Relationship Between Amiodarone Response prior to Ablation and One-Year Outcomes of Catheter Ablation for Atrial Fibrillation

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Abstract

Background: Catheter ablation for atrial fibrillation (AF) is a common therapeutic strategy for patients with either paroxysmal or persistent AF, but long-term ablation success rates are imperfect. Maintenance of sinus rhythm immediately prior to ablation with anti-arrhythmic drug (AAD) therapy has been associated with improved outcomes in patients undergoing ablation. Amiodarone has superior efficacy relative to other AADs. Whether failure of amiodarone to maintain sinus rhythm prior to ablation for either paroxysmal or persistent AF is associated with poor outcomes is unknown. **Methods**: A total of 307 patients who received amiodarone in a one-year window before undergoing catheter ablation for AF were included. Patients were divided into amiodarone success (n=183) and amiodarone failure (n=124) groups based on the response to pre-ablation amiodarone treatment. Analysis of procedural outcomes as a function of response to amiodarone therapy was performed. Patients were followed for at least 12 months post-ablation to assess outcomes (adverse events and arrhythmia recurrence). Procedural success was defined by the absence of documented arrhythmia (>30s) without any anti-arrhythmic agents beyond a 90d blanking period. **Results**: Following ablation for either paroxysmal or persistent AF, freedom from any recurrent atrial arrhythmia at 1y was 57.7% for the entire cohort. One-year freedom from recurrent arrhythmia in the amiodarone success group was comparable to that in the amiodarone failure group (55.7% vs 60.5%; p=0.54). Success rates following ablation did not vary by the response to amiodarone when analyzed for paroxysmal or persistent AF subgroups. **Conclusion**: Failure to restore and maintain sinus rhythm with amiodarone prior to ablation for either paroxysmal or persistent AF is not a predictor of ablation procedural failure. Amiodarone failure alone should not deter practitioners from considering ablation therapy for patients with AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide and contributes to a variety of pathophysiological consequences including reduced functional capacity, increased risk of thromboembolism, heart failure, depression, and dementia (1,2,3). Catheter ablation for patients with either paroxysmal or persistent AF (PAF or persAF) has become a common therapeutic option, particularly for patients intolerant of anti-arrhythmic drug (AAD) therapy (4). The cornerstone of catheter ablative therapy for both PAF and persAF patients remains pulmonary vein isolation (PVI). While superior to AAD therapy in preventing recurrent AF, ablation remains imperfect in preventing AF recurrence in a substantial minority of patients (5,6).

Assessing the likelihood of AF ablation success is clearly important when considering the risk/benefit profile associated with ablation therapy. Several studies have demonstrated improved ablation outcomes in patients restored to normal sinus rhythm (NSR) with AAD therapy in the run-up phase to ablation for persAF (7,8,9). However, these investigations excluded PAF patients, used a variety of AADs, and employed ablation strategies beyond standard PVI. More importantly, patients who did not maintain sinus rhythm despite amiodarone therapy were explicitly excluded from investigation (9).

No studies, to our knowledge, have focused exclusively on therapeutic response to amiodarone as a screening tool for the prediction of AF ablation outcomes. The current investigation hypothesized that failure of amiodarone to maintain sinus rhythm in the pre-ablation window would correlate with increased post-ablation recurrence of AF. Use of amiodarone is often confined to a particular subset of AF patients (those with coronary artery disease, heart failure, advanced age); accordingly, in an effort to minimize confounding patient characteristics, we compared AF ablation outcomes in patients treated successfully with amiodarone (but who nevertheless opted for ablation) versus those in whom amiodarone was unsuccessful in maintaining NSR.

Methods

Patient Population

We performed a single-center, retrospective observational study of patients enrolled in a prospectively populated AF ablation database, approved by the Johns Hopkins IRB and maintained continuously at Johns Hopkins Hospital since 2002. Patients enrolled in the current investigation underwent ablation for either PAF or persAF from January 2014 through March 2019. In that period, 307 patients were identified who had received at least four weeks of continuous therapy with amiodarone for rhythm-control purposes in the one-year window prior to AF ablation. PAF patients were treated with Amiodarone at a minimum maintenance dose of 200mg per day for at least four weeks; persAF patients were treated with loading doses of amiodarone followed by maintenance dosing, and underwent electrical cardioversion (CDV) to restore NSR after at least two weeks of amiodarone therapy if necessary.

