Efficacy of the Stand-Alone Cox-Maze IV Procedure in Patients with Longstanding Persistent Atrial Fibrillation

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Abstract

Introduction: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and results in significant morbidity and mortality. The Cox-Maze IV procedure (CMP-IV) has been shown to have excellent efficacy in returning patients to sinus rhythm, but there have been few reports of late follow-up in sizable cohorts of patients with longstanding persistent AF, the most difficult type of AF to treat. Methods & Results: Between May 2003 and March 2020, 174 consecutive patients underwent a stand-alone CMP-IV for longstanding persistent AF. Rhythm outcome was assessed postoperatively for up to 10 years, primarily via prolonged monitoring (Holter monitor, pacemaker interrogation, or implantable loop recorder). Fine-Gray regression was used to investigate factors associated with atrial tachyarrhythmia (ATA) recurrence, with death as a competing risk. Median duration of preoperative AF was 7.8 years (interquartile range [IQR] 4.0-12.0 years), with 71% (124/174) having failed at least one prior catheter-based ablation. There were no 30-day mortalities. Freedom from ATAs was 94% (120/128), 83% (53/64), and 88% (35/40) at 1, 5, and 7 years, respectively. On regression analysis, preoperative AF duration and early postoperative ATAs were associated with late ATAs recurrence. Conclusion: Despite the majority of patients having a long-duration of preoperative AF and having failed at least one catheter-based ablation, the stand-alone CMP-IV had excellent late efficacy in patients with longstanding persistent AF, with low morbidity and no mortality. We recommend consideration of stand-alone CMP-IV for patients with longstanding persistent AF who have failed or are poor candidates for catheter ablation.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with prevalence estimates increasing globally over the last decade.[1] Patients with AF have significant morbidity and mortality secondary to symptoms detrimental to quality-of-life, hemodynamic compromise, and embolic stroke.[1,2] Many treatment modalities have been used to reduce the global burden of this disease, including antiarrhythmic drugs (AADs), catheter-based ablation, and surgical ablation (SA).

While relatively ubiquitous in clinical practice, medical management with AADs has had poor efficacy and has been associated with significant adverse side effects.[3–6] Given advances in percutaneous interventional techniques, catheter-based ablations have been utilized more frequently, and have had excellent success rates, particularly in patients with paroxysmal AF.[6] However, even the best outcomes in published series have only shown 52% freedom from AF at 10 years.[7] In addition, these studies have shown that patients with long-standing persistent AF tend to have inferior freedom from recurrent atrial tachyarrhythmias (ATAs) when compared to those patients with paroxysmal AF.[6–10]

The Cox-Maze procedure was introduced in 1987, and was the first successful interventional treatment for AF.[11] Since then, a multitude of different surgical techniques have been developed, utilizing a variety of lesion sets and ablation technologies. However, the most-effective SA technique has remained the Cox-Maze procedure.[11] While initial "cut-and-sew" iterations of this technique were time-intensive and complex due to need to create multiple incisions in the atrial myocardium, the introduction of bipolar radiofrequency ablation and cryoablation has simplified the procedure significantly.[12] This has led to the development of the Cox-Maze IV procedure (CMP-IV).[13,14] The CMP-IV has excellent efficacy as shown by our group and others[15–17], with 77% freedom from ATAs at 10 years[18]. The late survival benefit associated with concomitant CMP-IV has also been well-established.[19] Most importantly, it has sharply reduced both operative times and complication rates, leading to more widespread adoption of surgical ablation, particularly in patients referred for concomitant cardiac surgery.[12,19,20]

While used most commonly in the setting of other concomitant cardiac surgery (e.g. mitral valve repair or replacement), the Cox-Maze IV has been shown to be efficacious and safe as a stand-alone procedure.[21,22] Our group has previously shown equal efficacy of the stand-alone CMP-IV in restoring sinus rhythm (SR) amongst patients with paroxysmal and non-paroxysmal AF at early follow-up. Few studies have described outcomes at late follow-up in sizable cohorts of patients.[21–23] This study examined our early-, mid-, and late-term outcomes of the stand-alone CMP-IV amongst 174 consecutive patients with long-standing persistent AF. This group was selected for analysis because it is recognized to be the most difficult to treat, and it is the most commonly referred for surgical ablation.[15]

Methods

This study was approved by the Washington University School of Medicine Institutional Review Board. Informed consent and permission for release of information were obtained from all patients with a waiver of consent. Our institutional Society of Thoracic Surgery (STS) database was used for preoperative demographic data, operative details, and complications using STS definitions. Data pertaining to rhythm follow-up were prospectively entered into our institutional AF outcomes database. Missing data were ascertained through chart review, contact with patients, and from referring physicians as needed.

