar outcomes to the current study, with an 82.2% freedom from recurrence of atrial arrhythmia in early PAF patients with no AAD history.²⁴ It should be noted that outcomes might be improved in patients undergoing ablation prior to trials of antiarrhythmic drugs and thus early in the course of their disease.. A recent study of a pulsed field ablation (PFA) system of 150 paroxysmal AF patients had a markedly higher rate of documented recurrence (33.8 vs the present 19.1) and more repeat ablations (8% vs the present 4.4%).²⁵ A recent randomized controlled trial comparing PFA to thermal (Cryo and RF) ablation modalities also aids in putting this data in perspective, ADVENT reported a 73% and 71% effectiveness for PFA and thermal ablation, respectively.²⁶ The effectiveness of thermal ablation in that trial was comparable to the present findings, though the Bayesian analysis used in ADVENT makes direct comparison to traditional KM analysis challenging. Further insights into the relative effectiveness of cryoablation and novel PFA systems may have significant impact on the landscape of AF treatment.

Limitations:

FROZEN AF is a large, multicenter, multicountry prospective trial to assess the safety and effectiveness of POLARx for cryoablation of PAF in drug-refractory patients. While all endpoints were met and the study conclusions are clear, the trial design has limitations: 1) This study enrolled drug refractory PAF patients, thus did not directly address use in other patient populations, such as those with persistent AF or patients with early AF that have not yet been on AADs, 2) Though the study was conducted with a primary arm of 325 patients that received PVI with POLARx and an extension arm of 50 pts treated with the variable size POLARx FIT, it was essentially a single arm design and did not directly compare cryoablation to alternative therapies, 3) The trial was run across 55 centers with a wide range of patients treated per center with a minimum of 1 and a maximum of 48. Thus, many operators were relatively inexperienced with the device. While this precluded examination of learning curves, as few operators treated enough patients to make examination of procedure times or outcomes over time meaningful, the high freedom from recurrence with so little device use speaks to the ease of use of the device. 4) Additionally, the size of the extension arm limits the conclusions that can be reached about the novel variable size cryoballoon, which allows ablation at either 28mm or 31mm without catheter change out. To better understand how this new option may transform workflow and patient outcomes, future studies should examine acute and chronic endpoints in larger patient cohorts.

Conclusions:

The present findings suggest an excellent safety and performance profile for the novel 28mm cryoablation system, with safety and effectiveness comparable to other ablation therapy. Additionally, the development of a variable sized balloon may further increase safety and effectiveness of PVI cryoablation. Considering recent findings that support early rhythm control, single shot technologies, such as cryoballoon ablation, may see increased utilization as first line treatment for PAF.

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

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Figures:

Figure 1. Balloon Size and Freeze Profile Characterization

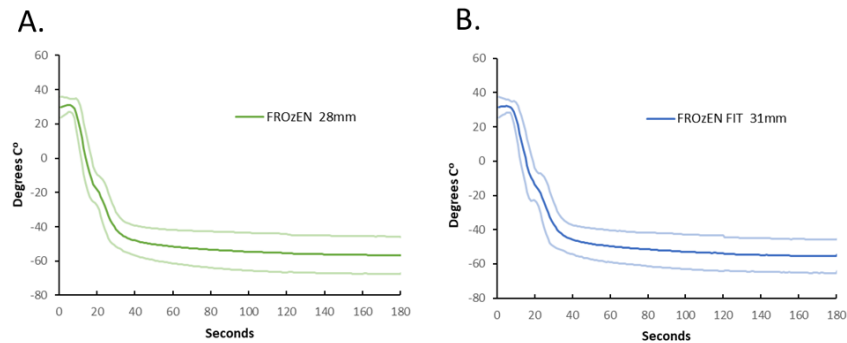


Figure 1. Aggregate freeze curve profiles of console export data from all available (A.) FROZEN AF (28mm), and available (B.) 31mm FIT Extension ablations. Plots generated as mean of all second-by-second console exported freeze curve data. Upper and lower lines reflect 2 standard deviations from the mean of data at each one second time point.