Patients were divided into two groups based on clinical response to amiodarone. The amio-success group (n=183) maintained NSR for the entirety of therapy with amiodarone and presented for PVI in NSR. The amio-failure group (n=124) included patients who were loaded for with amiodarone for a minimum of 4 weeks and cardioverted if necessary, but who nevertheless experienced either recurrent episodes of PAF or persAF.

Patient characteristics were systematically recorded and included age, gender, comorbidities, history of anti-arrhythmic use and cardioversion, AF subtype (paroxysmal, persistent, or long standing persistent), and baseline echocardiographic parameters (left atrial size and left ventricular ejection fraction [LVEF]). Procedural data including pre-procedural imaging, peri-procedural anticoagulation approach, ablation information (RF v. cryoballoon; PVI only v. PVI with non-PV targets; target power, force, and temperature parameters) were similarly recorded.

Arrhythmia recurrence and peri-procedural complications were ascertained based on monitoring strategies suggested in the consensus document [1]. Arrhythmia recurrence was defined as any AF or atrial tachyarrhythmia (AT) sustained for >30 s recorded by a surface electrocardiogram or rhythm monitoring device after a 90-day blanking period. Procedure-related complications, including vascular complications, major bleeding, phrenic nerve palsy, cerebral embolism, pericardial effusion/tamponade, atrioesophageal fistula, or extended hospitalization (>48 h) were assessed. All patients were observed in the hospital for a minimum of one-night post-ablation. Routine follow-up (history, exam, and electrocardiography) was performed at the outpatient clinic or by a local cardiologist at 3, 6, and 12 months, and additionally, if prompted by symptoms. Holter or event monitors were arranged for patients in whom symptoms suggestive of AF developed in the post-blanking follow-up period. Pacemaker interrogation records were also used for arrhythmia recurrence monitoring when available. AAD therapy, if present at the time of ablation, was discontinued at the 3-month follow-up visit based on the operator's discretion. Reinitiation of AAD therapy post-blanking period was considered a procedural failure. Outcomes were assessed via electronic health records.

Peri-Procedural Anticoagulation and Imaging

Catheter ablation in patients treated with warfarin was performed without interruption. Patients treated with direct oral anticoagulants (DOACs) held anticoagulation for a maximum of 24 h prior to the ablation procedure, with resumption 4 h post-procedure. Anticoagulation was continued for a minimum of 3 months

following ablation for all patients.

Patients underwent routine transesophageal echocardiography (TEE) immediately prior to ablation to exclude LAA thrombus unless TEE was clinically contraindicated. Patients unable to undergo preprocedural TEE were systemically anticoagulated for at least one month prior to ablation. Additionally, patients underwent pre-procedure cardiac CT or MRI to delineate left atrial anatomy. Electroanatomic mapping (EAM) data collected during the procedure was merged with the pre-acquired CT or MRI at the operator's discretion.

Ablation Procedure

All patients underwent the ablation procedure with general anesthesia. All patients underwent detailed EAM with either CARTO or ESI mapping systems following vascular and left atrial access prior to and following ablation. Patients presenting in AF underwent cardioversion to NSR prior to EAM. All patients underwent PVI as the principle ablative strategy of the procedure. Additional non-PV targets (linear lesions; low-voltage areas) were ablated at the operator's discretion.

Catheter ablation was performed using either an irrigated, contact force-sensing RF ablation system (Biosense Webster, etc., or Abbot/ESI) or a cryoballoon ablation catheter (Arctic Front and Arctic Front Advance, Medtronic Inc.). For patients undergoing RF ablation, target power delivery to the anterior and posterior LA walls was 35–45 and 25–35 W, respectively. Patients undergoing cryo-balloon ablation underwent fluoroscopic positioning of a 28- or 23mm cryo-balloon to achieve complete PV occlusion assessed by contrast injection. A minimum of two freeze-thaw cycles (3 min duration) were applied to each vein, sufficient to achieve PV isolation as assessed by a multipolar mapping catheter.

All patients had an esophageal temperature probe in place during ablation, with temporary cessation of lesion application if esophageal temperature deviation occurred. Phrenic nerve pacing was performed during cryo-balloon ablation in right-sided pulmonary veins in all cases, with cessation of ablation upon any diminution in the force of diaphragmatic contraction.

PV isolation was assessed in all cases after a 20-minute waiting period by demonstrating an entrance block to each vein, assessed during sinus rhythm on post-ablation EAM. Exit block was demonstrated at the operator's discretion, as was occult PV reconnection during adenosine infusion.