Patient Population

From May 2003 to March 2020, 286 patients underwent elective stand-alone SA. Patients who underwent ablation procedures other than biatrial CMP-IV (n=18) or who did not have a complete left-sided lesion set (n=21) were excluded, leaving 247 patients. Of these remaining patients, our analysis was limited to only those who had long-standing persistent AF (n=174). Roughly half of this final cohort underwent sternotomy as compared to a minimally invasive right mini-thoracotomy (RMT). These operative techniques have been previously described by our group.[24]

Rhythm Follow-Up

Patient follow-up was performed with a prospectively-defined schedule at 3, 6, and 12 months, and annually thereafter. At each follow-up visit, patients underwent history and physical evaluations, as well as electrocardiograms (ECGs). Routine prolonged monitoring was initiated in 2006 and included either 24-48 hour Holter monitoring, pacemaker interrogation, or implantable loop recording (ILR).

91 percent of patients (146/161) underwent prolonged monitoring at some point in their follow-up; 76% (109/143), 56% (40/73), and 60% (24/40) of patients underwent prolonged monitoring at 1-, 5- and 7-year follow-up, respectively. ATA recurrence was defined as any episode of AF, atrial flutter, or atrial tachycardia lasting longer than 30 seconds, in accordance with the 2017 Heart Rhythm Society (HRS) consensus statement[10]. ATA recurrence was examined in two ways. In the stricter of the two methods, we considered any ATA recurrence that occurred greater than 3 months postoperatively to be a permanent failure, regardless of duration of ATA or symptoms. In our second method, we looked at the percent of patients in SR at each time point, such that a patient who, for example, had a recurrence at 3 years could still be recognized as being ATA-free at 5 years if they were in SR at that time. We consider this method to be more clinically relevant given it takes into account that individual episodes of recurrence can be short and infrequent. This allows for differentiation between, for example, a patient who has multiple episodes of ATA a day a patient who has had only one or two 1-minute long episodes of ATA over their entire postoperative lifetime. Any patient who required an interventional procedure for rhythm control after the ninety-day

blanking period was considered a treatment failure.

Perioperative Care

Postoperative AADs and anticoagulants were administered to all patients unless contraindicated.[18] Patients who experienced postoperative ATAs unresponsive to AADs were cardioverted prior to discharge unless contraindicated (primary contraindication was documented left atrial [LA] clot). AADs were discontinued in patients in SR at 2-3 months postoperatively. Anticoagulants were discontinued at 3-6 months postoperatively for patients who both had no ATAs on prolonged monitoring and no evidence of atrial stasis or thrombus on echocardiography, irrespective of their CHA_2DS_2-VASc score.[25] In the immediate postoperative period patients with persistent junctional bradycardia were allowed 5-7 days for sinus node recovery. After this time, if patients were symptomatic, a dual chamber pacemaker was inserted. Median follow-up time was 4.0 years (interquartile range [IQR] 1.3-7.5 years). At 1, 5, and 7 years, 94.4% (135/143), 94.5% (69/73) and 88.0% (35/40) of patients available for follow-up had documented rhythm data, respectively.

Postoperative Complications

Major complications during the first 30 postoperative days included cerebrovascular accident, mediastinitis, pneumonia, sepsis, renal failure requiring dialysis, intra-aortic balloon pump, or reoperation. A patient was considered to have had a postoperative ATA if they had any episode or either AF or an ATA lasting longer than 30 seconds during their postoperative hospital stay.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD) or as a median with interquartile range (IQR), as appropriate. Student'st -test compared means of normally distributed continuous variables, while Mann-Whitney U test was used for skewed distributions. Categorical variables were expressed as frequencies and percentages with outcomes compared using either χ^2 or Fisher's Exact test, as appropriate. A p -value <0.05 was considered statistically significant.

Freedom from ATAs on/off AADs was calculated at each prospectively defined follow-up timepoint. Composite endpoint survival (freedom from first ATAs recurrence and death) was reported as a Kaplan-Meier estimate and presented alongside the cumulative incidence functions (CIFs) for both ATAs recurrence and death.[26] The probability of being both alive and free from any ATAs recurrence (remaining in sinus rhythm for the study duration) was equivalent to the probability of experiencing neither of the competing risks.[27] Seventeen clinically relevant variables were evaluated using univariable and multivariable Fine-Gray regression to identify factors associated with ATAs recurrence. Data analysis was performed using SAS Studio 3.8 on SAS 9.4 (SAS Institute Inc., Cary NC, USA), SPSS version 25 (SPSS Inc., Chicago, IL, USA), and R 3.6.3 using the *cmprsk* package (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics and Preoperative Clinical History

