Three-year outcomes of the postapproval study of the AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation Trial

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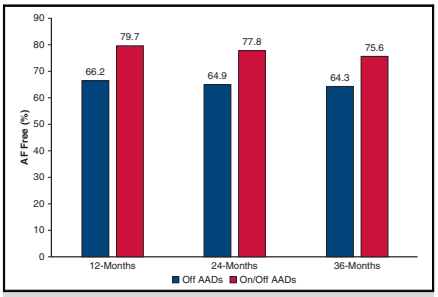
ABSTRACT

Objectives: The Cox Maze IV operation is commonly performed concomitant with other cardiac operations and effectively reduces the burden of atrial fibrillation. Prospective randomized trials have reported outcomes early and at 12 months, but only single-center late durability results are available. As part of the postapproval process for a bipolar radiofrequency ablation system, we sought to determine early and midterm outcomes of patients undergoing the Cox Maze IV operation.

Methods: A prospective, multicenter, single-arm study of 363 patients (mean age, 70 years, 82% valve surgery) with nonparoxysmal atrial fibrillation (mean duration, 60 months, 94% Congestive heart failure, Hypertension, Age $\geq$ 75, Diabetes, Stroke, VAScular disease, Age 65-74, Sex category $\geq$2) undergoing concomitant Maze IV atrial fibrillation ablation at 40 sites with 70 surgeons was performed between June 2010 and October 2014. Compliance with the study lesion set was 94.5%, and 99% had left atrial appendage closure. Freedom from atrial fibrillation was determined by extended monitoring, with a 48-hour Holter monitor minimum.

Results: There were no device-related complications. Freedom from atrial fibrillation off antiarrhythmic medications at 1, 2, and 3 years was 66%, 65%, and 64%, respectively, and including those using antiarrhythmics was 80%, 78%, and 76%, respectively. Warfarin was used in 49%, 44%, and 40%, respectively.

Conclusions: In patients with nonparoxysmal atrial fibrillation, compliance with the protocol was high, and freedom from atrial fibrillation off antiarrhythmics was high and sustained to 3 years. The safety and effectiveness of the system and Cox Maze IV procedure support the Class I guideline recommendation for concomitant atrial fibrillation ablation in patients undergoing cardiac surgery. (J Thorac Cardiovasc Surg 2020;■:1-9)



Freedom from AF over 36 months was stable.

CENTRAL MESSAGE

A PAS with bipolar radiofrequency and a Maze IV lesion set had high protocol compliance and freedom from AF at 36 months of 75.6% and 64.3% on and off antiarrhythmics, respectively.

PERSPECTIVE

Procedure training for physicians enhances the use of a standardized lesion set to perform the Cox Maze IV procedure. This follow-up study provides data showing excellent durability of successful Cox-Maze IV outcomes supporting recent Class I indications for performing concomitant surgical ablation for patients undergoing cardiac surgery.

See Commentary on page XXX.

ADULT

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Abbreviations and Acronyms
AF = atrial fibrillation
CABG = coronary artery bypass grafting
FDA = Food and Drug Administration
PAS = postapproval study

Surgical ablation for atrial fibrillation (AF) is widely applied concomitant with other cardiac operations such as valve operations and coronary artery bypass.[1-3] Published multicenter randomized trials, single-center trials, Society of Thoracic Surgeons database reports, and single-center reports have documented low procedure morbidity and mortality, and high freedom from AF in follow-up in patients undergoing surgical ablation compared with control patients (untreated AF) and suggest that AF ablation reduces perioperative and late mortality.[1-7] This body of work led to a recommendation in 2007 by the Society of Thoracic Surgeons and Heart Rhythm Society to perform concomitant ablation, which was reiterated in 2012 and in 2017.[8] In 2017, the Society of Thoracic Surgeons gave AF surgical ablation a Class I recommendation to restore sinus rhythm (level A for mitral surgery and level B for aortic valve replacement and coronary artery bypass grafting [CABG]).[6]

The cut-and-sew Cox Maze III procedure was successful but not widely adopted because of the complexity of the operation and limited opportunities to learn the procedure.[9] Its adoption became higher after a variety of technologies were developed to recreate the ablation lesion set, which was renamed the "Cox-Maze IV" and primarily performed using bipolar radiofrequency clamps and cryosurgical ablation to the valve annuli.[10,11] However, the Food and Drug Administration (FDA) labeling for the clamps did not specify that they were to be used for AF ablation; therefore, industry could not discuss with surgeons the AF ablation procedure or the use of the clamps. The AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation trial (FDA-approved Protocol # CP2011-1, Clinicaltrials.gov: NCT01694563) data led to the FDA and Centers for Medicare & Medicaid approval of bipolar radiofrequency clamps manufactured by AtriCure (Mason, Ohio) specifically for the treatment of nonparoxysmal AF.[12] A condition of that approval was that the company develop an educational course for surgeons and perform a nonrandomized postapproval study (PAS) to better understand the safety and effectiveness of the device and procedure.[13] The PAS was a multicenter (40 sites and 70 surgeons), single-arm study using the Cox-Maze IV lesion set for patients with nonparoxysmal AF. This is the first report from the PAS including safety, perioperative outcomes, and effectiveness with 3 years of follow-up.

MATERIALS AND METHODS

Trial Design and End Points

Patient inclusion and exclusion criteria defined a group of patients with nonparoxysmal AF undergoing other cardiac operations, and AF ablation was performed during those procedures (Table E1). Definitions of AF were taken from published guidelines[4] and include paroxysmal AF and recurrent AF (≥2 episodes) that terminated spontaneously within 7 days. Episodes of AF 48 hours or less that were terminated with electrical or pharmacologic cardioversion were also classified as paroxysmal AF episodes. Persistent AF is continuous AF sustained beyond 7 days. Episodes of AF in which a decision was made to electrically or pharmacologically cardiovert the patient after more than 48 hours of AF, but before 7 days, were also classified as persistent AF episodes. Long-standing persistent AF is continuous AF greater than 12 months duration. The performance of a successful cardioversion (sinus rhythm >30 seconds) within 12 months of an ablation procedure with documented early recurrence of AF within 30 days did not alter the classification of AF as long-standing persistent. For both types of AF, 2 electrocardiograms (eg, 12-lead electrocardiogram, Holter monitor, event monitor, implantable loop recorder, pacemaker interrogation, Zio Patch [iRhythm, San Francisco, Calif]) documenting AF taken at least 7 days apart were required. For patients with long-standing persistent AF with sustained AF 7 days of more, Holter monitor, event monitor, implantable loop recorder, Zio Patch, or pacemaker interrogation recordings were required to show continuous AF more than 12 months. The AF classifications were not independently adjudicated.