Statistical Analysis

Continuous data were analyzed using the student's t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Categorical data were analyzed using the $\chi 2$ test. Values are presented as mean $\pm$ standard deviation or median and interquartile range (Q1-Q3) according to distribution for continuous data and count and percentage for categorical data unless otherwise stated. The cumulative probability of survival free from atrial arrhythmia was displayed according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test. Follow-up for all patients was censored one year after ablation. A p-value of <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, New York) and STATA Version 13 (Stata Corp, College Station, TX).

Results

From January 2014 through March 2019, 1210 patients underwent ablation for AF and consented to enrollment in our AF ablation database. Of these, 307 patients had been treated in the one-year period prior to ablation with amiodarone for a minimum of 4 weeks as part of a rhythm-control strategy. Amiodarone-treated patients had either PAF (n=146) or persAF (n=161). Patients who had symptomatic PAF or persAF despite amiodarone treatment also underwent CDV prior to ablation for rhythm control (n=228).

Patients who maintained NSR on amiodarone but opted for ablation in lieu of ongoing AAD therapy and presented for the ablation procedure in NSR were defined as the amio-success cohort (n=183). Patients who had breakthrough AF (either episodic PAF or persAF), or who presented for ablation in ongoing AF,

were defined as the amio-failure cohort (n=124). Patient identification and categorization flows are shown in**Figure 1** .

There were no differences in age, ethnicity, gender, BMI, CHADS-VASC score, LA size, or AF duration (time from identification to ablation) between the amio-success and amio-failure groups. The amio-success group was comprised of 96 (52.5%) patients with PAF and 87 (47.5%) patients with persAF, while the amio-failure group was comprised of 50 (40.3%) patients with PAF and 74 (59.7%) patients with persAF (p=0.03). Clinical and imaging characteristics for each group are provided in**Table 1** .

Procedural Results

Procedural characteristics and outcomes are provided in **Table 2** .

Of the 307 patients treated with amiodarone, 228 (74.3%) underwent CDV during the pre-ablation period as part of a rhythm-control strategy. This included 105 of the 124 amio-failure patients (84.5%) and 123 of the 183 amio-success patients (67.2%). The average time from CDV to subsequent ablation was the same (3months) in the amio-failure and amio-success groups.

Patients underwent either RF (n=251; 81.8%) or cryoballoon (n=55; 18.2%) ablation. There was no difference in ablation modality used between the amio-success and amio-failure patients. Of the 307 patients, 218 (74.3%) underwent index catheter ablation. Patients in the amio-failure group presented either in AF (n=97; 78.2%) or in atrial flutter (n=27; 21.8%). PVI-only was the dominant ablation strategy, performed in 199/307(64.8%) patients. Extra-PVI ablation sites were targeted in 108/307 patients (35.1%) and included roof line lesion sets (26/307) and focal targets (10/307). Extra-PVI ablation was performed in 52 of the 183 amio-success cohort (28.4%) and 56 of the 124 amio-failure cohort (45.1%)

All 307 patients were followed for at least 12 months to survey for arrhythmia recurrence after a 3m blanking period. AAD therapy was discontinued in all patients during the blanking period. Off-drug arrhythmia-free survival rates in the amio-success and amio-failure cohorts were calculated using Kaplan-Meier survival curves (**Figure 2**). The overall 1-year success rate was 57.7% and was not different in the amio-success cohort (55.7%) versus the amio-failure cohort (60.5%; p=0.54). Recurrent arrhythmias included recurrent AF (30.3%), atrial flutter (9.1%), focal atrial tachycardia (0.3%), or a combination of AF and flutter (2.6%) and did not differ between amio-success and amio-failure cohorts.

Ablation success rates in the patients treated for PAF were similar in the amio-success and amio-failure cohorts (55.2 versus 66.0%; p=0.27;**Figure 3A**). Similarly, patients with persAF had similar ablation outcomes between the two cohorts, with freedom from AF in 56.3% and 56.8% of patients in the amio-success and amio-failure groups (p=0.91; **Figure 3B**).

Complications occurred in 9 of the 307 patients studied (2.9%) and included vascular access site issues (0.7%), aspiration pneumonia (0.3%), pulmonary embolism (0.3%), and cardiac tamponade (1.6%) (**Table 3**). There was no difference in complication rates between the amio-success and amio-failure cohorts.