The mean age at time of operation in this patient population was 60.1±10.1 years (table 1). The majority of patients (72%) were male, and all patients were White. Over the entire follow-up period, 24% of patients (36/150) had an ATA recurrence. There were no significant differences in age, sex, or preoperative BMI between groups by rhythm outcome (ATA freedom versus ever recurrence). There were also no significant differences between groups by rhythm outcome in rates of preoperative BMI [?] 30, hyperlipidemia, peripheral vascular disease, prior cerebrovascular accident, CHA_2DS_2-VASc score, hypertension, history of cigarette smoking, chronic lung disease, or diabetes mellitus. No patient had preoperative renal failure. The majority of patients (77%, 134/174) had a CHA_2DS_2-VASc score greater than or equal to 2, i.e. a 2.9% or greater risk of stroke/transient ischemic attack/systemic embolism per year.[28]

Characterization of Preoperative Cardiac Function and Atrial Fibrillation

Overall, 4% (7/174) of patients had a history of myocardial infarction, while 85% (148/174) had some degree of congestive heart failure symptoms associated with their AF (table 2). Mean left ventricular ejection fraction was 54+-13%, and 41% (72/174) of patients had New York Heart Association Class III or IV heart failure.[29] There were no significant differences between groups by rhythm outcome for any of these variables.

Overall median length of time in AF was 7.8 years (IQR 4.0-12.0 years), and mean left atrial diameter was 4.8+-1.0 cm. The majority of patients (71%, 124/174) had failed at least one prior catheter-based ablation attempt, with a median number of failed attempts of 2 (IQR 1-3). None of these variables varied significantly between groups by rhythm outcome. Patients who remained ATA-recurrence free over the follow-up period did have a significantly lower rate of preoperative pacemaker or implantable cardioverter defibrillator placement (6% versus 22%, p =0.0095) compared to those who had an ATA recurrence.

Operative Characteristics

Roughly half of patients underwent sternotomy (48%) versus right mini thoracotomy (table 3). Median cardiopulmonary bypass (CPB) time was 152.0 minutes (IQR 116.0-178.0), and median aortic cross-clamp time was 55.0 minutes (IQR 36.0-68.0). The majority of CMP-IV lesion sets were created using a non-irrigated bipolar radiofrequency ablation clamp (79% 137/173; AtriCure Inc., Mason OH, USA), with the remainder created using irrigated bipolar radiofrequency devices (Medtronic PLC, Minneapolis MN, USA). Cryoablation was used for all ablations near the tricuspid and mitral valve annuli. There were no significant differences between groups by rhythm outcome in operative approach, ablation device usage, or median CPB or aortic cross-clamp time.

Postoperative Characteristics and Complications

Patients with ATA recurrence had a significantly longer median postoperative hospital length of stay compared to those without recurrence (8 days [IQR 7-9.5] versus 7 days [IQR 5-10]; table 4). Patients who remained ATA-recurrence free over the entire follow-up period had significantly shorter median intensive care unit (ICU) length of stay (41 hours [IQR 25-75] versus 73 hours [IQR 35-101,p =0.0090) and shorter median mechanical ventilation time (3 hours [IQR 1-6] versus 5 hours [IQR 4-16], p =0.0003) compared to those who had an ATA recurrence.

Major postoperative complications were low in this population overall (table 4). There were no mortalities within 30 days of surgery. The overall major complication rate was only 9% (15/174). Two patients required reoperation, one for bleeding and one for sternal dehiscence, and one patient had postoperative sepsis. Five patients developed pneumonia. One patient had postoperative renal failure which transiently required dialysis; no patient required permanent dialysis. Three patients (1.7%) had a cerebrovascular accident (CVA) in the 30 day postoperative period, and one (0.6%) had a late CVA, which occurred 4 years postoperatively. There were no significant differences in rates of major postoperative complications between groups by rhythm outcome.

The majority of patients were in sinus rhythm at time of hospital discharge (78% 136/174), with 8% (13/174) requiring pacemaker placement postoperatively. Neither of these variables were significantly different between groups by rhythm outcome (table 4). Patients who remained ATA-recurrence free over the follow-up period were significantly less likely to have had postoperative ATAs during their initial hospital stay (37%, 42/114 versus 56%, 20/36, p =0.0468) compared to those who had an ATA recurrence.