Rhythm evaluation was performed by an independent core laboratory based on a 48-hour Holter monitor, Zio Patch, or permanent pacemaker interrogation recording performed at 12, 24, and 36 months postoperatively. All rhythm evaluations (Holter monitor, Zio Patch, or permanent pacemaker interrogation) were reviewed by the same core laboratory for consistency. For all assessments, the Rhythm strips were provided to the core laboratory for interpretation. For pacemaker interrogation, adjudication for any subject with an AF episode greater than 30 seconds in duration within the visit window (example: 12 months ± 60 days) was considered a failure. Patients were also followed by referring cardiologists who made decisions regarding anticoagulation and antiarrhythmic drug use in follow-up.

The primary effectiveness end point was defined as the proportion of patients free from AF (ie, no episodes lasting >30 continuous seconds of AF, atrial flutter, or atrial tachycardia) while off class I and III antiarrhythmic drugs for at least 4 weeks (except amiodarone, which must be discontinued 12 weeks before assessment) at 12, 24, and 36 months postoperatively. The primary safety end point was defined as the proportion of patients with any serious device or ablation procedure-related adverse events, excluding pacemaker implantation, within 30 days postprocedure or hospital discharge, as adjudicated by the Clinical Events Committee. A preestablished performance goal was set at 47.8% of patients expected to achieve freedom from AF.

The secondary safety outcomes were a composite of major adverse events. These included serious adverse events occurring postoperatively within 30 days postprocedure or hospital discharge (whichever was later), including death (include deaths after 30 days or hospital discharge if the death is procedure related), stroke (resulting in significant permanent disability), transient ischemic attack, myocardial infarction, and excessive bleeding (requiring >2 units of blood replacement and surgical intervention).

Statistical Methods

Descriptive analyses were provided for patient demographics, clinical device/procedural success, medical histories, and comorbidities. The primary safety hypothesis test was conducted using a 1-sided exact binomial test for proportions at the 0.05 overall level of significance. Serious device and ablation procedure-related AE rates and confidence intervals were

summarized at discharge, 30 days, and 1 year with a hypothesis test performed on the cumulative 30-day serious device and ablation procedure-related AE rate.

The efficacy outcome rate of freedom from AF, off antiarrhythmic drugs along with confidence intervals were summarized at 1, 2, and 3 years (ie, 12-, 24-, 36-month follow-ups), with a hypothesis test performed on the 3-year success outcome. The primary efficacy hypothesis test was conducted using a 1-sided exact binomial test for proportions at the .05 overall level of significance. Secondary outcomes were summarized for the analysis population and certain subpopulations. Two-sided 95% confidence intervals were calculated for all presented rates. Overall survival since enrollment was estimated using the Kaplan–Meier estimator. Probabilities of stroke, cardioversion, or catheter ablation over time were estimated using the cumulative incidence functions calculated using semi-competing risks methodology.

As a sensitivity analysis for the primary efficacy analysis at 36 months, missing outcome data (sinus rhythm) were imputed only for those patients who were alive at 36 months and had no sinus rhythm data. We used 25 imputation runs based on fully conditional specification, as implemented in SAS PROC MI.[14] Sinus rhythm data were imputed on the basis of a logistic regression model whose explanatory variables were type of AF, age, gender, time since AF onset, AF status at 12 and 24 months, time to study exit, and occurrence of a cardioversion or catheter ablation before 36 months, except during a 90-day postintervention blanking period. Imputed values were combined using Rubin's rule. All statistical analyses were performed in SAS v 9.4 (SAS Institute, Inc, Cary, NC).

Cox-Maze IV Lesion Set

A complete biatrial Cox Maze IV lesion set was required by the study protocol using the AtriCure Bipolar System. This technique included radiofrequency energy to create pulmonary vein isolation constructed by bilateral antral pulmonary vein isolation with inferior and superior connecting lesions; cryoablation lines to the mitral and tricuspid valves; and radiofrequency lines to both the left and right atrial appendages. Confirmation of pulmonary vein isolation was not a study end point and therefore not required. The right atrial lesion set was optional. On the basis of the type of concomitant surgery or patient presentation, there were some situations in which some lesions were not able to be performed at the surgeon's discretion. A diagram of the lesion set is shown in Figure 1.

Surgeon training. With the beginning of the PAS trial on August 15, 2012, 70 surgeons were trained by expert surgeons on the use of the devices and surgical techniques used to perform the Maze-IV lesion set in this clinical trial. All participating surgeons successfully completed a training and certification program that included didactic training, case observation, and surgeon proctoring. This course included online and trainer-led curriculum reviewed by the FDA. The curriculum was developed and overseen by a group of independent, recognized physician AF experts. The course was focused on the safety and effectiveness of the surgical treatment for AF. In addition, proctors were available as needed and for follow-up discussion, as well as clinical support from industry.