DISCUSSION

Main Findings

We performed a single-center, retrospective review of 307 patients treated with amiodarone for a minimum of one month as a part of a rhythm-control strategy that culminated in catheter ablation for AF. We hypothesized that failure of rhythm control on amiodarone would predict increased rates of AF recurrence following ablation, but found that our hypothesis was incorrect; patients who did and did not achieve rhythm control on amiodarone prior to PVI had equivalent rates of freedom from recurrent atrial arrhythmia following ablation, suggesting that response to amiodarone is not an adequate litmus test for considering PVI in AF patients.

Clinical Relevance

Our study included a relatively large cohort of AF ablation patients with a unique characteristic – the use of amiodarone in the pre-ablation period for purposes of rhythm control. We were able to use this substantial cohort of amio-treated patients to investigate whether therapeutic response to the drug predicted ablation outcomes with standard ablation approaches (a predominantly PVI-based strategy; irrigated, force-sensing RF or second-generation cryoballoon cathters).

Previous studies of AAD use before AF ablation have focused on three main ideas: response to AADs as a test to predict ablation outcome; AAD maintenance of sinus rhythm to allow atrial reverse remodeling prior to ablation; and AAD therapy to minimize non-PV foci targeted during the ablation procedure.

Miyazaki and colleagues analyzed the relationship between pre-ablation response to bepridil (a calcium-blocking anti-anginal) and ablation outcomes in 82 patients with persAF exclusively (7). Their study found that post-ablation AF freedom was greater in the patients who cardioverted pharmacologically with the bepridil (no electrical cardioversion performed) than in the patients who did not cardiovert with bepridil therapy. Kang and colleagues conducted an analogous study investigating pre-ablation electrical cardioversion efficacy in AF patients. They found that those persAF patients (94) who were more easily cardioverted pre-ablation (lower energy; fewer shocks) had improved ablation outcomes as compared to patients who were more difficult to cardiovert (11).

Our study tests a similar idea to the one investigated by Miyazaki and Kang: does pre-procedure response to a rhythm-control strategy (AAD or cardioversion) predict response to catheter ablation for AF? Unlike the previous reports mentioned, we found that pre-procedure response to amiodarone was not a reliable predictor of post-ablation outcomes. We were able to study a large cohort of patients relative to these previous reports. All patients were restored to sinus rhythm (unlike the Miyazaki study) prior to ablation, making ours more an investigation of trigger suppression rather than termination of ongoing AF. Finally, and importantly, most of our patients received what many would consider standard therapy for patients with PAF or persAF (PVI only), rather than extensive (and often pro-arrhythmic) supplemental ablation beyond PVI.

A second type of study, focusing on atrial structural and electrical remodeling with AAD therapy to maintain NSR in the pre-ablation window, is supported by pre-clinical investigations of amiodarone on atrial electrophysiology. Amiodarone therapy in canine models of AF prevents action potential shortening, depressed conduction velocity, interstitial fibrosis deposition, and AF inducibility (12,13). Based on that idea of pre-ablation conditioning with amiodarone, Benak and colleagues investigated 62 persAF patients treated with amiodarone and cardioversion three months prior to anticipated PVI (9). They selected the patients who maintained NSR on amiodarone and performed PVI, finding comparable ablation results to a matched cohort of patients with PAF. They did not perform ablation in the group of persAF patients who did not maintain NSR on amiodarone. Our investigation extends the findings of the Benak study, in which patients who failed amiodarone therapy were not allowed to undergo PVI; our results suggest that this group should not have ablation therapy denied them solely because of failure to respond to amiodarone treatment.

Finally, a number of studies have demonstrated that pre-treatment with amiodarone limits the number of non-PV targets seen at the time of ablation, allowing for reduced procedural and ablation times (14,15,16). These investigations used an extensive ablation approach for patients with persAF, with routine lesion application targeting non-PV sites. We believe that the ablation approach in our investigation reflects broad trends in the field of catheter ablation for both persAF and PAF, with an emphasis on PVI and a de-emphasis on the routine application of potentially pro-arrhythmic lesion sets (lines, low-voltage homogenization, etc.) (17).

Limitations

Our study has several limitations. It is a single-center, non-randomized, retrospective study. Given the study's retrospective nature, there could be a possibility of selection bias. In addition, the lack of continuous ECG monitoring after ablation could have resulted in the underestimation of arrhythmia recurrence. Use of electronic health records to document the recurrence of arrhythmia and complications could result in under-reporting of both. Ablation strategies were significantly different between the two groups. Lastly, we

acknowledge that amiodarone therapy is not routinely indicated in the PAF patients; early rhythm control using catheter ablation is now common, so the PAF cohort in our study may be considered a unique study population.