Rhythm Follow-Up

Overall freedom from ATAs was 94% (120/128), 83% (53/64), and 88% (35/40) at 1, 5, and 7 years, respectively (Figure 1). Freedom from ATAs and AADs was 87% (111/128), 69% (44/64), and 68% (27/40) at the same time points. At each timepoint, the percentage of patients on warfarin was 23% (30/133), 30% (20/67), and 32% (12/37), respectively. By competing risks analysis to first ATA recurrence, the probability of remaining alive and free of ATAs was estimated to be 91%, 76%, and 63% at follow-up years 1, 5, and 8, respectively (Figure 2 and Table 5). The estimated incidence of first ATA recurrence was 7%, 18%, and 25%, respectively. Estimated mortality at these time points was 2%, 6%, and 12%, respectively. Amongst patients who did have recurrence of ATA, the median number of recurrences was 2 (IQR 1-3) over the entire follow-up period, with 61% (22/36) of these patients having only 1-2 recurrences.

Predictors of ATAs Recurrence

Univariable analysis of seventeen preoperative and perioperative variables was performed to evaluate potential predictors of ATAs recurrence (Table 6). On multivariable Fine-Gray regression, increased preoperative duration of AF (SHR 1.92, 95% CI (1.16, 3.17),p =0.011) and early postoperative ATAs (SHR 2.06, 95% CI (1.06, 4.00), p =0.033) were associated with increased risk of ATAs recurrence. The relationship between AF duration and ATA recurrence is depicted in Figure 3. Despite significance on univariable regression, increased left atrial size was not predictive of future ATAs recurrence on multivariable regression (p =0.116). Number of prior catheter ablations was also not a significant predictor of recurrence (p =0.325).

Discussion

The CMP-IV remains the most effective treatment for AF, and has been shown to be effective for both paroxysmal and non-paroxysmal AF.[13–15,18] There have been few published reports on the late results of the CMP-IV in patients with longstanding persistent AF, who composed the most common subgroup of patients referred for surgical ablation.[12]

Our results showed excellent and durable success with the CMP-IV for longstanding persistent AF from early through late follow-up amongst 174 consecutive patients. Freedom from ATAs and freedom from both ATAs and AADs was 88% and 68% respectively at 7 years postoperatively. This is particularly impressive in this group of difficult-to-treat patients, with a median preoperative duration of AF of 7.8 years and a mean LA diameter of 4.8cm, the majority of whom (71%, 124/174) had failed one or more catheter ablations. Our findings support the use of surgical ablation as a treatment of symptomatic AF refractory to AADs in patients who have failed or are poor candidates for catheter-based interventions, as recommended by the HRS, STS, and European Cardiac Arrhythmia Society.[2,10,30]

The late results of the CMP-IV in our population were superior to previous studies published on catheter ablation in longstanding persistent AF.[7,8] Within our cohort, ATA-free survival at 5 and 7 years was 83% and 88%, compared with 24% AF-free survival at 10 years in persistent AF patients in one study [7], and just 17% ATAs recurrence-free survival at 5 years after a single catheter ablation in persistent AF patients in another[8]. This suggests that the CMP-IV should be considered in lieu of catheter ablation in selected patients at high risk for failure (i.e. large left atrial volume, long duration of preoperative AF).

The late results of the CMP-IV in our population were also superior to other surgical ablation techniques.[31,32] At 5 years follow-up, our cohort had a 76% ATA-free survival, compared to one study's 29% AF-free survival in longstanding persistent AF patients after LAA exclusion, pulmonary vein isolation, and ganglionated plexi ablation [32] at the same time point. This supports the use of the full CMP-IV lesion set for surgical ablation in patients with long-standing persistent AF who have failed catheter ablation, especially in light of our low complication rates. There was no significant relationship between the type of ablation device used and freedom from ATA recurrence, though there was a trend toward better late outcomes with dry bipolar radiofrequency clamps.

The stand-alone CMP-IV was performed with minimal morbidity and no 30-day mortality, regardless of surgical approach. There was only one late CVA (0.6%). Postoperative pacemaker placement (7.5%, 13/174) was comparable to previously published studies, with 85% of those pacemakers (11/13) placed for sick sinus syndrome, and 15% (2/13) placed for complete heart block.[12,22] Patients with ATA recurrence had significantly longer median postoperative hospital length of stay, ICU length of stay, and mechanical ventilation time, compared to those without recurrence. This may have been secondary to differences in patients' underlying baseline health, but could also indicate that greater stress in the postoperative period contributed to eventual recurrence.