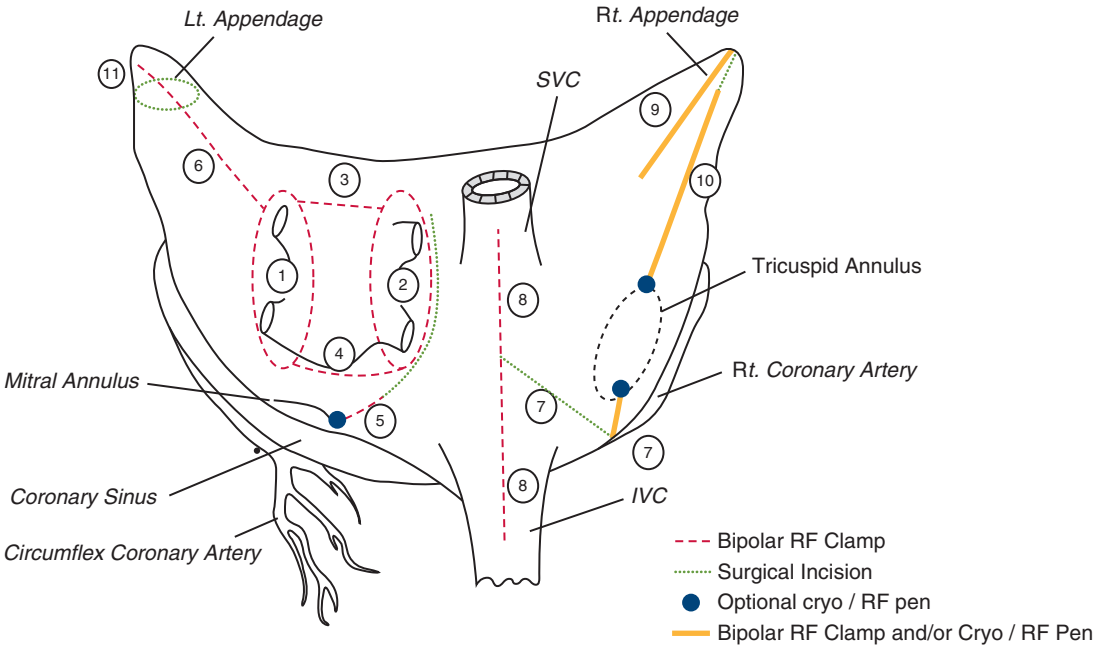
RESULTS

Between June 29, 2010, and October 3, 2014, 365 patients were enrolled at 40 centers in the United States (Figure 2). The surgeries across the 40 centers were performed by 70 surgeons averaging 5 cases (range, 1-40) with a median of 3 cases (Figure E1). Some 55% of the centers enrolled at least 7 patients, and the average number of cases per center was 9 (range, 1-42). Table 1 details the subject demographics and baseline characteristics. The patients treated in the study ranged in age from 37 to 88 years, with a mean age of 70 years. Preoperative permanent pacemakers were present in 9.9% (36/365) of patients, and 8.0% (29/363) of patients had a history of catheter ablation of AF. Details of follow-up completeness are shown in Table E2.

The complete, biatrial Cox-Maze IV procedure was performed in 94.5% of cases (343/363). The most common deviation (4%; 14/363) from the Cox-Maze IV was omission of right atrial lesions (Table 2). Isolated valve surgery predominated as the most common procedure, performed in 35.8% of patients (130/363), and CABG plus double valve surgery was performed the least in 6.6% of patients (24/363). Other surgical procedures included double valve surgery in 23.4% of patients (85/363), CABG only in 17.9% (65/363), and CABG plus valve surgery in 16.3% (59/363) (Table E3). Overall, 82% of the patients had a valve operation.

A total of 1.1% (4/365) of serious ablation procedure-related events were reported in patients during the first 30 days or during the initial hospitalization; there were no serious device-related events reported during this same time period. The events reported included adjudicated and nonadjudicated events as follows: cardiac arrest occurring 1 day postoperation; ventricular tachycardia occurring during hospitalization; pulmonary vein tear occurring during procedure; and blood loss requiring transfusion occurring during procedure. Thirty-five secondary safety outcome events occurred in 8.8% (32/365) of patients (Table 3). Death occurred in 5.5% (20/365), and respiratory failure was the most common cause (n = 5), all occurring 30 days or less (or before discharge). Excessive bleeding occurred in 1.9% (7/365) and stroke in 1.6% (6/365) of patients. All strokes occurred within 2 days after surgery. Myocardial infarction occurred in less than 1% (3/365) of patients. During the first 30 days or during the initial hospitalization, a new permanent pacemaker was required in 15.2% (50/329). Total new permanent pacemaker implantation throughout the trial was required in 23.7% (78/329). The most common indication for pacemaker use was sinoatrial node dysfunction in 7.9% (26/329), as adjudicated by the Clinical Events Committee. A total of 80.5% (281/349) of patients were anticoagulated (with warfarin) at the time of hospital discharge, and 81.8% (279/341) were anticoagulated at 30 days postprocedure.

At study completion, 82.1% (298/363), 72.2% (262/363), and 67.2% (244/363) of patients completed the 12-, 24-, and 36-month visits, respectively. Rhythm follow-up at these visits (using Holter monitor, Zio Patch, or pacemaker interrogation) was available in 90.9% (271/298), 92.4% (242/262), and 93.4% (228/244) of the patients. At the 12-, 24-, and 36-month visits, 49% (146/298), 44.1% (115/261), and 40.4% (69/171) of patients, respectively, were on warfarin at the discretion of the treating physician at that time.



Pulmonary Veins **(Mandatory):**		
	Lesion	Energy Source
1	Left PV Isolation (left PVI)	AtriCure Synergy OLL2 or OSL2 Clamp
2	Right PV Isolation (Right PVI)	AtriCure Synergy OLL2 or OSL2 Clamp

Left side lesions **(Mandatory):**		
Lesion #	Lesion	Energy Source
3	Box lesion – "ROOF" line	AtriCure Synergy OLL2 or OSL2 Clamp
4	Box lesion – "FLOOR" line	AtriCure Synergy OLL2 or OSL2 Clamp
5	Mitral valve annulus	Initiate lesion with AtriCure Synergy OLL2 or OSL2 Clamp (mandatory); completion lesion at level of annulus with AtriCure Transpolar Pen or Cryo
6	Connecting lesion from left atrial appendage to the left PVI lesion	AtriCure Synergy OLL2 or OSL2 Clamp
Right Atrial Lesions (**Recommended;** if not performed must provide clinical justification)		
7	Lesion from atriotomy to tricuspid valve annulus	AtriCure Synergy OLLS or OSL2 Clamp; complete lesion at level of annulus with AtriCure Transpolar Pen or Cryo
8	Ablation of SVC	AtriCure Synergy OLL2 or OSL2 Clamp
8	Ablation of IVC	AtriCure Synergy OLL2 or OSL2 Clamp

OPTIONAL LESIONS#:		
Right side lesions:		
9	Right anterior freewall appendage lesion	AtriCure Synergy OLL2 or OSL2 Clamp OR Clamp and AtriCure Transpolar Pen/Cryo; OR Cryo
10	Right atrialappendage to annulus lesion	AtriCure Synergy OLL2 or OSL2 Clamp OR Clamp and AtriCure Transpolar Pen/Cryo; OR Cryo
Left side lesions:		
11	Left atrial appendage lesion	AtriCure Synergy OLL2 or OSL2 Clamp

FIGURE 1. Lesion set diagram for the Cox-Maze IV procedure. A complete biatrial Cox Maze IV lesion set was required by the study protocol using the AtriCure Bipolar System (Mason, Ohio). The lesions and description of the devices used for each ablation line are illustrated. *SVC*, Superior vena cava; *IVC*, inferior vena cava; *PV*, pulmonary vein; *PVI*, pulmonary vein isolation; *OLL*, open long left curved ablation clamp; *OSL*, open short left curved ablation clamp.

