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Persistent atrial fibrillation ablation with contact force sensing catheter: The prospective multicenter PRECEPT Trial

Short title: Persistent AF ablation: the PRECEPT Trial

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ABSTRACT

Background: While the safety and effectiveness of catheter ablation of paroxysmal AF is established, there are limited data on outcomes in patients with persistent AF (PsAF). As such, no ablation catheter is currently approved by the FDA for PsAF ablation.

Objectives: To evaluate the safety and effectiveness of catheter ablation of PsAF using a porous tip contact force (CF)-sensing catheter.

Methods: The prospective, multicenter, nonrandomized PRECEPT study was conducted at 27 sites in the United States and Canada. Enrollment criteria included documented symptomatic PsAF and nonresponse or intolerance to ≥1 antiarrhythmic drug (Class I or III). Individualized treatment approach was used including pulmonary vein isolation (PVI) with ablation of additional targets permitted at investigators' discretion. To optimize treatment outcomes, a 3-month post-ablation medication adjustment period followed by a 3-month therapy consolidation period were included. Arrhythmia recurrences were stringently monitored by monthly and symptomatic transtelephonic monitoring, electrocardiogram, and Holter, for up to 15 months post-ablation.

Results: Of 381 enrolled participants, 348 had the investigational catheter inserted and underwent ablation. The primary adverse event (PAE) rate was 3.8% (14 events in 13 participants). Kaplan Meier analyses estimated the primary effectiveness success rate of 61.7% and clinical success rate of 80.4% at 15 months.

Conclusions: The results demonstrate the clinical safety and effectiveness of PsAF ablation using CF-sensing technologies. The PAE was within the expected range and similar to those reported in historical studies of paroxysmal AF ablation.

Keywords: atrial arrhythmia; pulmonary vein isolation; transtelephonic monitoring; porous tip catheter; symptomatic AF

Condensed abstract

The PRECEPT study evaluated the safety and effectiveness of catheter ablation of persistent atrial fibrillation (PsAF) using a porous tip contact force (CF)-sensing catheter (n=381). The primary adverse event rate was 3.8%. The primary effectiveness success and clinical success rates were 61.7% and 80.4% at 15 months, respectively. Results demonstrate clinical safety and effectiveness for PsAF ablation using CF-sensing technologies.

Abbreviations

AAD = antiarrhythmic drug

AFL = atrial flutter

AT = atrial tachycardia

CF = contact force

CI = confidence interval

LA = left atrium/left atrial

PsAF = persistent atrial fibrillation

PV = pulmonary vein

PVI = pulmonary vein isolation

RF = radiofrequency

INTRODUCTION

Radiofrequency (RF) catheter ablation therapy, with the aim of achieving electrical isolation of the pulmonary veins (PVs), is the cornerstone of treatment for atrial fibrillation (AF).[1] The superiority of catheter ablation of drug-resistant paroxysmal AF in comparison to antiarrhythmic drug (AAD) therapy has been well established, with continued improvements in success rates demonstrated over the past decade with advancement in ablation technologies, especially following the introduction of contact-force (CF)-sensing catheters.[1-4] In a significant portion of patients, paroxysmal AF progresses to more chronic forms of arrhythmia, including persistent atrial fibrillation (PsAF), defined as AF that continues beyond 7 days.[8]

The increased AF burden resulting from PsAF is associated with an higher risk of stroke, heart failure, and mortality compared with paroxysmal AF.[9] Although approximately one-third of AF catheter ablation procedures worldwide are currently performed for persistent or long-standing persistent AF, there are currently limited data on outcomes of AF ablation in patients with non-paroxysmal AF.[1,8] To date, there is no ablation catheter approved by the FDA for PsAF.
The PRECEPT study (NCT02817776) is the first prospective, multicenter US investigational device exemption (IDE) clinical study designed to evaluate the safety and effectiveness of catheter ablation in patients with PsAF using the STSF porous tip CF catheter.

METHODS

The institutional review board or ethics committee at each of the 27 participating centers approved the study protocol (see the Supplemental Materials for a list of the clinical sites and participating investigators). All patients enrolled in the study provided written informed consent.

Study design

This prospective, multicenter, nonrandomized clinical study was designed to evaluate the safety and effectiveness of the THERMOCOOL SMARTTOUCH® SF (STSF) catheter (Biosense Webster, Inc., Irvine, California) in the treatment of drug refractory symptomatic PsAF compared to predetermined performance goals. The ablation catheter has been described in detail elsewhere.[6,7]

The study design is summarized in Figure 1. As accepted in the most recent Consensus Statement,[1] a 3-month medication adjustment period followed by a 3-month therapy consolidation period (i.e., blanking period) were included post ablation. Dose modification of the currently used AAD, addition of a new AAD, and substrate remodeling might occur during the medication adjustment period. During the subsequent therapy consolidation period, the status of the medication adjustment was assessed and repeat ablation was performed as necessary. Cardioversion was allowed if the arrhythmia recurrence persisted during the therapy consolidation period. Participants were followed up at 1, 3, 6, 9, 12, and 15 months post-ablation. Arrhythmia recurrences were stringently monitored: electrocardiograms were obtained at baseline, discharge, 6, 9, 12, and 15-month visits and 24-hour Holter monitoring was performed at baseline, 6, 12, and 15-month visits; transtelephonic monitoring (TTM) transmissions were performed monthly or when symptoms occurred during the 9-month evaluation period. All recordings were independently adjudicated by a core lab for consistency in interpretation. An independent safety monitoring committee reviewed and adjudicated all adverse events.

Study population

Eligible participants had documented symptomatic PsAF, defined as continuous AF sustained beyond 7 days but less than 1 year, and nonresponse or intolerance to at least one antiarrhythmic drug (AAD) (Class I or III).

Study exclusion criteria included age younger than 18 years, continuous AF for more than 12 months duration, ejection fraction < 40%, left atrial (LA) diameter ≥ 50 mm, documented LA thrombus, previous AF ablation, coronary artery bypass graft procedure in the last 6 months, any cardiac surgery within the past 2 months, carotid stenting or endarterectomy, prior valvular cardiac surgical procedure, presence of an implanted cardioverter-defibrillator, New York Heart Association (NYHA) functional class III or class IV, myocardial infarction within the previous 2 months, thromboembolic event in the previous 12 months, history of clotting or bleeding disorders, significant pulmonary disease, contraindication to anticoagulation medications, and life expectancy under 12 months.

Ablation procedure

After transseptal puncture, electro-anatomical mapping was performed using the Carto 3 system with either the Lasso catheter or Pentaray NAV catheter (Biosense Webster, Inc., Irvine, California). Ablation was performed with the STSF catheter guided by the Visitag module, using the following recommended settings: location stability of 3 mm, a minimum time of 3 seconds, and a force-over-time filter of less than 50%. Isolation of all PVs was required. Linear ablation lines were only required to treat documented macro-reentry atrial tachycardias and limited to the LA roof line, mitral valve isthmus line, LA floor line, and cavotricuspid isthmus. A right atrial cavotricuspid isthmus linear ablation was required in cases with documented typical atrial flutter either prior to or during the procedure. Ablation of spontaneous non-PV triggers or those induced by adenosine or isoproterenol were at operator's discretion. Complex fractionated atrial electrogram ablation (LA, right atrial, and coronary sinus) was performed only if normal sinus rhythm was not spontaneously restored after ablation of PV and non-PV triggers and substrate modification with linear ablation. PVI was confirmed via entrance block with the Lasso or

Pentaray catheter. After PVI confirmation, a 30-minute waiting period from the last RF application was required, with adenosine/isoproterenol challenge to rule out dormant reconduction.

Safety outcomes

The primary safety endpoint was the incidence of primary adverse events (PAEs) occurring within 7 days of the initial and repeat ablation procedures using the study catheter.. PAEs included: death, atrioesophageal fistula, cardiac tamponade/perforation, myocardial infarction, stroke/cerebrovascular accident, thromboembolism, transient ischemic attack (TIA), diaphragmatic paralysis, pneumothorax, heart block, PV stenosis, pulmonary edema, pericarditis, and major vascular access complication or bleeding. PV stenosis and atrioesophageal fistulas occurring more than 7 days after the index procedure were also considered PAEs.

Effectiveness outcomes

The primary effectiveness endpoint was freedom from documented recurrence of AF/atrial flutter (AFL)/atrial tachycardia (AT) episodes of 30 seconds or longer duration and freedom from additional 5 failure modes at 15 months: acute procedural failure, use of non-study catheter, repeat procedures, use of new/higher dose AAD, surgical ablation (Figure 1).

Secondary effectiveness outcomes included acute procedural success (defined as confirmation of entrance block in all PVs) and single procedure success (defined as freedom from documented AF/AT/AFL recurrence during the evaluation period after a single ablation procedure; any repeat ablation procedures after the index procedure were deemed effectiveness failure for this analysis). Since most PsAF studies reported atrial arrhythmia recurrences by standard-of-care ECG/Holter monitoring only, an exploratory analysis using only atrial arrhythmia recurrences as detected by ECG/Holter up to 12 months follow-up was also performed for comparison with

published data. Freedom from repeat ablation was analyzed at 12 and 15 months. Clinical success was defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes of 30 seconds or longer) evaluated after all ablation procedures at 15 months.

Statistical methods

Patient demographic, cardiovascular medical history, AAD history, baseline CHA2DS2-VASc score, AF history, and procedure data were summarized descriptively. Categorical variables were presented using frequencies and percentages. Continuous variables were presented using mean and standard deviation.