Figure 2: Safety

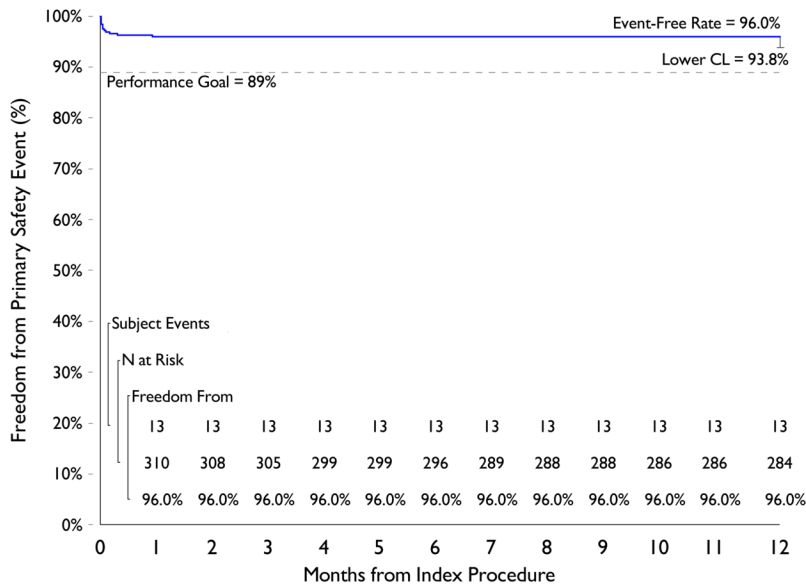


Figure 2. Safety endpoint data. This primary arm of the study had a KM event free rate of 96%, which met the 89% performance goal.

Figure 3: Effectiveness

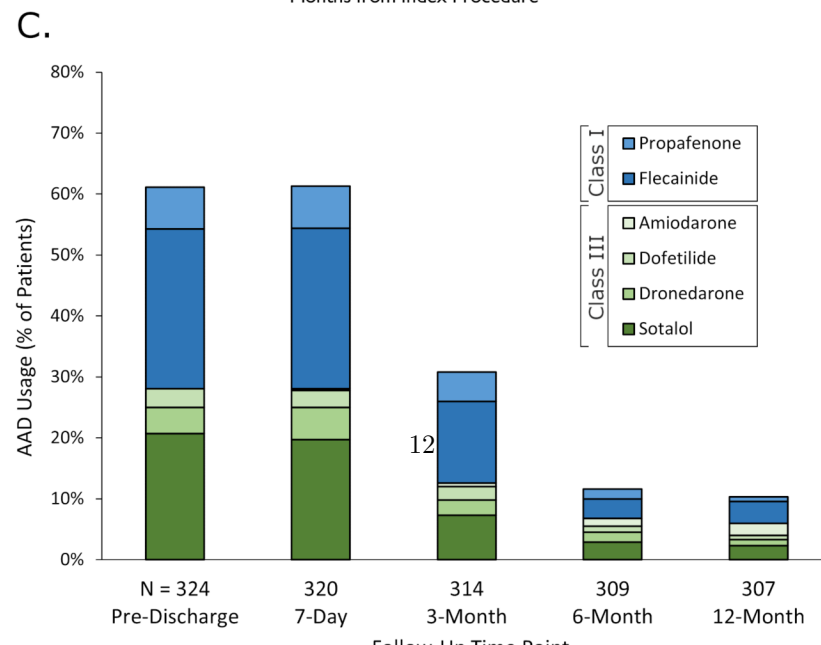
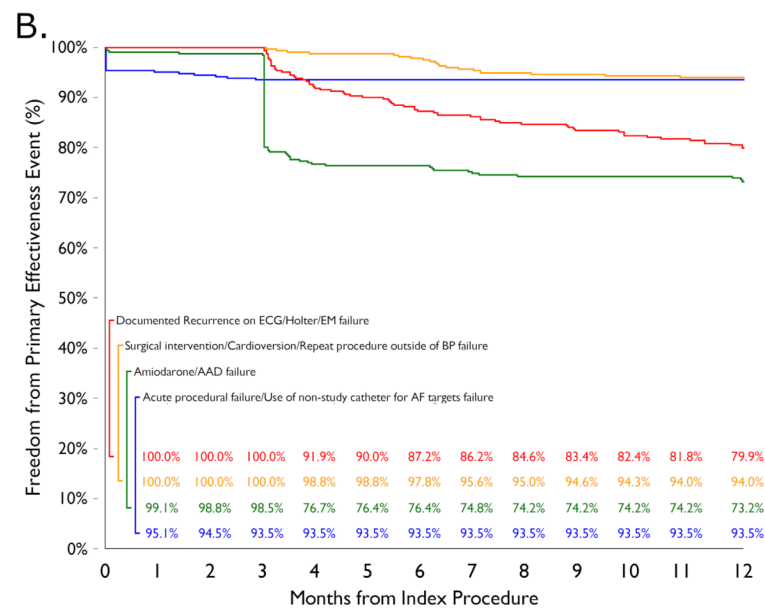
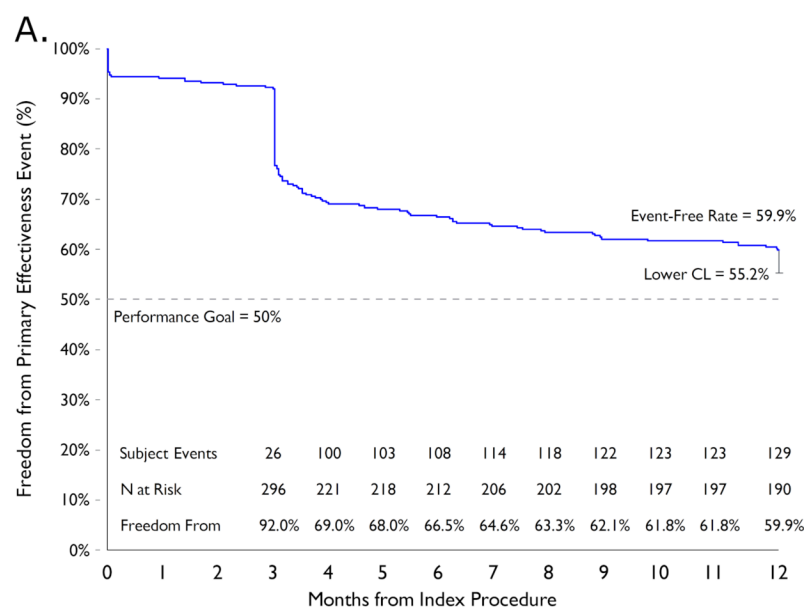