The primary effectiveness hypothesis for this study was to demonstrate a superiority success rate at 36 months follow-up in patients treated with the AtriCure Synergy Ablation System compared with a pre-established performance goal of 47.8%. The primary success, which factored in failure due to antiarrhythmic drugs, was 66.2%

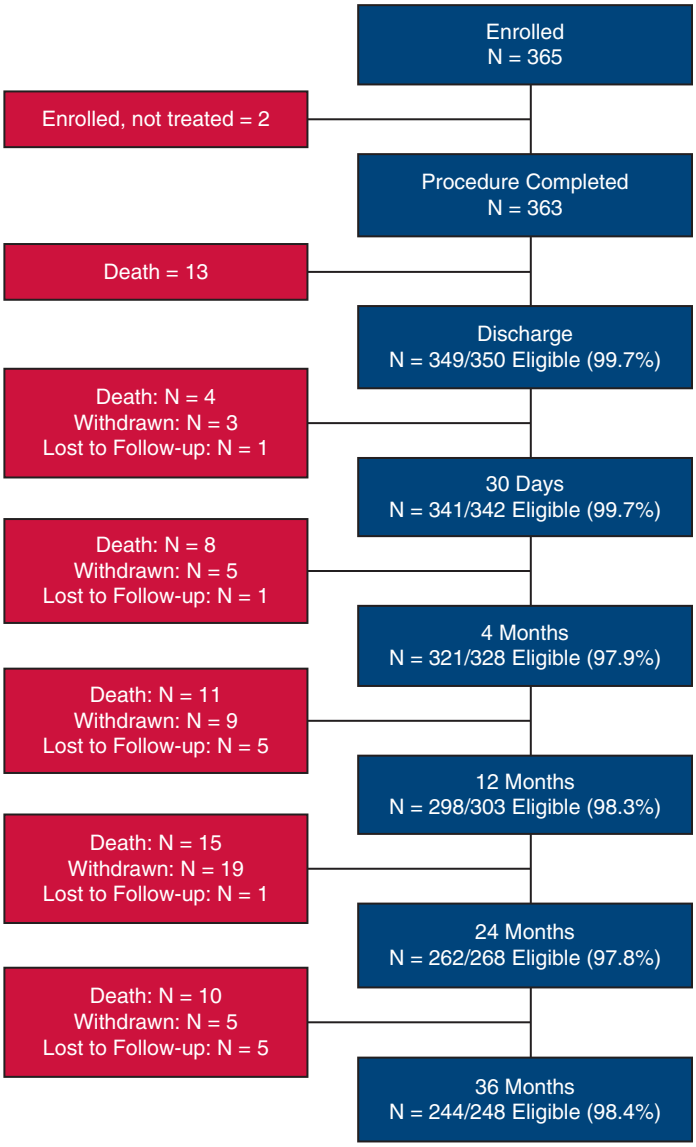


FIGURE 2. Study consort diagram. Patient enrollment and status throughout the study period are illustrated in this cohort diagram.

(184/278) (95% CI, 60.3-71.7) at 12 months; 64.9% (159/245) (95% CI, 58.6-70.9) at 24 months; and 64.3% (146/232) ($P < .0001$; 95% CI, 56.4-69.2) at 36 months. The observed primary success rate at 36 months was significantly higher than the pre-established performance goal of 47.8% ($P < .001$); thus, superiority was established. Of the 159 patients in sinus rhythm at 2 years, 143 had heart rhythm information available at 3 years. Of these 143, 114 (79.7%) continued to be in sinus rhythm at 3 years. Among the 86 patients in AF at 2 years, 76 had heart rhythm information at 3 years. Of the latter, 75 (98.7%) remained in AF at 3 years.

Secondary success was defined as freedom from AF regardless of antiarrhythmic drug use and required rhythm documentation (7 patients did not have follow-up rhythm assessment). The sensitivity analysis based on sinus rhythm multiple imputation among 3-year survivors showed a 56.1% success rate (95% CI, 42.6-69.6), with a 1-sided P value of .2202 against the null hypothesis of 47.8% or less success rate. The secondary success at 12 months was 79.7% (216/271) (90% CI, 75.3-83.7) at 12 months; 77.3% (187/242) (90% CI, 72.4-81.6) at 24 months; and 73.7% (168/228) (90% CI, 68.5-78.5) at 36 months (Figure 3).

Overall survival at 1, 2, and 3 years since ablation was 89.8%, 84.7%, and 81.7%, respectively (Figure 4, *A*). Freedom from stroke at the same time marks was 97.2%, 95.9%, and 95.6%, respectively (Figure 4, *B*).

In patients who experienced AF recurrence, no data were available regarding subsequent electrophysiology

TABLE 1. Summary of patient characteristics

Variable	Total N = 365 (%)
Age, y	69.8 ± 9.3
Male	217 (59.5)
Caucasian	331 (90.7)
New York Heart Association functional class III or IV	146 (40.0)
Duration of AF (mo)	60.0 ± 84.2
Type of AF	
Paroxysmal	1 (0.3)
Persistent	207 (56.7)
Long-standing persistent	157 (43)
Prior cardiac surgery (reoperation)	47 (12.9)
Renal failure	44 (12.1)
Chronic obstructive pulmonary disease	72 (19.7)
Diabetes	113 (31.0)
Body mass index (kg/m^2)	30.5 ± 6.4
Preoperative pacemaker	36 (9.9)
CHADS score risk category	
Low risk (score = 0)	0
Medium risk (score = 1)	22 (6.1)
High risk (score ≥2)	340 (93.9)
Not assessed	3 (0.8)

Values are N (%), median ± standard deviation. *AF,* Atrial fibrillation; *CHADS*, congestive heart failure history, hypertension, age, diabetes, stroke or transient ischemic attack.

mapping. Figure E2 shows cumulative incidence functions for late reinterventions (catheter ablations or cardioversions). There were 14 catheter ablations (7 for AF, 6 for atrial flutter, 1 for atrial tachycardia) and 91 cardioversions (62 for AF, 27 for atrial flutter, 1 for both AF and flutter, 1 for atrial tachycardia) outside the 90-day postablation blanking period. Three-year cumulative probabilities of cardioversion or catheter ablation were 15.10% and 1.44%, respectively.

TABLE 2. Details of the ablation procedure

Ablation procedure summary	Total N = 363
Complete Maze procedure	343 (94.5)
Lesion not completed*	20 (5.5)
Right pulmonary vein isolation	1 (0.3)
Mitral valve annulus lesion	2 (0.6)
Connecting lesion from left atrial appendage to left pulmonary vein lesion	5 (1.4)
Superior vena cava	13 (3.6)
Inferior vena cava	13 (3.6)
Atriotomy to tricuspid valve annulus	14 (3.9)
Left atrial appendage exclusion performed	359 (99)
Exclusion method	
Clipped	174 (48.5)
Sutured	133 (37.1)
Stapled	43 (12.0)
Snared	1 (0.3)
Other	8 (2.2)

Values are N (%). *Some patients may have multiple lesions not completed.