On Fine-Gray multivariable regression, the only two factors predictive of late ATAs recurrence were preoperative length of time in AF and early postoperative ATAs. This is similar to previously published results from both our group and others.[15,33,34]

Although this study is one of the largest in the literature to report late rhythm outcomes for stand-alone surgical ablation in patients with longstanding persistent AF, it is not without limitations. This study was retrospective and nonrandomized, thus subject to inherent selection bias. All operations were performed at a single institution, with most completed by a single, highly-experienced surgeon (n=164). This may limit generalizability to other centers. Referral patterns and patient selection may have had an impact on our results. Moreover, sample size may have contributed to the variability of these results and increased risk of type II error. An inherent limitation in the study design was the lack of continuous monitoring on all patients, which can lead to interval censoring and underestimation of ATAs recurrence. However, the majority of patients underwent prolonged monitoring during follow-up, and Fine-Gray regression does not assume non-informative censoring. Moreover, the number of patients both followed longer than 5 years and who had prolonged monitoring is higher than most previously published studies. While the majority of patients underwent prolonged monitoring, AF burden was not recorded in the available medical record for most of these patients, precluding a burden-based analysis. Burden calculations are only possible in patients with pacemakers or implantable loop recorders (ILRs), which were present in only a small minority of our patients. We have previously studied the utility of ILR use following CMP-IV, and found that ILR use did not increase ATA detection compared to Holter monitoring or ECG.[35] Given this, it is unlikely that increasing available burden data via more liberal use of ILRs would significantly alter our findings.

Conclusion

The stand-alone CMP-IV had superior 5 and 7 year recurrence-free survival rates for patients with longstanding persistent AF compared to published reports of other surgical and catheter-based ablation techniques. The stand-alone CMP-IV was equally effective regardless of surgical approach, or number of previous catheter ablations. There were no mortalities and the rate of morbidity was low. On Fine-Gray regression, preoperative time in AF and early postoperative ATAs were predictive of late ATAs recurrence. Based on these findings, we recommend consideration of stand-alone CMP-IV for symptomatic patients with longstanding persistent AF who have failed catheter ablation or are poor candidates for catheter-based therapies.

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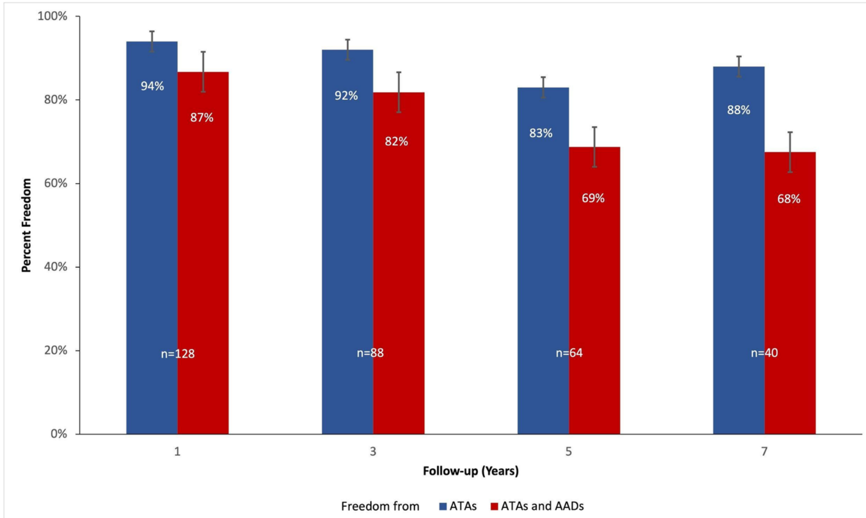

Figure 1. Seven year follow-up after stand-alone Cox-Maze IV in patients with longstanding persistent atrial fibrillation, showing freedom from atrial tachyarrhythmia (ATA) recurrence and freedom from both ATA recurrence and antiarrhythmic drugs (AAD) at 1, 3, 5, and 7 years postoperatively with standard error bars.