Figure 3. A) This study had an effectiveness freedom from event rate of 59.9%, which met the performance goal of 50%. Notably, examination of components of the composite efficacy endpoint (B) revealed differential contributions over time of the distinct components. Examination of Anti-arrhythmic drug usage in study patients over time (C) showed that usage of Class I/III drugs dropped dramatically over the course of the study.

Figure 4. FIT Safety and Effectiveness

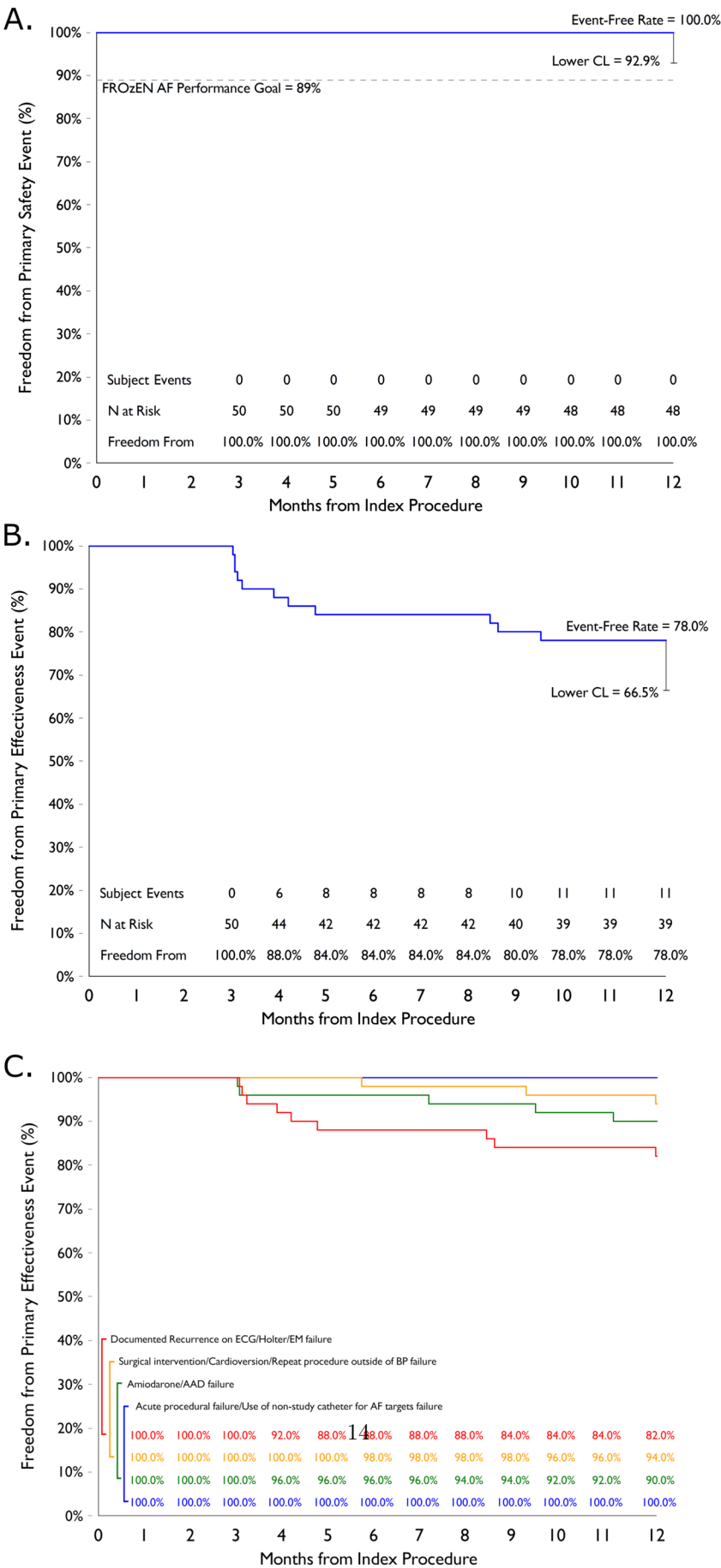


Figure 4. Examination of the FIT extension arm revealed a safety event free rate of 100% (A), which met the overall study safety goal of 89%. KM analysis of performance data in the FIT extension arm showed an overall effectiveness