The primary safety endpoint was evaluated using the exact test for a binomial proportion at a two-sided significance level of 5%. The upper bound of the one-sided exact 97.5% confidence interval of the primary safety endpoint rate was compared to the performance goal of 16%. Kaplan-Meier analyses were conducted separately on the primary effectiveness endpoint, single procedure success, clinical success, and repeat procedure during the evaluation period in the effectiveness population. To identify factors associated with the primary effectiveness outcomes, univariable and multivariable logistic regression models were fit to the data. In the first steps, univariate logistic regression models were used to evaluate the association between demographics, baseline medical history, and procedural data with the primary effectiveness endpoint. Continuous variables were divided into categories such as age (<60, 60-70, >=70 years), CHA_2DS_2-VASc score at baseline (>=2, <2), number of class I/ III AAD Failed at baseline (>=1, 0), contact force high range (grams) (>40, 30 - 40, <=30), total RF application duration (min) (> 60, 30 - 60 vs. <=30), and baseline AFEQT score (>=50 vs. <50). In the second step, if any statistically significant associations were observed at a 0.10 level in the univariate logistic regression, the variables were considered for the multivariable model.

Based on a primary effectiveness performance goal of 40% and an anticipated freedom from AF recurrence rate of 50%, 330 subjects were required to obtain at least 90% power at a two-sided significance level of 0.05 using the exact binomial method. The safety population consisted of all enrolled participants who had undergone insertion of the study catheter and was used as the analysis population for the primary safety endpoint. The effectiveness population included participants who were enrolled, met all eligibility criteria, and underwent RF ablation with study catheter for study-related arrhythmia. All statistically analyses were performed in SAS Studio 3.4 or SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients

Between July 27, 2016, and February 6, 2018, 381 participants were enrolled in the study. Participant disposition and accountability are detailed in Figure 2. Of the 381 enrolled participants, 348 had the investigational catheter inserted and comprised the safety population. All participants in the safety population underwent RF ablation. Four participants had missing 3 months data for safety assessment and thus were removed from the primary safety endpoint analysis. The effectiveness population comprised 333 participants after exclusion of 14 participants who did not meet inclusion criteria and one participant who was ablated with a non-study catheter. The overall follow-up visit compliance rate was 96%. At each follow-up visit (7 days, 1-15 months), the compliance rates were 90% or higher (91-99%). The compliance rate for the 15-month follow-up visit was 94%. Participant characteristics at study baseline are described in Table 1 and Supplemental Table 1.

All participants underwent PVI, with 193 procedures (55.5%) completed with only PVI. The remaining 44.5% included additional non-PV targets (complex fractionated atrial electrograms, non-PV triggers, and substrate modification).

Safety outcomes

Overall, 14 primary adverse events were reported for 13 participants (Table 2). The primary adverse event rate was 3.8% (13/344) and one-sided exact 97.5% upper confidence bound was 6.4%, significantly less than the specified performance goal of 16.0%. Therefore, the results met the protocol-established performance criteria for primary safety. Eleven events were resolved without sequelae. One patient with cardiac tamponade underwent a surgical repair procedure, during which an ablation and left atrial appendage closure were also performed. One case of phrenic nerve paralysis occurred, and the injury persisted at the final follow-up.

Effectiveness outcomes

Acute procedural success (confirmation of entrance block on all PVs) was achieved in 330 out of 333 participants (99.1%). Kaplan Meier estimated the 15 months primary effectiveness success rate of 61.7% (Figure 3 A). The one-sided exact 97.5% lower confidence bound of 54.1% was significantly higher than the pre-determined performance criteria of 40.0%, and the primary effectiveness performance criteria was met. Twenty (20) patients had failed the primary effectiveness endpoint due to the use of new or higher doses of AAD. Among the patients who reached primary effectiveness endpoint, 18% (32/178) were on Class I/III AAD that were previously ineffective. Among those, 1.7% (3/178) patients were on amiodarone. In contrast, of the 381 enrolled patients, 34.4% (131/381) had used amiodarone at baseline.

Kaplan Meier estimates of single procedure success rate was 64.2% by all 3 study arrhythmia monitoring methods (Figure 3B). Clinical success of freedom from documented symptomatic

atrial arrhythmia was 80.4% at 15 months post-procedure (Figure 3C). Kaplan Meier estimates of freedom from all documented and documented symptomatic atrial arrhythmia off Class I/III AAD was 57.7% and 64.7%, respectively.

To facilitate indirect comparison of study results to published data, exploratory analysis of single procedure success by Holter/ECG monitoring only at 12 months follow-up with 3-months blanking was performed with a success rate of 73.2%.

Repeat ablation

Overall, 378 procedures (index and repeat) were performed for 333 participants in the effectiveness population, including 19 repeat ablations during the blanking period (5.7%) and 26 repeat ablations after the blanking period (7.8%). The mean number of procedures performed per participant was 1.14. At 12 and 15 months, the Kaplan-Meier estimated freedom from repeat ablation was 89.2% and 86.1%, respectively (Figure 3D).

Risk factors associated with primary safety and effectiveness outcomes

Logistic regression modeling was performed to identify potential risk factors associated with primary effectiveness (Table 3). Multivariable modelling indicated that female sex, presence of left ventricular systolic dysfunction, and low Atrial Fibrillation Effect on Quality-of-Life score at baseline (≤50) were associated with a higher risk of primary effectiveness failure.

Stability tag settings

Carto data were available for 298 procedures, 294 of which had stability time/location range captured. A total of 55,400 Visitag points with stability time were identified in 294 procedures. The most frequently selected settings were stability time 3–5 seconds (72.4%) and location stability of ±3 mm (33.7%) or ±1.5mm (30.4%; Figure 4). Most operators did not use the Force-over-Time (FOT, 88.5% Visitag points with FOT = 0) feature of the Visitag module.

Procedure details

Table 4 summarizes ablation procedure parameters. The average total procedure time was 178.0 minutes. Of this time, fluoroscopy was used for an average of 15.3 minutes per procedure. Mean ablation time, from the time of the first RF application to the time of the last application, was 107.7 minutes.

DISCUSSION

PRECEPT is the first IDE clinical study with stringent atrial arrhythmia monitoring that demonstrated the long-term safety and effectiveness of RF catheter ablation in drug-refractory symptomatic PsAF using the STSF catheter guided by the Visitag module. The rate of PAEs was low (3.8%) with a long-term overall protocol-defined success rate of 62% and clinical success rate of 80%.

The PRECEPT study established the safety of PsAF RF ablation. Despite the higher risk factors and comorbidities inherent to the PsAF population, the low rate of PAEs in the current study is similar to that reported in paroxysmal AF ablation studies.[3,4,6] Notably, there were no unexpected AEs, deaths, strokes, atrioesophageal fistulas, or cases of PV stenosis. Cardiac tamponade was the most frequently reported PAE in the PRECEPT study with a rate of 1.5%, which is within the acceptable 0.2–5% range reported in current international consensus statement,[1] and similar to the rates of 1.2–1.3% reported in two worldwide surveys of AF procedure safety.[10,11]

Comparison of the current results to published data on ablation of PsAF is challenging. Patients with PsAF are highly heterogeneous across different studies, and few studies have used stringent arrhythmia monitoring (such as regular TTM transmissions) and with contemporary ablation technologies. To put the PRECEPT study findings into perspective, we did an indirect comparison of our results with previously published studies by two approaches: first, comparison

with studies that used stringent arrhythmia monitoring; and second, comparison with studies that used standard-of-care monitoring.

Few studies utilized stringent arrhythmia monitoring with regular TTM. First, the STAR AF II study compared ablation of PsAF with PVI alone versus PVI plus ablation of electrograms showing complex fractionated activity or PVI plus additional linear ablation across the LA roof and mitral valve isthmus.[12] The study employed arrhythmia monitoring using Holter and TTM transmission, but was conducted before the availability of CF catheters. The single procedure success rate reported in STAR AF II was 37–49% at 18 months, lower than 64% reported in PRECEPT. Consistent with this finding is the lower repeat ablation rate in PRECEPT (7.8%) compared with STAR AF II (21-33%; Figure 5). In the latest STOP PERSISTENT AF trial,[13] an FDA-regulated IDE study similar to PRECEPT, PsAF patients (with less than 6 months of PsAF history) were treated with cryoballoon catheters using a PVI-only approach, yielding a 12-month success rate of 55% and freedom from repeat ablation of 87%s. In contrast, PRECEPT included a broader group of PsAF patients (PsAF up to 1-year duration) with higher baseline comorbidities and resulted in a better outcome. The difference in outcome may be partially explained by the fact that some patients in PRECEPT received additional ablation beyond PVI, which is likely to be needed in some patients with PsAF.

The majority of the PsAF ablation studies utilized standard-of-care monitoring to assess arrhythmia recurrence, with 12-lead ECG and limited Holter monitoring and only limited or no TTM. In order to compare the current study with these study findings, we performed an exploratory analysis of the PRECEPT results using only data on atrial arrhythmia as detected by ECG and/or Holter monitoring (Figure 5). Exploratory analysis of single-procedure success rate at 12 months with ECG/Holter monitoring was estimated at 73% in PRECEPT. This rate is

similar to the 71% rate at 12-month follow up reported in the recent TOUCH AF study, which used 48-hour Holter and 12-lead ECG arrhythmia monitoring at each clinic visit, but limited loop recording or TTM only when the patient reported symptoms.[14] Two recent publications which included older RF or non-RF ablation technologies reported 12-month single procedure success rates for PsAF ablation between 61–67%, slightly lower than that observed in PRECEPT.[15,16] In both publications, enrolled patients had a low prevalence of structural heart disease. Specifically, in the Cryo4Persistent AF study, patients enrolled were on average slightly younger, had a lower prevalence of comorbidities (e.g. hypertension, diabetes, or coronary artery disease), and a lower stroke risk compared with the participants enrolled in PRECEPT, and the study only allowed for PVI ablation,[15] likely due to the aforementioned patient characteristics. These prior results, when put in perspective with PRECEPT (higher single-procedure success rate in patients with a greater comorbidity burden but with an individualized and optimized treatment approach) makes the findings of the study especially encouraging in comparison.