TABLE 3. Composite secondary safety end points

Parameter	No. of events*	Patients with event
Acute major adverse event within 30 d postprocedure	35	32 (8.8)
Death	20	20 (5.5)
≤30 d (or before discharge)	20	20 (5.5)
>30 d, procedure related	0	0 (0)
Stroke	6	6 (1.6)
Stroke (with significant permanent disability)	6	6 (1.6)
Transient ischemic attack	0	0 (0)
Myocardial infarction	3	3 (0.8)
Excessive bleeding (>2 units blood and surgical intervention)	7	7 (1.9)

*As adjudicated if available or reported by the site. Values are N (%).

DISCUSSION

Durable Freedom From Atrial Fibrillation Off Antiarrhythmic Medication

This study, like several recent studies, found high (79.7%; 66.2%) freedom from AF on or off antiarrhythmics at 12-month follow-up.[9,10,15] This success rate is encouraging considering the characteristics of the patients: mean AF duration 60.0 ± 84.2 months with a history of AF greater than 12 months in 64% (233/365) and 99.7% long-standing persistent or persistent AF. A unique finding in this prospective study was the continued freedom from AF seen at 36 months (75.6%; 64.3%), a duration of follow-up unreported in prior multicenter studies and reports. We did not seek to replicate prior randomized studies in concomitant surgery because each showed higher freedom from AF in the AF-treated group than control.[12,15-27] Instead, this study focused on procedure training to achieve high lesion set compliance and safe use of the devices and a focus on success beyond 12 months.

Training and Safety

After device approval, AtriCure was allowed to train surgeons on use of the device and the Cox-Maze IV procedure to maximize safety and effectiveness. This was done by small group conferences, proctoring, and an examination. Compliance with the Cox-Maze IV protocol lesion set was high (94.5%) and higher than in other multicenter trials. There were no device malfunctions or complications from the device. There were no deaths due to the AtriCure Synergy Ablation System or the ablation procedure. There was a 1.1% (4/365) rate of ablation procedure-related complications, and we included investigator-reported causes

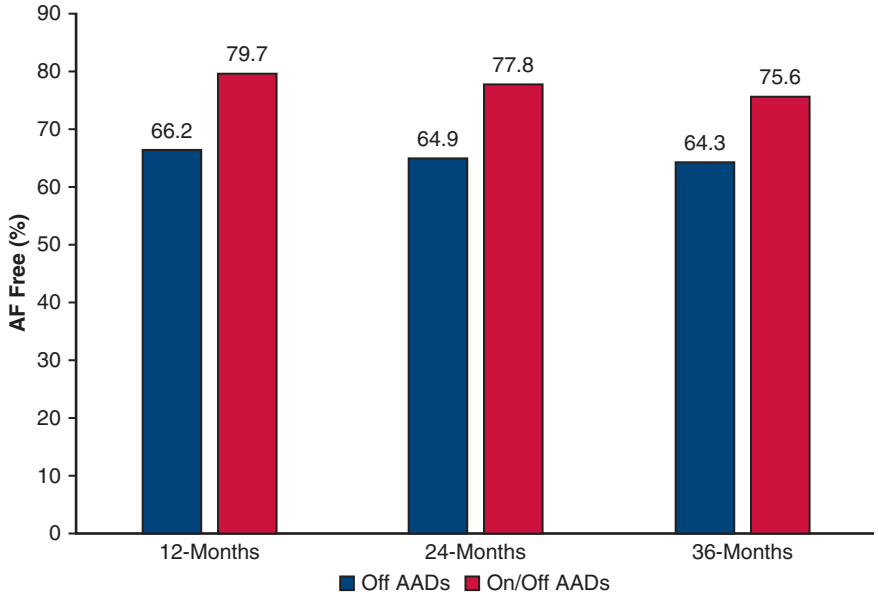


FIGURE 3. Primary outcomes. Primary effectiveness (freedom from AF off antiarrhythmic drugs) and secondary effectiveness (free from AF with or without antiarrhythmic drugs) at prespecified 3 annual time periods documented sustained effectiveness of the Cox-Maze IV procedure. *AF,* Atrial fibrillation; *AAD,* antiarrhythmic drug.

such as cardiac arrest, ventricular tachycardia, blood loss requiring transfusion, and pulmonary vein tear. The patient population was complex: mean age 70 years; 12.5% (45/363) reoperations; 23% (85/363) double valve operations; 7% (26/365) New York Heart Association FC III or IV. There were perioperative deaths and complications, but not adjudicated to the device or procedure per the Clinical Events Committee. The Clinical Events Committee adjudicated any adverse event that occurred within 30 days postprocedure or hospital discharge, which was potentially device or ablation procedure related. As have others, we observed a significant rate of permanent pacemaker use, not surprising in a population with complex valve operations.[28] The Clinical Events Committee also adjudicated the reason for permanent pacemaker implantation within the first 30 days postprocedure or during the initial hospitalization.

Surgical Atrial Fibrillation Ablation Perspective

The cut-and-sew Maze III procedure was designed to prevent large reentrant circuits thought to be responsible for AF from continuing to circulate. The idea was to perform "…an operation capable of interrupting all the potential macroreentrant circuits that could occur in the atria." such that it would be "…impossible for an electrical impulse to emanate from any point in the atria and return to that point without crossing a suture line," but still allow the sinus impulse to "…reach the AV node to drive the ventricles." Perhaps the most important lesion of the Maze was isolation of the pulmonary veins. Done at that time to address reentry around the pulmonary veins, as was subsequently appreciated, this lesion set also performed the crucial task of isolating active sources of ectopy, thought to initiate (or occasionally sustain) AF.[26] Of note, there have been 3 proposed mechanisms of AF: reentrant driver or drivers, focal drivers, and multiple wavelets, although the latter was recently shown to be unlikely.[27] To date, there is still no definitively accepted mechanism of what sustains AF in patients, and that includes the patients in our trial who had concomitant cardiac pathology. AF ablations are largely empiric. However, the body of preexisting experience with the Maze lesion set, and the good (although not perfect) results of our study provide evidence of the lesion set's late efficacy. We suggest the meticulous attention to the details of the Cox Maze IV procedure was important.