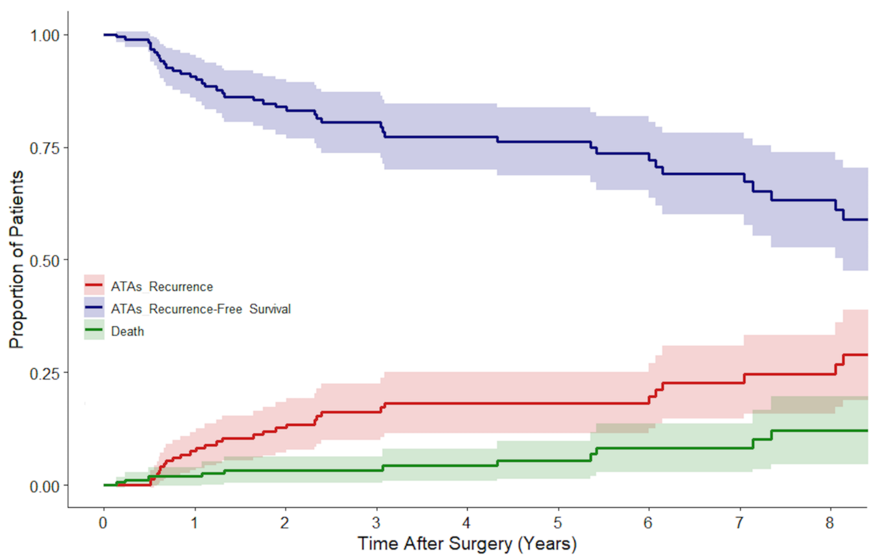

Figure 2. Competing risks of atrial tachyarrhythmias (ATAs) recurrence (red) and death (green) following stand-alone Cox-Maze IV procedure for longstanding persistent atrial fibrillation are depicted by cumulative incidence functions. ATAs recurrence-free survival (blue) is depicted as a composite endpoint, equivalent to the probability of experiencing neither of the competing risks.

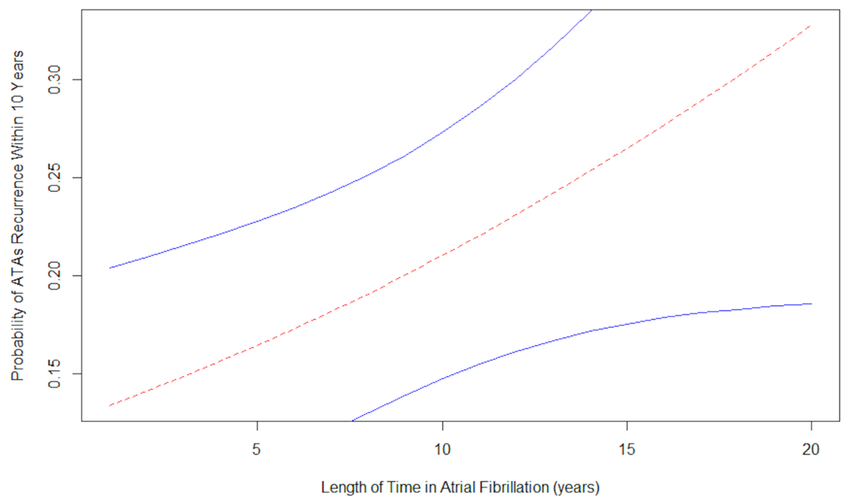

Figure 3. Estimation of the probability of atrial tachyarrhythmias (ATAs) recurrence within ten years based on length of time in atrial fibrillation prior to Cox-Maze IV (red dashed line) with 95% confidence intervals (solid blue lines).

Table 1: Baseline Patient Characteristics. For patients that had follow-up of at least 6 months or longer postoperatively, characteristics were compared across rhythm outcomes. There were no significant differences between groups by freedom from versus recurrence of ATAs for any of these variables (alpha = 0.05).

Variable	**Total Study Population**	**Patients free from ATAs**	**Patients with ATA recurrence**	**Statistical Significance**
Number of Patients (% of Total Population)	174	76% (114/150)	24% (36/150)	
Mean Age (±SD)	60.1 years (±10.1) (n = 174)	59.7 years (±9.8) (n = 114)	61.9 years (±11.0) (n = 36)	p = 0.2626*
% Male Sex	72% (126/174)	72% (82/114)	69% (25/36)	p = 0.7737+
% White Race	100% (174/174)			
% Mean BMI (±SD)	32.0 (±6.8) (n = 174)	31.9 (±6.8) (n=114)	32.1 (±8.0) (n=36)	p = 0.8706*
% with BMI [?]30	59% (102/174)	59% (67/114)	56% (20/36)	p = 0.7332+
% with HLD	55% (95/174)	55% (63/114)	61% (22/36)	p = 0.5370+
% with PVD	5% (9/174)	4% (5/114)	11% (4/36)	p = 0.2191++
% with prior CVA	14% (23/161)	14% (17/125)	17% (3/36)	p = 0.6431+
% with CHA_2DS_2-VASc [?] 2	77% (134/174)	76% (87/114)	75% (27/36)	p = 0.8720+

% with HTN	67% (116/174)	65% (74/114)	69% (25/36)	$p = 0.6168$+
% Ever Smokers	36% (62/174)	33% (38/114)	44% (16/36)	$p = 0.2260$+
% with Chronic Lung Disease	10% (17/174)	9% (10/114)	14% (5/36)	$p = 0.3556$++
% with DM	14% (25/174)	14% (16/114)	14% (5/36)	$p = 0.9824$+
% with Renal Failure	0% (0/174)			

ATA = atrial tachyarrhythmia, BMI = body mass index, CVA = cerebrovascular accident, DM = diabetes mellitus, HLD = hyperlipidemia, HTN = hypertension, PVD = peripheral vascular disease, SD = standard deviation.