It is possible that a higher success rate may have been observed if the PRECEPT study had included only "early persistent" patients with lower underlying comorbidities.[1] In the recent PRAISE study, which utilized a novel CF-sensing catheter and an automated CF stability module and enrolled relatively lower-risk patients (mean CHA_2DS_2Vasc score of 1, majority of patients without structural heart disease), 95% of patients were in sinus rhythm and recurrence of arrhythmia was documented in only 20% of patients at 12-month follow up, similar to outcomes observed in paroxysmal AF patients.[17]

It is worth noting both Cryo4Persistent AF and PRAISE studies, which included largely persistent AF patients with fewer comorbidities employed a PVI-only ablation strategy, likely based on AF disease presentation. This is in contrary to PRECEPT where ablation strategies

were at the discretion of the investigators, representing more closely standard-of-care practice with broader range of patient population. The 2017 Consensus Statement recognized the range of disease presentation and ablation outcome of persistent AF patient. Specifically, responses of "early" and "late" persistent AF patients may be different in that those with more advanced disease presentation may have worse outcome similar to long-standing persistent AF patients.[1] There is currently no consensus on appropriate patient segmentation (i.e. "early" vs "late" PsAF) and associated optimal ablation strategy for PsAF. These questions need to be evaluated in future trials.

The primary effectiveness endpoint of the PRECEPT study was based on the conventional outcome of freedom from recurrence of any documented atrial arrhythmia episodes lasting 30 seconds or longer, an outcome which may not be clinically relevant to individual patients with PsAF. A clinically meaningful definition of success in this population is freedom from documented symptomatic AF/AFL/AT recurrence, as AF symptoms represent the main burden on patients' quality of life, and the goal of AF ablation treatment is symptomatic relief. PRECEPT results showed a clinical success rate of 80% at 15 months. Many individuals with AF experience symptoms such as palpitations and dyspnea with exertion. Data from the ORBIT-AF Registry have shown that a higher AF symptom burden is associated with a lower quality of life and higher rates of hospitalization.[18] An analysis of data from the STAR AF study demonstrated that quality of life after AF ablation was improved regardless of procedural outcomes as defined by the study protocol, and that quality-of-life scores were negatively affected only in patients with a high symptomatic burden of arrhythmia recurrence. The results suggested that a

significant reduction in symptom burden improves quality of life even in the absence of total elimination of AF episodes.[19]

Study limitations and future research needs

The PRECEPT study was not designed to compare outcomes with different ablation strategies. While PVI remains the cornerstone of AF ablation even in PsAF population,[1] in the current study, approximately half of the patients received additional ablation beyond PVI at the investigators' discretion. The underlying assumption of a one-size-fit-all concept for most PsAF ablation studies deserves re-evaluation and consideration. It is important to understand underlying patient characteristics for clinical decision making towards different ablation strategies that may be tailored to individual patient's needs.

The gold standard for defining success in catheter ablation studies is arrhythmia-free survival over a 12-month follow-up, as measured by a 30-second episode of AF. There is increasing consensus that a more clinically relevant outcome is needed for defining treatment success. For PsAF treatment, a more clinically meaningful treatment goal for patients is reduction of symptoms and associated AF burden. The CLOSE to CURE study recently showed a near 100% reduction in atrial tachyarrhythmia burden, as measured by an implantable loop recorder, during 2 years of follow up after paroxysmal AF ablation.[20] Results from PRECEPT showed an 80% symptomatic arrhythmia free survival at 15-month follow-up. Future studies are needed to evaluate associated reduction in atrial arrhythmia burden from continuous monitoring following catheter ablation treatment.

CONCLUSION

The PRECEPT study demonstrated the clinical safety and effectiveness of PsAF ablation using CF-sensing technologies with protocol-defined effectiveness of 62% and clinical success of 80%.

The PAE rate was within the acceptable and expected range and similar to that for paroxysmal AF ablation. Comparison of with other multicenter studies suggests individualized ablation approach base on patient's clinical presentation may optimize treatment outcome.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge: Drug-refractory symptomatic persistent atrial fibrillation (PsAF) can be successfully and safely treated by radiofrequency catheter ablation using contact-force-sensing technologies.

Translational Outlook 1: While PRECEPT showed a high rate of freedom from symptomatic atrial arrhythmia, future studies should evaluate reductions in AF burden and associated quality of life in more detail.

Translational Outlook 2: There is currently no consensus on appropriate patient segmentation and associated optimal ablation strategy for PsAF, so the findings of PRECEPT need to be expanded upon in future studies comparing different ablation strategies in this patient population.

REFERENCES

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *J Interv Card Electrophysiol.* 2017;50(1):1-55.

2. Macle L, Frame D, Gache LM, Monir G, Pollak SJ, Boo LM. Atrial fibrillation ablation with a spring sensor-irrigated contact force-sensing catheter compared with other ablation catheters: systematic literature review and meta-analysis. *BMJ Open.* 2019;9(6):e023775.

3. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *Journal of the American College of Cardiology.* 2014;64(7):647-656.

4. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.* 2010;303(4):333-340.

5. Bertaglia E, Fassini G, Anselmino M, et al. Comparison of ThermoCool(R) Surround Flow catheter versus ThermoCool(R) catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. *J Cardiovasc Electrophysiol.* 2013;24(3):269-273.

6. Chinitz LA, Melby DP, Marchlinski FE, et al. Safety and efficiency of porous-tip contact-force catheter for drug-refractory symptomatic paroxysmal atrial fibrillation ablation: results from the SMART SF trial. *Europace.* 2018;20(FI_3):f392-f400.

7. Maurer T, Rottner L, Makimoto H, et al. The best of two worlds? Pulmonary vein isolation using a novel radiofrequency ablation catheter incorporating contact force sensing technology and 56-hole porous tip irrigation. *Clin Res Cardiol.* 2018;107(11):1003-1012.

8. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. *Eur Heart J.* 2017;38(1):20-26.

9. Chen LY, Chung MK, Allen LA, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation.* 2018;137(20):e623-e644.

10. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation.* 2005;111(9):1100-1105.

11. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2010;3(1):32-38.

12. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812-1822.

13. Calkins Hea. Arctic Front Advance Cryoballoon Ablation for Persistent Atrial Fibrillation: 12 Month Efficacy and Safety Results from the Global Perspective Multicenter STOP PERSISTENT AF Study. 2020; Presented at: The 25th Annual International AF Symposium; January 23-25, 2020; Washington, D.C.

14. Conti S, Weerasooriya R, Novak P, et al. Contact force sensing for ablation of persistent atrial fibrillation: A randomized, multicenter trial. *Heart Rhythm.* 2018;15(2):201-208.

15. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: results from the multicenter CRYO4PERSISTENT AF trial. *JACC Clin Electrophysiol.* 2018;4(11):1440-1447.

16. Voskoboinik A, Moskovitch JT, Harel N, Sanders P, Kistler PM, Kalman JM. Revisiting pulmonary vein isolation alone for persistent atrial fibrillation: A systematic review and meta-analysis. *Heart Rhythm.* 2017;14(5):661-667.

17. Hussein A, Das M, Riva S, et al. Use of ablation index-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent atrial fibrillation patients. *Circ Arrhythm Electrophysiol.* 2018;11(9):e006576.

18. Freeman JV, Simon DN, Go AS, et al. Association between atrial fibrillation symptoms, quality of life, and patient outcomes: results from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes.* 2015;8(4):393-402.

19. Mantovan R, Macle L, De Martino G, et al. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol.* 2013;29(10):1211-1217.

20. Duytschaever M, De Pooter J, Demolder A, et al. Long-term impact of catheter ablation on arrhythmia burden in low-risk patients with paroxysmal atrial fibrillation: The CLOSE to CURE study. *Heart Rhythm.* 2019.

FIGURES

Figure 1. Schedule of follow-up, arrhythmia monitoring, and definition of primary effectiveness failure modes*

*Patients had a phone follow-up visit at 7 days. Clinic follow-up visits occurred at 1, 3, 6, 9, 12, and 15 months.

**All symptomatic cardiac episodes should be recorded and transmitted via TTM at the time of event(s).

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; ECG, electrocardiogram; HM, Holter monitoring; PV, pulmonary vein; SCR, scheduled clinical review; TTM, transtelephonic monitoring.

Figure 2. Participant accountability and disposition

Figure 3. Kaplan-Meier analysis of (A) time to primary effectiveness failure, (B) single procedure failure, (C) documented symptomatic AF/AFL/AT recurrence, and (D) repeat ablation through 15 months post procedure (Effectiveness population, N=333)

AF, atrial fibrillation; AT, atrial tachycardia; AFL, atrial flutter.

Figure 4. Operator-configured Visitag (A) stability time and (B) stability range per Visitag point (Safety Population, N=348)

Figure 5. Single procedure freedom from AF/AT/AFL recurrence in studies of PsAF ablation

AAD, antiarrhythmic drug; AF, atrial fibrillation; AT, atrial tachycardia; AFL, atrial flutter; CB, cryoballoon; CB2, second□generation CB; CF, contact force; ECG, electrocardiogram; PsAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; RF, radiofrequency; TTM, transtelephonic monitoring.