Study Limitations

All reports of freedom from AF, after surgical or catheter ablation, have the inherent limitation that episodes of paroxysmal AF can be missed even though follow-up monitoring is performed according to the rigorous criteria set by the Heart Rhythm Society guidelines. The definitions of AF used in this study are mismatched to current definitions because this study protocol was written before the recent updates. As in most surgical studies, the decision to use antiarrhythmic medications and oral anticoagulation is at the discretion of the referring cardiologist and not mandated by protocol. Surgeon preference directed the fashion in which the clamp was applied and the number of clamp

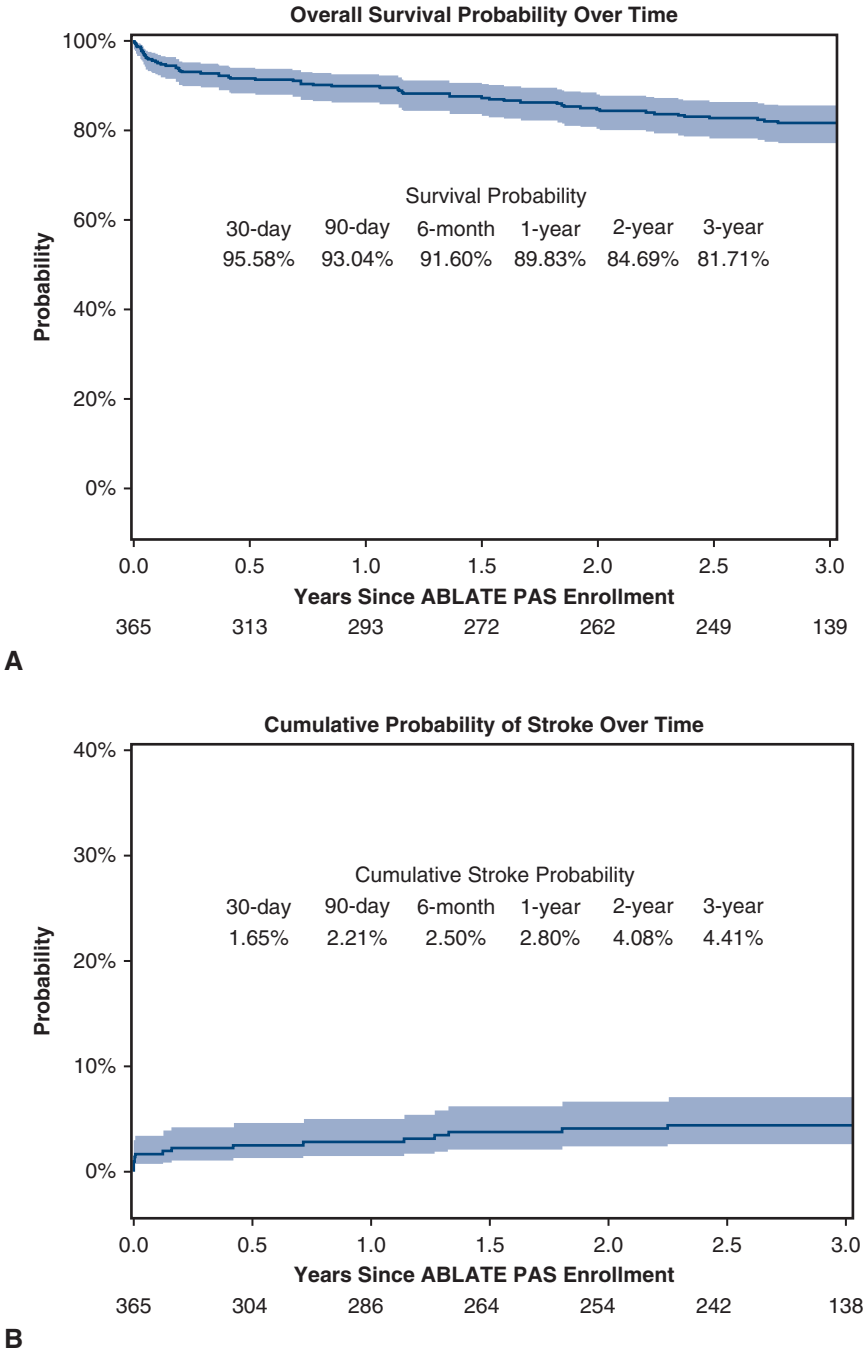


FIGURE 4. Survival and stroke outcomes. A and B, Overall survival estimates and cumulative incidence function for probability of stroke as well as the number of patients at risk are shown during the 3-year follow-up. *ABLATE*, AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation; *PAS,* postapproval study.

applications. Iterative changes to the training course will be made as experience accrues.

CONCLUSIONS

This multicenter trial demonstrated a high compliance with the Maze IV lesion set after extensive surgical training and emphasized the importance of a standardized approach when performing the Cox Maze IV procedure. High freedom from AF that was durable for 3 years is a new addition to the AF literature. The results of this PAS support the Class I recommendation for concomitant AF ablation in patients undergoing cardiac surgical procedures.

Conflict of Interest Statement

Dr McCarthy is Principal Investigator of the Trial, but receives no compensation; Edwards Lifesciences: consultant and royalties. Abbott: Advisory Board; AtriCure: Honorarium. Dr Philpott: consultant for AtriCure. Dr Waldo: consultant for Biosense Webster, AtriCure, and Milestone Pharmaceuticals; Speaker for Pfizer and Bristol-Myers Squibb. Drs Andrei, Barnhart, and Gerdisch: consultants for AtriCure. Drs Gaynor and Ndikintum are employed by AtriCure. Dr Calkins: consultant for AtriCure, Medtronic and Boeringer Ingelheim, and receives research support from Boston Scientific. Dr Shemin: consultant for AtriCure and Edwards Lifesciences. All other authors reported no conflicts of interest.

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The authors recognize contributions of selected site Primary Investigators for the AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation Trial listed in the Appendix.