*Two-way t-test with Pooled variances

+Chi-squared test

++Two-sided Fisher's Exact test

Table 2: Baseline Cardiac Function and History. For patients that had follow-up of at least 6 months or longer postoperatively, cardiac function and history were compared across postoperative rhythm outcomes. *P* values are bolded to indicate a significant difference between groups by postoperative ATA status (alpha = 0.05).

Variable	Total Study Population	Patients free from ATAs	Patients with ATA recurrence	Statistical Significance
% with prior MI	4% (7/174)	4% (4/114)	6% (2/36)	$p = 0.6303$++
% with CHF	85% (148/174)	85% (97/114)	81% (29/36)	$p = 0.5179$+
Mean LVEF (±SD)	54% (±13.3) (n = 172)	55% (±13.5) (n = 112)	54% (±11.6) (n = 36)	$p = 0.6300$*
% with NYHA HF Class III or IV	41% (72/174)	43% (49/114)	36% (13/36)	$p = 0.4655$+
Median length of time in AF (IQR)	7.8 years (4.0-12.0) (n = 174)	7.0 years (3.2-11.0) (n = 114)	10.0 years (4.9-14.5) (n = 36)	$p = 0.0858$§
Mean LA diameter (±SD)	4.8 cm (±1.0) (n = 158)	4.7 cm (±1.0) (n = 105)	5.1 cm (±1.0) (n = 35)	$p = 0.0792$*
% failed catheter ablation	71% (124/174)	69% (79/114)	75% (27/36)	$p = 0.5124$+
Median number of failed catheter ablations (IQR)	2 (1-3) (n = 124)	2 (1-3) (n = 79)	2 (1-2) (n = 27)	$p = 0.7012$§
% with pacemaker and/or AICD¶	10% (17/174)	6% (7/114)	22% (8/36)	p **= 0.0095**++

AF = atrial fibrillation, AICD = automatic implantable cardioverter defibrillator, ATA = atrial tachyarrhythmia, CHF = congestive heart failure, HF = heart failure, IQR = interquartile range, LA = left atrium, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NYHA = New York Heart Association, SD = standard deviation.

*Two-way t-test with Pooled variances

+ Chi-squared test

++ Two-sided Fisher's Exact test

§ Mann-Whitney U test, two-sided normal approximation

¶ 2 patients had ICDs (for non-ischemic cardiomyopathy and neurocardiogenic syncope, respectively), 14 had pacemakers only, and 1 had no available data on device type.

Table 3: Operative Characteristics. For patients that had follow-up of at least 6 months or longer post-operatively, operative characteristics were compared across postoperative rhythm outcomes. There were no significant differences between groups by freedom from versus recurrence of ATAs for any of these variables (alpha = 0.05).

Variable	Total Study Population	Patients free from ATAs	Patients with ATA recurrence	Statistical Significance
% Sternotomy	48% (83/174)	52% (59/114)	53% (19/36)	$p = 0.9147$+
Median CPB time (IQR)	152.0 minutes (116.0-178.0) (n = 174)	145.5 minutes (114.0-179.0) (n = 114)	150.0 minutes (114.0-170.0) (n = 36)	$p = 0.9754$§
Median aortic cross-clamp time (IQR)	55.0 minutes (36.0-68.0) (n = 172)	54.0 minutes (35.0-67.5) (n = 112)	53.0 minutes (36.5-72.0) (n = 36)	$p = 0.7089$§
% AtriCure ablation device	79% (137/173)	81% (91/113)	67% (24/36)	$p = 0.0843$+

ATA = atrial tachyarrhythmia, CPB = cardiopulmonary bypass, IQR = interquartile range.

+ Chi-squared test

§ Mann-Whitney U test, two-sided normal approximation

Table 4: Postoperative Characteristics and Complications. For patients that had follow-up of at least 6 months or longer postoperatively, postoperative characteristics and complications were compared across postoperative rhythm outcomes. *P* values are bolded to indicate a significant difference between groups by postoperative ATA status (alpha = 0.05).