CENTRAL ILLUSTRATION

Title: Drug-refractory Symptomatic Persistent AF Can Be Successfully and Safely Treated by RF Catheter Ablation

TABLES

Table 1. Participant characteristics and medical history at study baseline

	Effectiveness Population (N=333)	Safety Population (N=348)
Male, n (%)	237 (71.2)	246 (70.7)
Age, mean (SD), years	65.4 (8.8)	65.4 (8.7)
Medical history, n (%)		
Coronary disease	74 (22.2)	77 (22.1)
Myocardial infarction	19 (5.7)	19 (5.5)
Hypertension	227 (68.2)	238 (68.4)
Cardiomyopathy	39 (11.7)	42 (12.1)
TIA/stroke	15 (4.5)	16 (4.6)
Atrial flutter	65 (19.5)	68 (19.5)
Diabetes	61 (18.3)	62 (17.8)
Obstructive sleep apnea	132 (39.6)	134 (38.5)
CHA_2DS_2-VASc score, mean (SD)	2.3 (1.5)	2.3 (1.5)
NYHA functional class, n (%)		
I	16 (4.8)	17 (4.9)
II	27 (8.1)	28 (8.0)
III	0	1 (0.3)
Unknown	9 (2.7)	9 (2.6)
Number of failed AADs at baseline, mean (SD)	1.3 (0.6)	1.3 (0.6)

Baseline AAD history, n (%)		
Class I	119 (35.7)	121 (34.8)
Class II	189 (56.8)	199 (57.2)
Class III	252 (75.7)	259 (74.4)
Class IV	60 (18.0)	62 (17.8)
Class V	13 (3.9)	14 (4.0)
LVEF, mean (SD)	56.2 (7.2)	56.2 (7.2)
LA dimension, mean (SD), mm	42.6 (5.1)	42.4 (5.1)
Symptomatic PsAF duration, mean (SD), months	15.9 (30.8)	15.5 (30.2)

AAD, anti-antiarrhythmic drug; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes, prior stroke or TIA, vascular disease, sex category; LA, left atrium; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PsAF persistent atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Table 2. Primary adverse events (Safety Analysis Population, N=344)

	n (%)
Death	0 (0.0)
Atrio-esophageal fistula	0 (0.0)
Cardiac tamponade	5 (1.5)
Myocardial infarction	0 (0.0)
Cerebrovascular accident/stroke	1 (0.3)
Thromboembolism	0 (0.0)
Transient ischemic attack	1 (0.3)
Diaphragmatic paralysis	1 (0.3)
Pneumothorax	0 (0.0)
Heart block	0 (0.0)
Pulmonary vein stenosis	0 (0.0)
Pulmonary edema (respiratory insufficiency)	1 (0.3)
Pericarditis	2 (0.6)
Major vascular access complication/ bleeding	3 (0.9)

Table 3. Univariable and multivariable logistic regression analysis of the primary effectiveness endpoint (n=333)

	Univariable Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Sex (male vs. female)	0.54	0.33, 0.90	0.018	0.56	0.32, 0.97	0.040
Number of DCCV in the past 180 days	1.26	0.96, 1.65	0.098	1.23	0.92, 1.64	0.168
Pulmonary hypertension (Yes vs. No)	7.76	0.90, 67.30	0.063	6.84	0.71, 65.66	0.096
Left ventricular systolic dysfunction (Yes vs. No)	4.20	1.09, 16.18	0.037	5.77	1.44, 23.20	0.014
Stroke (Yes vs. No)	3.14	0.92, 10.66	0.067	3.00	0.81, 11.14	0.101
Number of Class III AADs failed (≥1 vs. 0)	1.76	0.99, 3.14	0.053	1.70	0.93, 3.13	0.086
Contact force high range (grams) (>30 & ≤40 vs. ≤30)	1.37	0.77, 2.45	0.289	1.27	0.68, 2.36	0.446
Contact force high range (grams) (>40 vs. ≤30)	2.95	1.10, 7.96	0.032	2.31	0.77, 6.98	0.136
AFEQT score (High vs. Low)	0.56	0.34, 0.91	0.020	0.56	0.32, 0.96	0.034

AAD, anti-antiarrhythmic drug; AFEQT, Atrial Fibrillation Effect on Quality-of-Life; CI, confidence interval; DCCV, direct current cardioversion; RF, radiofrequency.

Table 4. Procedural data (Safety Population, n=348)

	Statistics
Anesthesia type, n/N (%)	
Conscious sedation	16/348 (4.6)
General anesthesia	332/348 (95.4)
Total procedure time, mean (SD), minutes (n=348)	178.0 (71.0)
Total ablation time, mean (SD), minutes (n=348)	107.7 (48.6)
Total fluoroscopy time, mean (SD), minutes (n=348)	15.3 (16.6)
Total RF application duration, mean (SD), minutes (n=348)	55.56 (23.0)
Total mapping time, mean (SD), minutes (n=348)	15.3 (17.5)
Fluid delivered via study catheters, mean (SD), mL (n=339)	886.3 (391.2)

RF, radiofrequency; SD, standard deviation.

SUPPLEMENTAL MATERIALS

Persistent atrial fibrillation ablation with contact force sensing catheter: The prospective multicenter *PRECEPT* Trial

TABLE OF CONTENTS

Supplemental Table 1. Summary of AAD use at baseline

	Safety Population (N=348) n/N (%)	Per-Protocol Population (N=333) n/N (%)
Class I	121/348 (34.8%)	119/333 (35.7%)
Flecainide	83/348 (23.9%)	81/333 (24.3%)
Propafenone	42/348 (12.1%)	42/333 (12.6%)
Class II	199/348 (57.2%)	189/333 (56.8%)
Atenolol	13/348 (3.7%)	12/333 (3.6%)
Bisoprolol	11/348 (3.2%)	11/333 (3.3%)
Carvedilol	33/348 (9.5%)	32/333 (9.6%)
Metoprolol	139/348 (39.9%)	131/333 (39.3%)
Nadolol	2/348 (0.6%)	2/333 (0.6%)
Nebivolol	5/348 (1.4%)	4/333 (1.2%)
Tenoretic	1/348 (0.3%)	1/333 (0.3%)
Class III	259/348 (74.4%)	252/333 (75.7%)
Amiodarone	121/348 (34.8%)	118/333 (35.4%)
Dofetilide	31/348 (8.9%)	29/333 (8.7%)
Dronedarone	82/348 (23.6%)	82/333 (24.6%)
Sotalol	90/348 (25.9%)	87/333 (26.1%)
Class IV	62/348 (17.8%)	60/333 (18.0%)
Diltiazem	59/348 (17.0%)	57/333 (17.1%)
Verapamil	3/348 (0.9%)	3/333 (0.9%)
Class V	14/348 (4.0%)	13/333 (3.9%)
Digoxin	14/348 (4.0%)	13/333 (3.9%)
Anticoagulation		
Anticoagulant	329/348 (94.5%)	315/333 (94.6%)
Acetylsalicylic Acid	34/348 (9.8%)	32/333 (9.6%)
Apixaban	135/348 (38.8%)	129/333 (38.7%)
Clopidogrel	8/348 (2.3%)	7/333 (2.1%)
Dabigatran	20/348 (5.7%)	19/333 (5.7%)

Edoxaban	3/348 (0.9%)	3/333 (0.9%)
Enoxaparin	1/348 (0.3%)	1/333 (0.3%)
Prasugrel	1/348 (0.3%)	1/333 (0.3%)
Rivaroxaban	117/348 (33.6%)	110/333 (33.0%)
Warfarin	53/348 (15.2%)	53/333 (15.9%)
Heparin	2/348 (0.6%)	2/333 (0.6%)
Other Cardiac Drug		
ACE Inhibitor	79/348 (22.7%)	76/333 (22.8%)
ARB	57/348 (16.4%)	55/333 (16.5%)
Antihypertensive	56/348 (16.1%)	56/333 (16.8%)
Antilipid / Statin	132/348 (37.9%)	124/333 (37.2%)
Diuretic	84/348 (24.1%)	82/333 (24.6%)

Clinical Sites and Investigators

Study Site	Principal Investigator
Texas Cardiac Arrhythmia Research 3000 N. IH-35, Suite 705 Austin, TX Site ID: 101	Andrea Natale, MD
Hospital of the Univ. Pennsylvania 3400 Spruce Street, 9 Founders Philadelphia, PA Site ID: 102	Francis Marchlinski, MD
Cleveland Clinic Foundation 9500 Euclid Ave Cleveland, OH Site ID: 107	Walid Saliba, MD
Duke University Medical Center 2301 Erwin Rd, Durham, NC Site ID: 108	Tristram Bahnson, MD
Florida Hospital 601 East Rollins Street, PO #99 Orlando, FL Site ID: 109	Scott Pollak, MD

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Additional Disclosures

Vivek Reddy's disclosures with medical companies include: Abbott (Consultant), Ablacon (Consultant, Equity), Acutus Medical (Consultant, Equity), Affera (Consultant, Equity), Apama Medical (Consultant, Equity), Aquaheart (Consultant, Equity), Autonomix (Consultant, Equity), Axon (Consultant), Backbeat (Consultant, Equity), BioSig (Consultant, Equity), Biosense-Webster (Consultant), Biotronik (Consultant), Boston Scientific (Consultant), Cardiofocus (Consultant), Cardionomic (Consultant), CardioNXT / AFTx (Consultant), Circa Scientific (Consultant, Equity), Corvia Medical (Consultant, Equity), East End Medical (Consultant, Equity), EBR (Consultant), EPD (Consultant, Equity), Epix Therapeutics (Consultant, Equity), EpiEP (Consultant, Equity), Eximo (Consultant, Equity), Farapulse (Consultant, Equity), Fire1 (Consultant, Equity), Impulse Dynamics (Consultant), Javelin (Consultant, Equity), Keystone Heart (Consultant, Equity), LuxCath (Consultant, Equity), Manual Surgical Sciences (Equity), Medlumics (Consultant, Equity), Medtronic (Consultant), Middlepeak (Consultant, Equity), Newpace (Equity), Nuvera (Consultant, Equity), Philips (Consultant), Stimda (Consultant), Surecor (Equity), Thermedical (Consultant), Valcare (Consultant, Equity) and Vizara (Equity).