rate of 78% (B). Component based KM analysis of the performance data showed that the largest cause of treatment failure was documented recurrence (C), where freedom from recurrence was 82%.

Figure 5. Representative Lesion Characterization

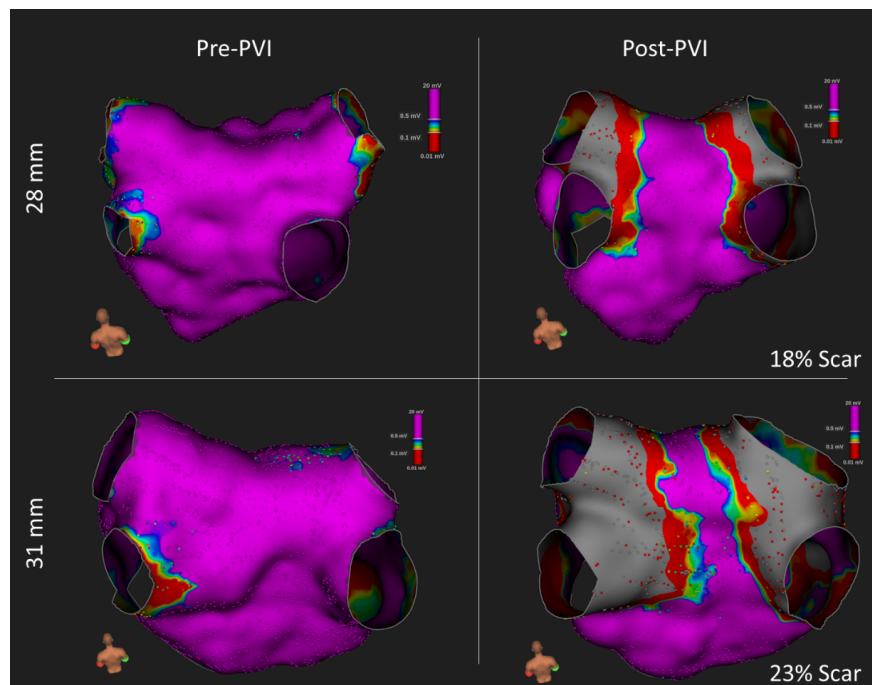


Figure 5. Representative images of pre- and post-isolation electroanatomic maps collected with an ultra-high definition mapping system and 64 electrode basket mapping catheter. Maps were collected by a single operator during a 28mm FROZEN AF case and a FIT Extension arm case where the 31mm configuration was used for all PVs. Fractional antral was calculated based on $(PV^{pre}-PV^{post})/PV^{pre}$, Voltage Bracket 0.1mV-0.5mV, scar defined as $<0.1mV$.