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Key Words: atrial fibrillation, Cox Maze IV procedure, bipolar radiofrequency, postapproval study

ADULT

APPENDIX E1

The authors recognize contributions of the following site Primary Investigators for the AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation Trial:

Mubashir Mumtaz, Pinnacle Health
Divyakant Gandhi, McLaren Hospital
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J. Michael Smith, Good Samaritan/TriHealth
Vigneshwar Kasirajan, VCU
Micahel Mauney, Missouri Baptist Medical Center
Marco Zenati, Veterans Affairs-Boston
Vaughn Starnes, USC University Hospital
Michael Moront, Toledo Hospital
Thomas Beaver, University of Florida
Clarence Owen, LeBauer Cardiovascular Research Foundation
Walter Dembitsky, Sharp Memorial Hospital
John Grehan, United Heart and Vascular Clinic
Robert Hagberg, Hartford Hospital
Goya Raikar, Oklahoma Heart Hospital
Michael DeFrain, Northside Hospital
James Wudel, Nebraska Heart Institute
Robert Moraca, Allegheny General Hospital
Ali Kjoynezhad, Cedars-Sinai Medical Center
Stephen Hazelrigg, SIU-memorial Medical Center
Ralph Damiano, Washington University/Barnes Jewish Hospital
Barry Bjorgaard, Altru Health System
David Heimansohn, Heart Center of Indiana
Mark Groh, Mission Hospital
Ernesto Jimenez, Tampa VA Cardiothoracic Surgery
Michael Jessen, UT Southwestern University Hospital
Edward Garrett, Cardiovascular Surgery Clinic
Brian Hummel, Lee Memorial Hospital, Dan Drake, Munson Medical Center
Gilbert Schorlemmer, St Mark's Hospital
Alan Markowitz, University Hospitals Cleveland Medical Center
Frank Shannon, William Beaumont Hospital

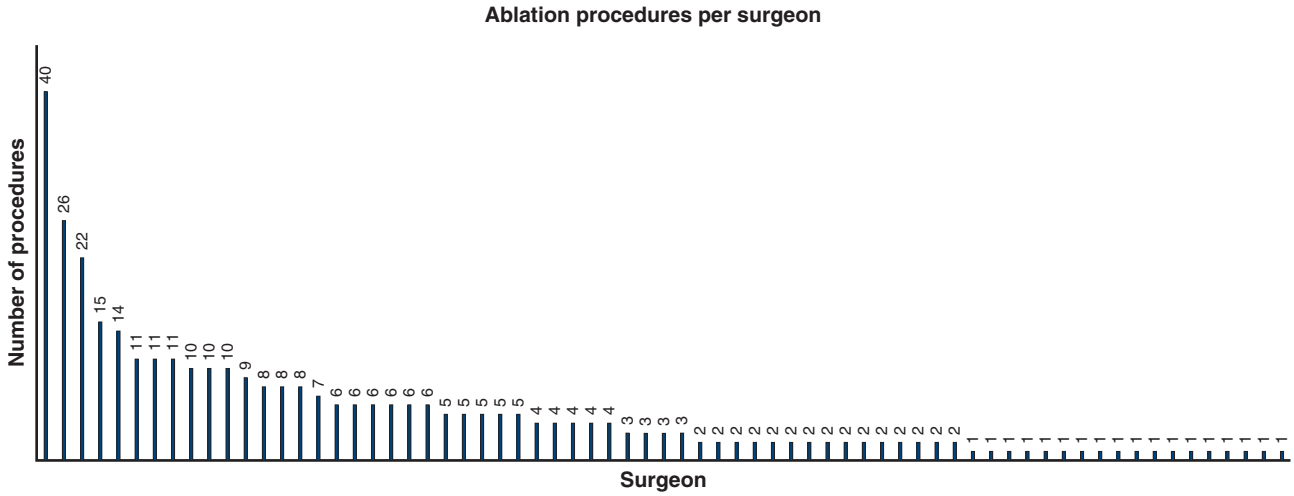

FIGURE E1. Number of ablation procedures per surgeon. This is a histogram of the number of cases performed by each surgeon participating in the study.