Central Illustration: Drug-refractory Symptomatic Persistent AF Can Be Successfully and Safely Treated by RF Catheter Ablation

PROSPECTIVE MULTICENTER STUDY (PRECEPT)

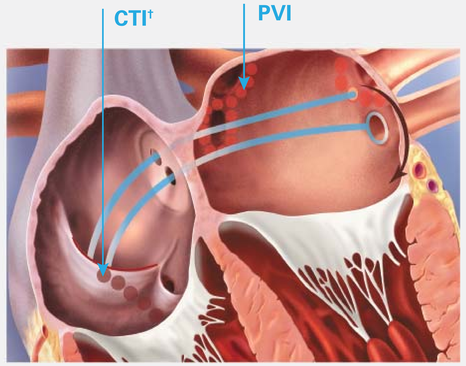
27
US & CANADIAN HOSPITALS

381
PATIENTS WITH DRUG REFRATORY SYMPTOMATIC **PERSISTENT AF**

71% male, 65 yrs
2.3 CHA_2DS_2-VASc score
16 mos in symptomatic persistent AF

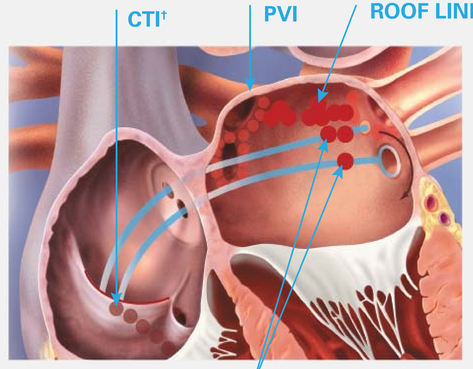
TAILORED RF ABLATION WITH CONTACT FORCE SENSING CATHETERS

PVI ONLY



OR

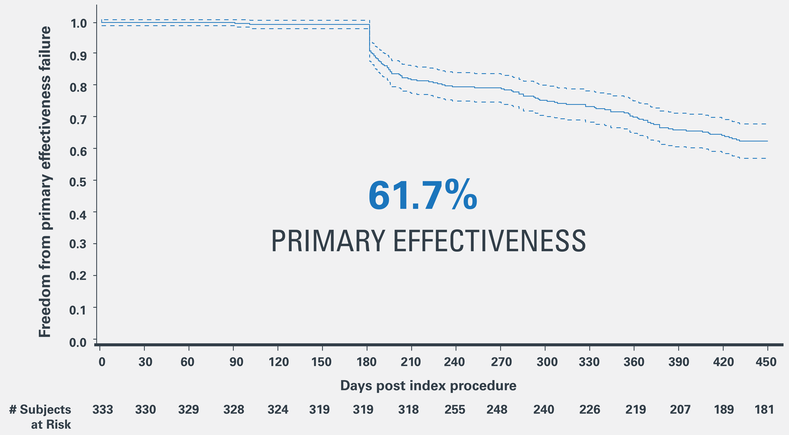
PVI+



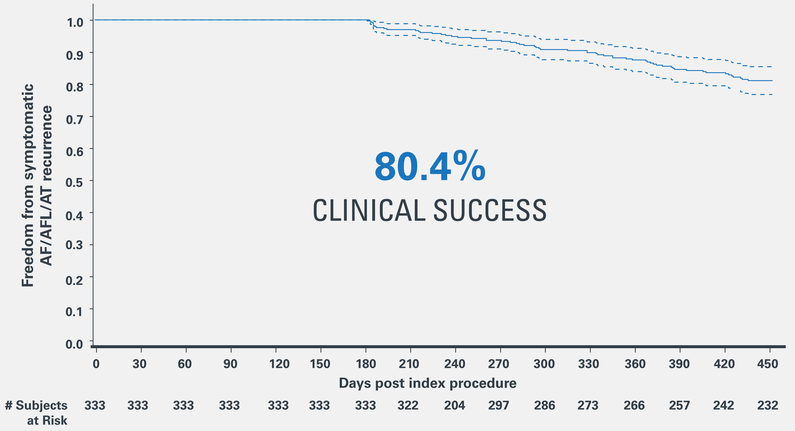
PVI+: additional left atrial ablation per operator's discretion
† CTI ablation with documented atrial flutter
CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation

KEY FINDINGS AT 15 MONTHS

3.8%
PRIMARY AE RATE

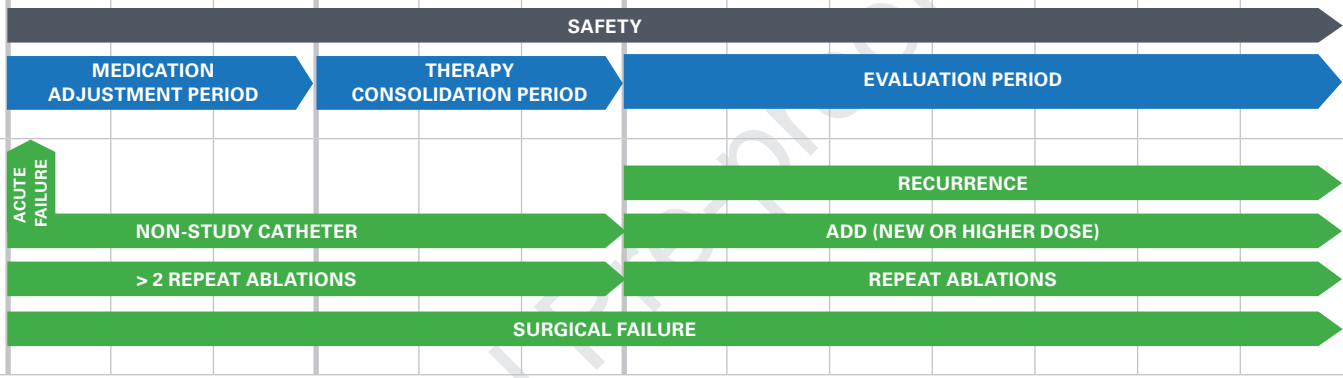


61.7%
PRIMARY EFFECTIVENESS



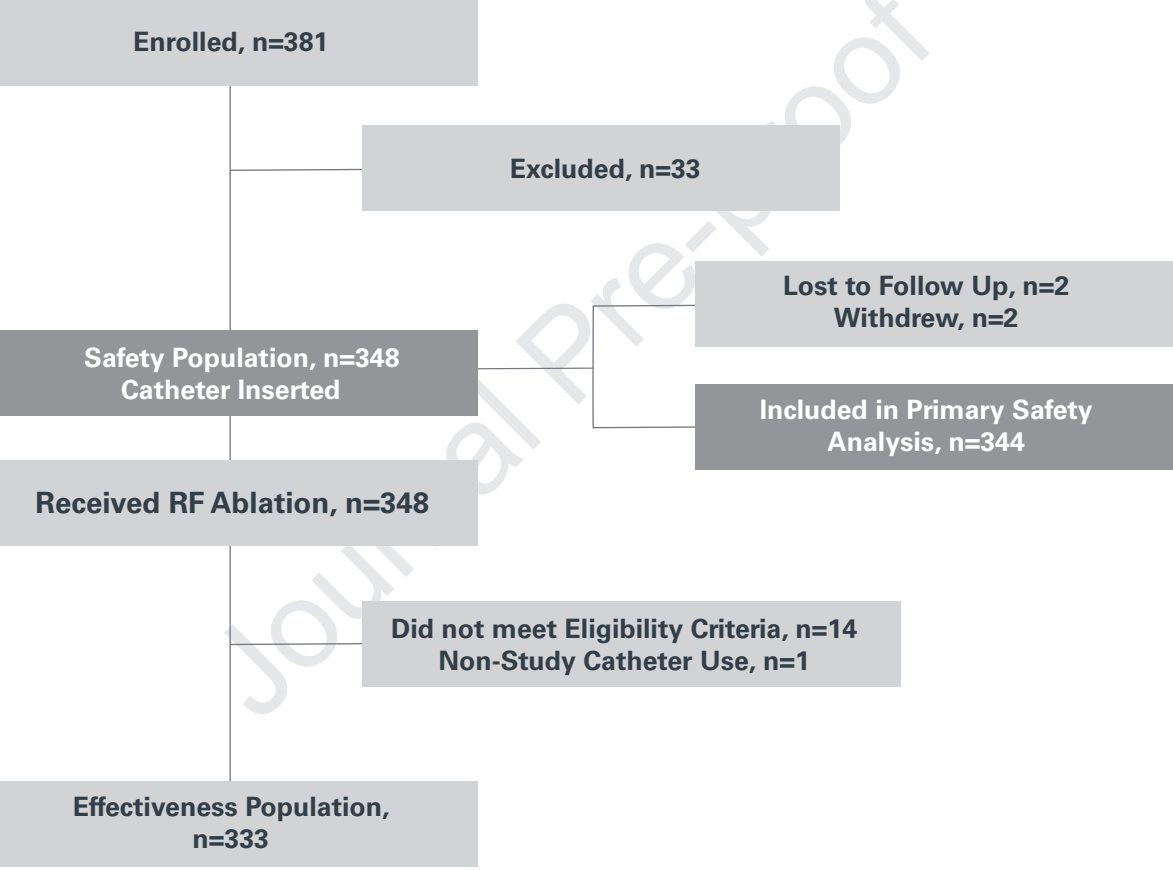
80.4%
CLINICAL SUCCESS

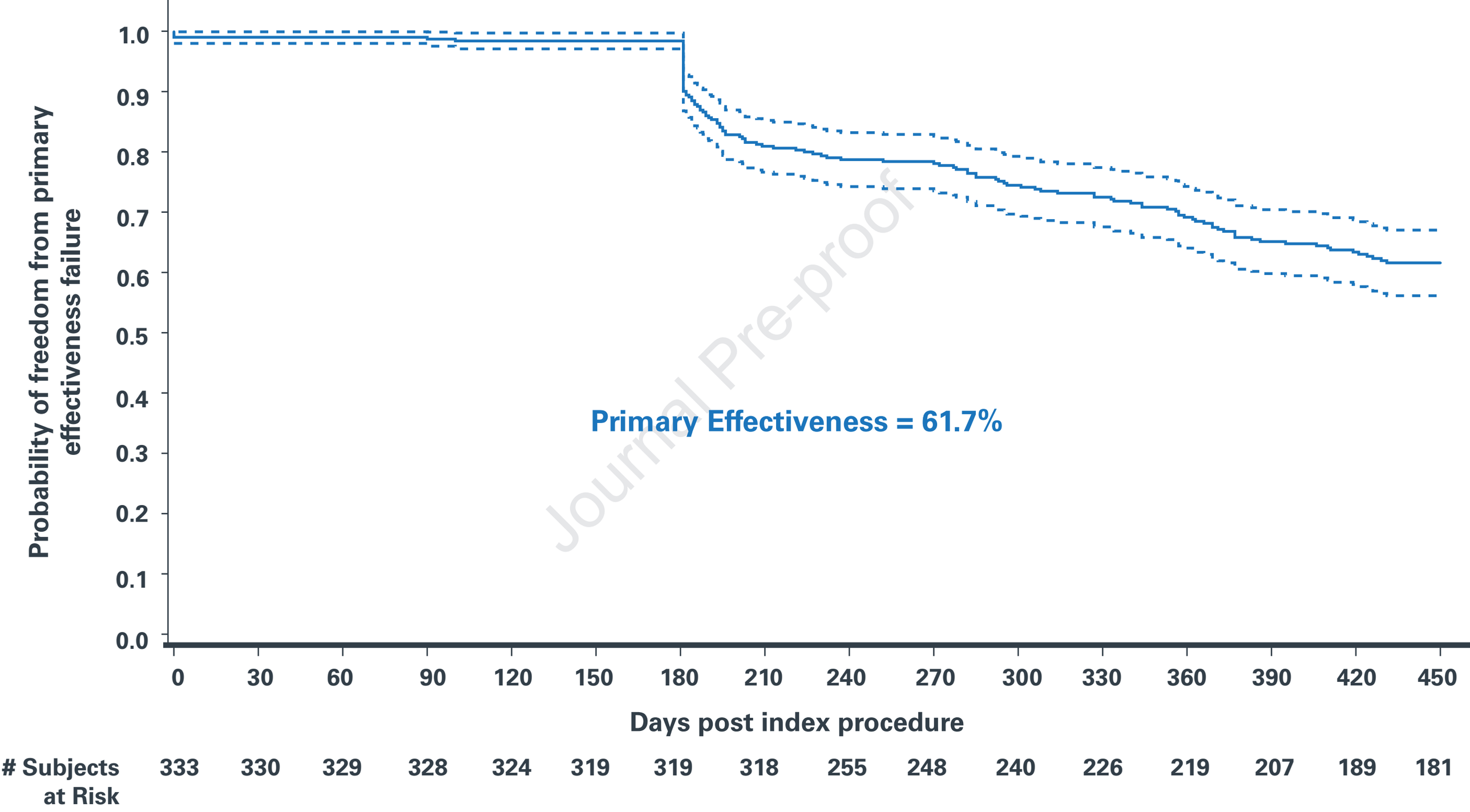
SCR	1-M	2-M	3-M	4-M	5-M	6-M	7-M	8-M	9-M	10-M	11-M	12-M	15-M
TTM**						x	x	x	x	x	x	x	x
ECG						x			x			x	x
HM						x						x	x