Variable	Variable	Total Study Population	Patients free from ATAs	Patients with ATA recurrence	Statistical Significance
Median postoperative hospital length of stay (IQR)	Median postoperative hospital length of stay (IQR)	7 days (6-10) (n = 174)	7 days (5-10) (n = 114)	8 days (7-9.5) (n = 36)	p = **0.0327**§
Median ICU length of stay (IQR)	Median ICU length of stay (IQR)	46.0 hours (25.5-92.0) (n = 173)	41.3 hours (25.0-75.3) (n = 113)	72.8 hours (34.8-101.0) (n = 36)	p = **0.0090**§
Median mechanical ventilation time (IQR)	Median mechanical ventilation time (IQR)	3.6 hours (1.5-6.0) (n = 150)	3.0 hours (1.0-6.0) (n = 121)	5.0 hours (3.7-16.0) (n = 29)	p = **0.0003**§

% readmitted within 30 days	% readmitted within 30 days	16% (27/174)	15% (17/114)	14% (5/36)	$p = 0.8797$+
	% requiring reoperation	1% (2/174)	1% (1/114)	0% (0/36)	$p = 1.0000$++
	% with PNA	2.9% (5/174)	2.6% (3/114)	2.8% (1/36)	$p = 1.0000$++
	% with sepsis	0.8% (1/126)	0% (0/87)	5.9% (1/17)	$p = 0.1635$++
	% with renal failure requiring dialysis	0.7% (1/154)	0% (0/100)	0% (0/30)	
	% with CVA	1.7% (3/174)	2.6% (3/114)	0% (0/36)	$p = 1.0000$++
	% with pacemaker placed postoperatively ¶	7.5% (13/174)	7.9% (9/114)	2.8% (1/36)	$p = 0.4524$++
	% with postoperative ATAs*	40.2% (70/174)	36.8% (42/114)	55.6% (20/36)	p = **0.0468**+
	% in sinus rhythm at hospital discharge	78.2% (136/174)	82.5% (94/114)	72.2% (26/36)	$p = 0.1808$+

ATA = atrial tachyarrhythmia, CVA = cerebrovascular accident, ICU = intensive care unit, IQR = interquartile range, PNA = pneumonia.

*Postoperative ATAs as defined by the Society for Thoracic Surgery as post-operative atrial fibrillation or ATAs during postoperative hospital stay.

+ Chi-squared test

++ Two-sided Fisher's Exact test

§ Mann-Whitney U test, two-sided normal approximation

¶ 11/13 pacemakers were placed for sick sinus syndrome, 2/13 were placed for complete heart block.

Table 5: Number at risk by year after standalone Cox-Maze IV and percentage of patients estimated to be in each state. Patients were assumed to be in one of three mutually exclusive states at each point during follow-up: alive and free from ATAs recurrence (composite endpoint), alive and having experienced first ATAs recurrence (CIF), or dead before ATAs recurrence (CIF).

Year	Number at Risk	Alive and Free from ATAs Recurrence	First Documented ATAs Recurrence	Death
1	139	91%	7%	2%
2	123	84%	13%	3%
3	100	81%	16%	3%
4	86	77%	18%	5%
5	81	76%	18%	6%
6	59	72%	20%	8%
7	48	69%	23%	8%
8	38	63%	25%	12%

ATA = atrial tachyarrhythmia, CIF = cumulative incidence function.

Table 6: Univariable and Multivariable Predictors of First ATAs Recurrence by Fine-Gray Regression. *P* values are bolded to indicate statistical significance.

Variable	Univariable Analysis *P*-Value	Univariable Analysis Subdistribution Hazard Ratio (95% CI)	Multivariable Anal *P*-Value
Age (years)	0.195	1.03 (0.99, 1.07)	
Male Sex	0.517	0.80 (0.40, 1.58)	
BMI (kg/m2)	0.890	1.00 (0.97, 1.03)	
Hyperlipidemia	0.551	1.23 (0.62, 2.44)	
Hypertension	0.610	1.20 (0.60, 2.37)	
NYHA Class III/IV	0.870	0.95 (0.48, 1.87)	
LVEF (%)	0.873	1.00 (0.98, 1.02)	
CHF	0.294	1.44 (0.73, 2.82)	
Ever Smoker	0.370	1.36 (0.69, 2.68)	
Preoperative Creatinine	0.211	2.49 (0.60, 10.40)	
Length of Time in AF (years)	**0.003**	**1.99 (1.27, 3.12)**	**0.011**
LA Size (cm)	0.079	1.37 (0.96, 1.94)	0.116
Number of Prior Catheter Ablations	0.325	1.13 (0.88, 1.45)	
CPB Time (hours)	0.040	1.71 (1.02, 2.86)	0.072
AtriCure energy device	0.828	0.93 (0.46, 1.86)	
Sternotomy	0.201	0.64 (0.32, 1.27)	
Postoperative ATAs*	**0.034**	**2.04 (1.05, 3.94)**	**0.033**

ATA = atrial tachyarrhythmia, BMI = body mass index, CI = confidence interval, CHF = congestive heart failure, CPB = cardiopulmonary bypass, LVEF = left ventricular ejection fraction, LA = left atrium, NYHA = New York Heart Association.

*Postoperative ATAs as defined by the Society for Thoracic Surgery as post-operative atrial fibrillation or ATAs during postoperative hospital stay.