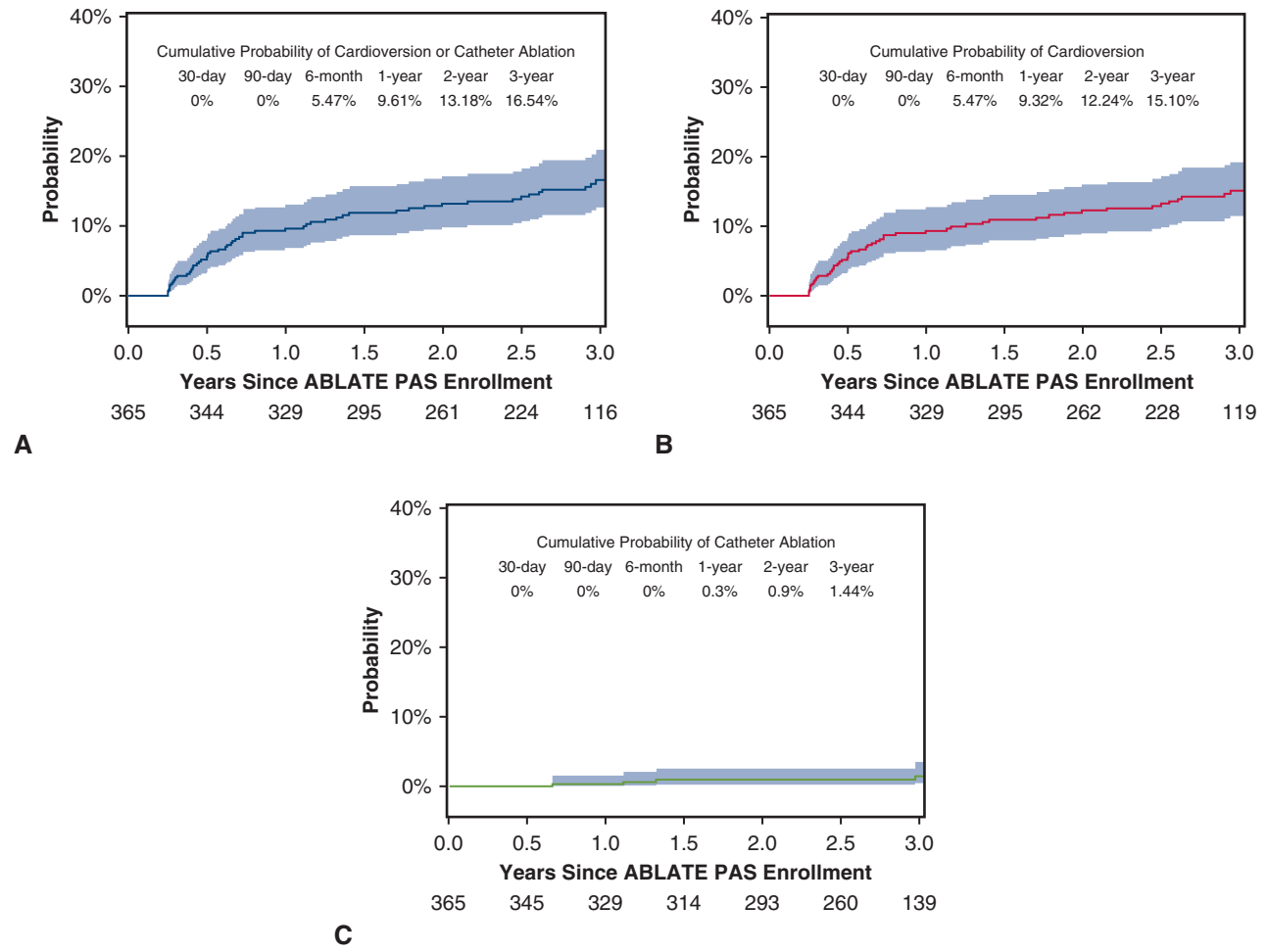

FIGURE E2. A-C, Probabilities of late reinterventions (cardioversions or catheter ablations) in follow-up after a 90-day blanking period postenrollment date. There were 14 catheter ablations and 91 cardioversions outside the 90-day postablation blanking period. *ABLATE*, AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation; *PAS,* postapproval study.

TABLE E1. Inclusion criteria and exclusion criteria

Inclusion criteria
Age ≥18 y
Patients with persistent or long-standing persistent AF defined in accordance to Heart Rhythm Society AF expert consensus statement (2012)[1]
Persistent AF is defined as continuous AF that is sustained beyond 7 d. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after >48 h of AF, but before 7 d, should also be classified as persistent AF episodes.
Long-standing persistent AF is defined as continuous AF of greater than 12 mo duration.; The performance of a successful cardioversion (sinus rhythm >30 s) within 12 mo of an ablation procedure with documented early recurrence of AF within 30 d should not alter the classification of AF as long-standing persistent.
Subject is scheduled to undergo elective open cardiac surgical procedure(s) to be performed on cardiopulmonary bypass for 1 or more of the following: CABG, mitral valve repair or replacement, aortic valve repair or replacement, and tricuspid valve repair or replacement. In conjunction with these procedures, patent foramen ovale or septal defect repair is allowed.
The patient (or their legally authorized representative) agrees to participate in this study by signing the Institutional Review Board–approved informed consent form.
Willing and able to return for scheduled follow-up visits.
Exclusion criteria
Stand-alone AF without indication(s) for concomitant cardiac surgery
Need for emergency cardiac surgery (ie, cardiogenic shock)
Preoperative need for an intra-aortic balloon pump or intravenous inotropes
Pregnancy or desire to become pregnant for the duration of the study (concomitant surgical procedure through the 36-mo follow-up period)
Enrolled in another clinical trial that could confound the results of this study

AF, Atrial fibrillation; *CABG,* coronary artery bypass grafting.

TABLE E2. Data completeness for AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation postapproval participants

Subject status	Total*
Subject consented [n]	365
Subject enrolled [n]*	365
Follow-up time in study (d)†	
Mean ± SD (N)	847.0 ± 406.2 (365)
Median (Min, Max)	1073 (0, 1346)
≤30 d (or hospital discharge)	6.3% (23/365)
Subject refused additional follow-up‡	0.8% (3/365)
Subject lost to follow-up	0.3% (1/365)
Subject deceased	4.7% (17/365)
Other	0.5% (2/365)
Procedure aborted	0.3% (1/365)
Subject exited day of procedure due to exclusion number 3	0.3% (1/365)
Status after 30 d, but before 4 mo	3.8% (14/365)
Subject refused additional follow-up‡	1.1% (4/365)
Subject lost to follow-up	0.3% (1/365)
Subject deceased	2.2% (8/365)
Other	0.3% (1/365)
Subject withdrew consent	0.3% (1/365)
Status after 4 mo, but before 12 mo	6.8% (25/365)
Subject refused additional follow-up‡	2.2% (8/365)
Subject lost to follow-up	1.4% (5/365)
Subject deceased	3.0% (11/365)
Investigator decision	0.3% (1/365)
Status after 12 mo, but before 24 mo	10.7% (39/365)
Subject completed§	1.1% (4/365)
Subject refused additional follow-up‡	4.4% (16/365)
Subject lost to follow-up	0.3% (1/365)
Subject deceased	4.1% (15/365)
Investigator decision	0.5% (2/365)
Other (patient not re-consented to continue in trial)	0.3% (1/365)
Status after 24 mo	72.3% (264/365)
Subject completed§	66.8% (244/365)
Subject refused additional follow-up‡	1.4% (5/365)
Subject lost to follow-up	1.4% (5/365)
Subject deceased	2.7% (10/365)
Time to study exit (d)	
Mean ± SD (N)	846.8 ± 406.5 (365)
Median (Min, Max)	1073 (0, 1346)

SD, Standard deviation. *All subjects treated with ablation procedure. †Study entry to last scheduled follow-up assessment or study exit. ‡Five subjects (05-102, 26-101, 28-102, 31-101, 31-102) refused additional follow-up before being approached to participate in the AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation (ABLATE) PAS. Seven subjects (04-109, 04-114, 06-103, 06-104, 25-102, 30-101, 30-102) refused to be re-consented for the ABLATE PAS, which included additional follow-up. §Subject competed AF protocol before initiation of ABLATE PAS protocol at their site.

TABLE E3. Details of surgical procedures performed in study

Surgical procedure type(s)	N = 363
CABG only	65 (17.9)
Valve surgery	130 (35.8)
Mitral valve repair/replacement	89 (24.5)
Aortic valve repair/replacement	36 (9.9)
Tricuspid valve repair/replacement	5 (1.4)
Double valve surgery	85 (23.4)
Aortic and mitral	12 (3.3)
Mitral and tricuspid	57 (15.7)
Aortic and tricuspid	16 (4.4)
CABG and valve surgery	59 (16.30)
CABG + mitral valve repair/replacement	37 (10.2)
CABG + aortic valve repair/replacement	20 (5.5)
CABG + tricuspid valve repair/replacement	2 (0.6)
CABG + double valve surgery	24 (6.6)
Aortic and mitral	2 (0.6)
Mitral and tricuspid	19 (5.2)
Aortic and tricuspid	3 (0.8)
Any mitral valve surgery	230 (63.4)

Values are N (%), median ± standard deviation. *CABG,* Coronary artery bypass grafting.

000 Three-year outcomes of the postapproval study of the AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation Trial

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A PAS with bipolar radiofrequency and a Maze IV lesion set had high protocol compliance and freedom from AF at 36 months of 75.6% and 64.3% on and off antiarrhythmics, respectively.