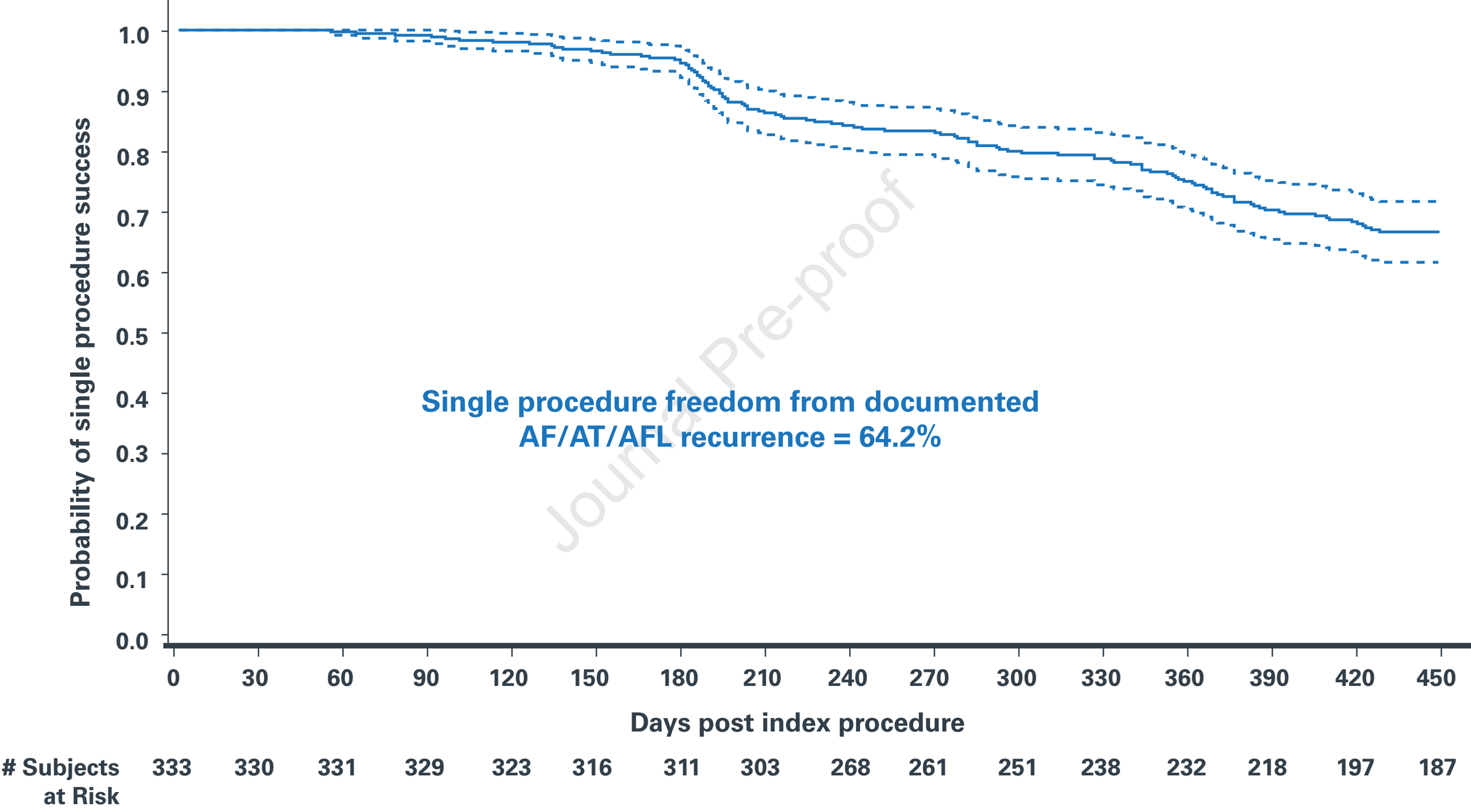


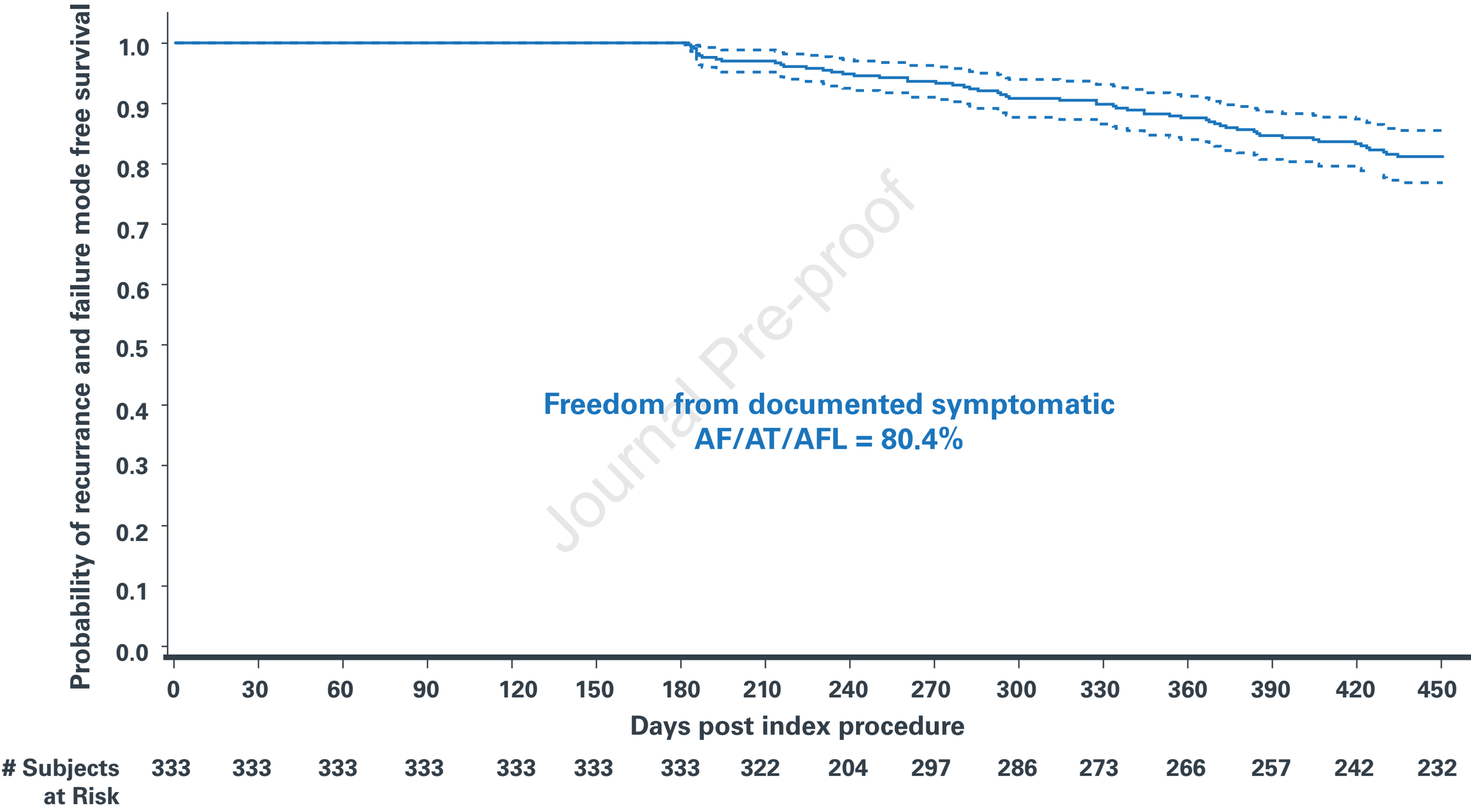
PRIMARY EFFECTIVENESS: FREEDOM FROM THE FOLLOWING FAILURE MODES

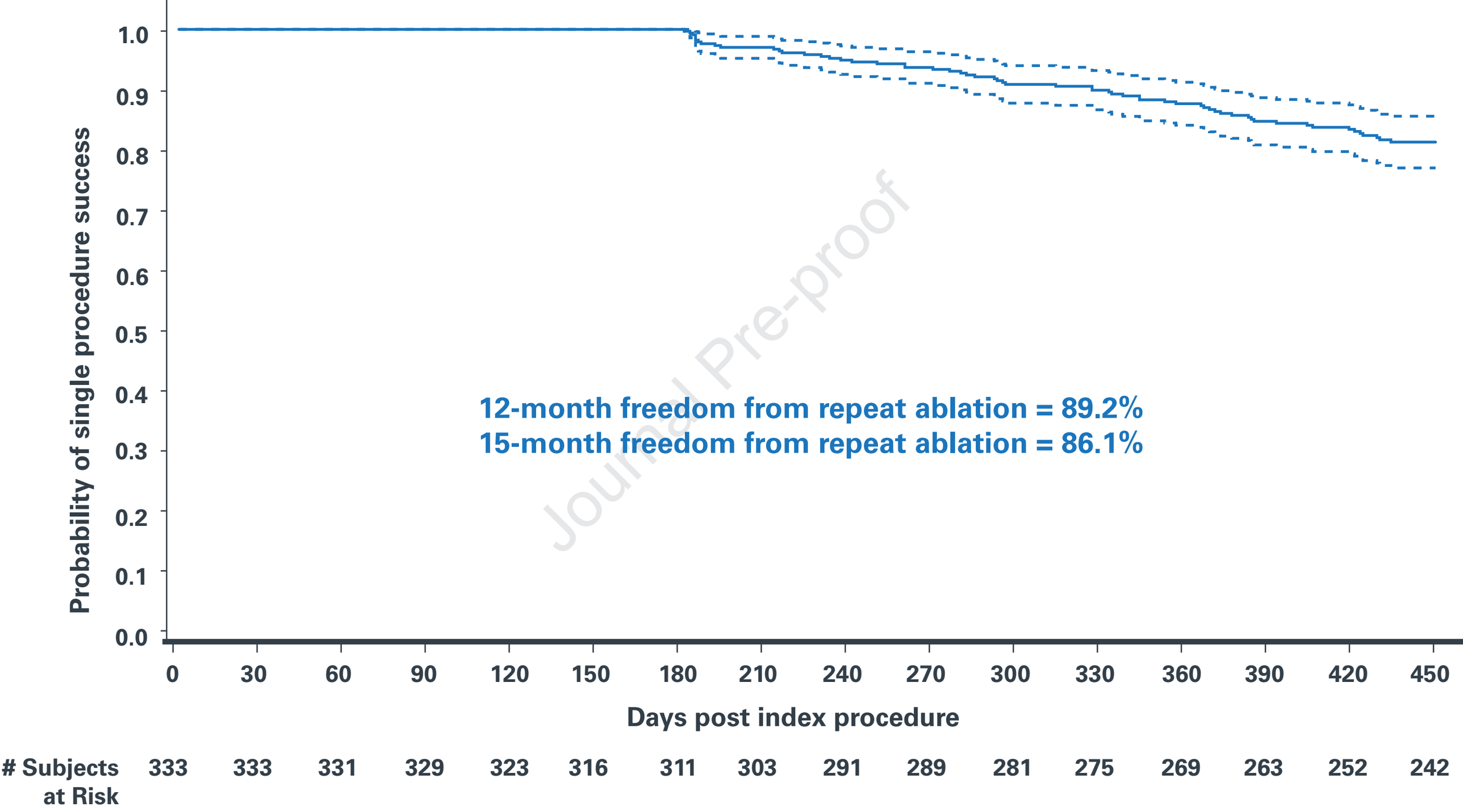
FAILURE MODE	DESCRIPTION	EVALUATION PERIOD
1. Recurrence	Documented AF/AFL/AT (>=30 sec) identified by TTM (monthly), HM (at 6, 12, 15M), ECG (at 6, 9, 12,15M), and other acknowledged devices (at 6, 9, 12, 15M)	Day 181-450
2. Acute Procedural Failure	1. Failure to confirm entrance block in all PVs 2. Use of non-study catheter in the index procedure	Day 0
3. Non-study Catheter Failure	Use of non-study catheter for repeat procedure for the treatment of study arrhythmia	Day 1-180
4. Repeat Ablation Failure	1. >2 repeat procedure during blanking period 2. Any repeat procedure post blanking	1. Day 1-180, 2. Day 181-450
5. AAD Failure	Taking New class I/III AAD for AF Taking previously failed AAD at a higher dose for AF	Day 181-450
6. Surgical Failure	Undergoing surgical AF ablation or AF surgery	Day 0-450

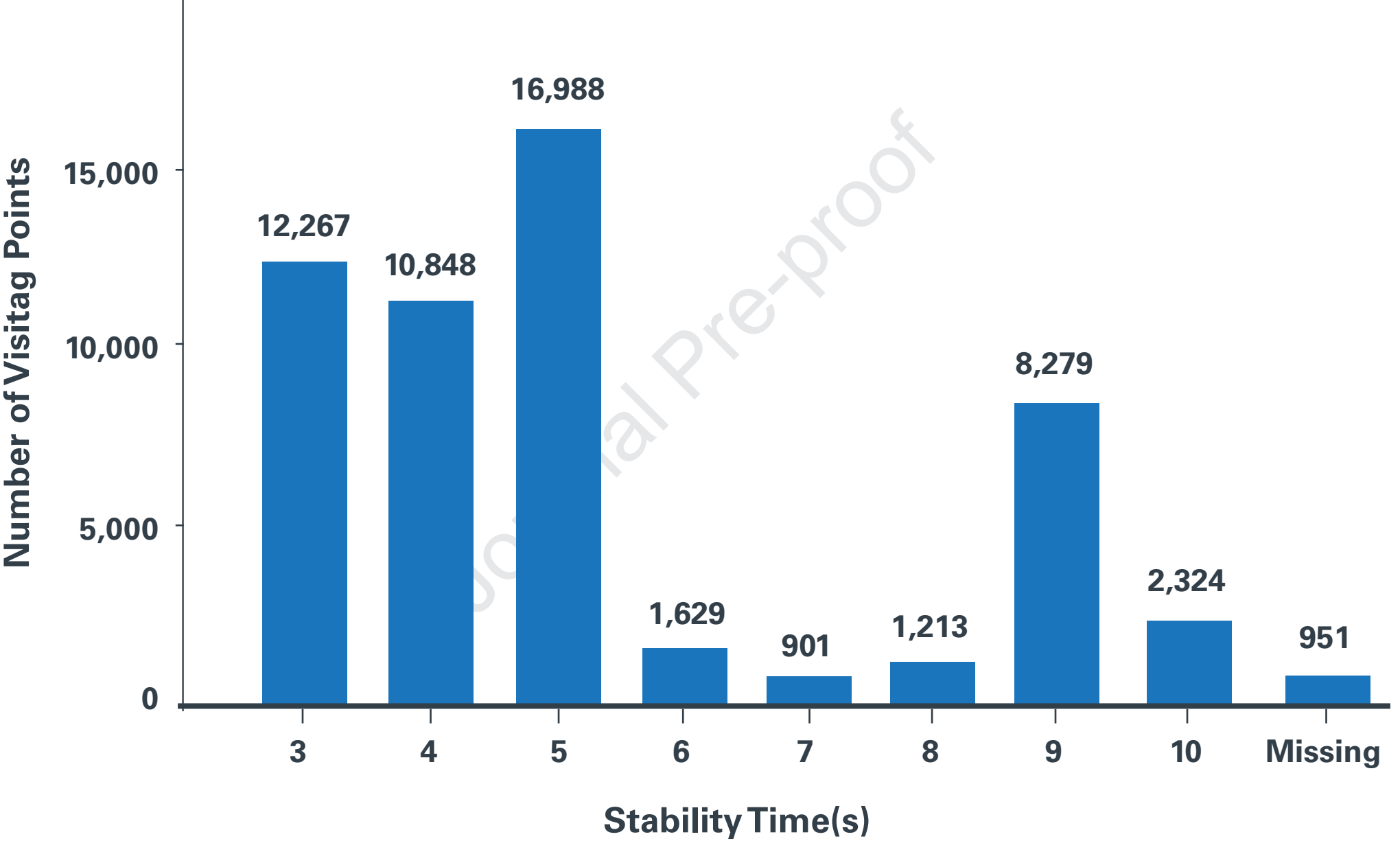


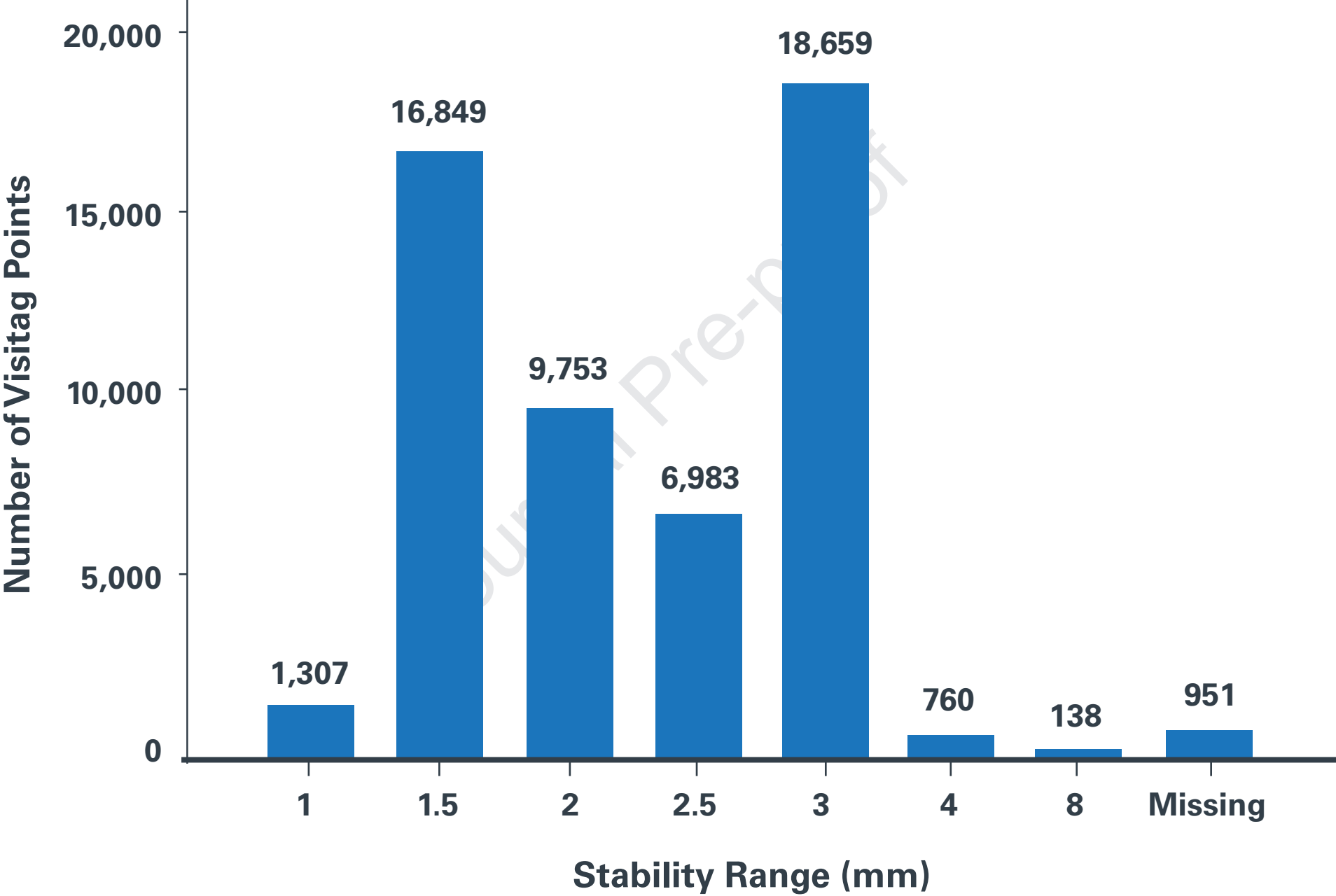


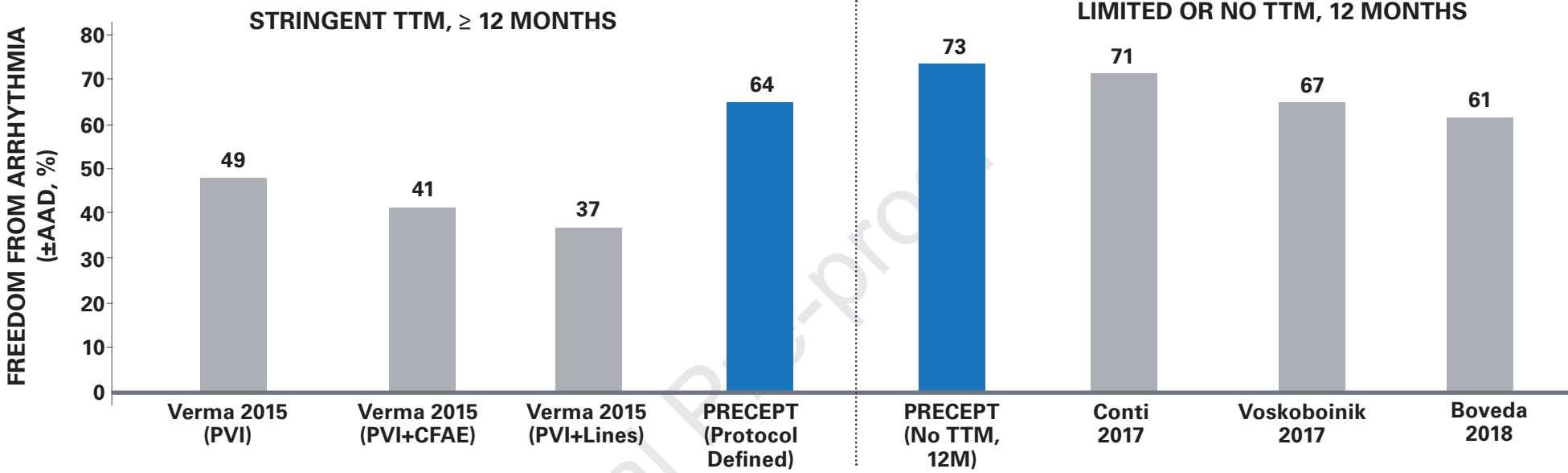









20,000
15,000
10,000
5,000
0
Number of Visitag Points
1,307
16,849
9,753
6,983
18,659
760
138
951
1
1.5
2
2.5
3
4
8
Missing
Stability Range (mm)



REFERENCE		VERMA 2015 (PVI)	VERMA 2015 (PVI+CFAE)	VERMA 2015 (PVI+LINES)	PRECEPT (PROTOCOL DEFINED)	PRECEPT (NO TTM, 12M)	CONTI 2017	VOSKOBOINIK 2017	BOVEDA 2018
Ablation Technology		Non-CF RF			**CF RF**	**CF RF**	CF RF	CB, Non-CF or CF RF	CB2
Arrhythmia Monitoring	12-lead ECG	Yes			**Yes**	**Yes**	Yes	Yes	Yes
	Holter Monitor	24-hr			**24-hr**	**24-hr**	48-hr	Mostly 24-hr	48-hr
	TTM	Stringent			**Stringent**	**None**	Limited	Mostly none	None
Follow-up Visit		3 to 18 months			**6 to 15 months**	**3 to 12 months**	3 to 12 months	Mostly 3 to 12 months	3 to 12 months
Repeat Ablation after blanking period		14 (22%)	67 (26%)	83 (33%)	**26/333 (7.8%)**	**31/333 (9.3%)**	21 (17%)	N/A	17 (17%)