Conclusion

Failure to restore and maintain sinus rhythm on amiodarone therapy is not a predictor of adverse ablation procedure outcomes and should not be used as a patient selection criterion for consideration of PVI.

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Figure 1. Patient identification and characterization

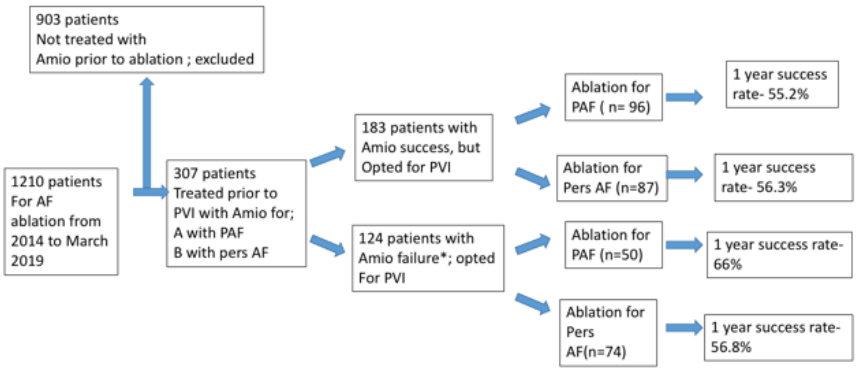

Table 1. Patient characteristics in the amio-failure and amio-success groups.

Characteristics	Total (n=307)	Amiodarone failure (n=124)	Amiodarone Success (n=183)	p-value
Age (years)	67 (60-73)	67 (58 -71.7)	68 (61 -74)	0.07
White, n (%)	272 (88.6)	112 (90.3)	160 (87.4)	0.93
Male, n (%)	217 (70.7)	88 (71)	129 (70.5)	0.92
Body mass index ($kg/m^{2)}$	29.8 (26.4 -34.2)	29.7 (26.3 – 34.3)	29.9 (26.4 -34)	0.91
Duration of AF (years)	3 (2 – 7)	3.5 (2–7)	3 (1.5 –6)	0.47
Duration of amiodarone therapy pre-ablation, years (months)	5 (3 – 15)	5 (2.2-13.7)	6 (3 -16)	0.42
AF type				**0.03**
Paroxysmal AF, n (%)	146 (47.6)	50 (40.3)	96 (52.5)	
Persistent AF, n (%)	161 (52.4)	74 (59.7)	87 (47.5)	
Congestive heart failure, n (%)	74 (24.1)	34 (27.4)	40 (21.9)	0.26
Hypertension, n (%)	207 (67.4)	80 (64.5)	127 (69.4)	0.37
Diabetes mellitus, n (%)	53 (17.3)	15 (12.1)	38 (20.8)	**0.04**
Stroke/TIA, n (%)	33 (10.7)	15 (12.1)	18 (9.8)	0.53
CHA_2DS_2-VASc score	2.0 (1.0 -3.0)	2 (1 – 3)	2.5 (2 – 4)	0.18
Obstructive sleep apnea, n (%)	56 (18.2)	31 (25)	25 (13.7)	**0.01**

Characteristics	Total (n=307)	Amiodarone failure (n=124)	Amiodarone Success (n=183)	p-value
Chronic kidney disease, n (%)	42 (13.7)	17 (13.7)	25 (13.7)	0.99
Hyperlipidemia, n (%)	133 (43.3)	56 (45.2)	77 (42.1)	0.59
Asthma/COPD, n (%)	22 (7.2)	8 (6.5)	14 (7.7)	0.68
Smoking history, n (%)	98 (32)	36 (29)	62 (34.1)	0.35
ACE inhibitor, n (%)	77 (25.2)	35 (28.5)	42 (23)	0.27
Angiotensin II receptor blocker, n (%)	65 (21.2)	24 (19.4)	41 (22.4)	0.52
Beta blocker/ Calcium channel blocker, n (%)	251 (81.8)	107 (86.3)	144 (78.7)	0.09
Statin, n (%)	156 (51)	64 (52)	92 (50.3)	0.76
Anticoagulation				0.06
None, n (%)	7 (2.3)	0 (0)	7 (3.8)	
Coumadin, n (%)	68 (22.1)	31 (25)	37 (20.2)	
Direct oral anticoagulant, n (%)	232 (75.6)	93 (75)	139 (76)	
LA diameter by TTE (cm)	4.4 (4.0-5.0)	4.5 (4.0-5.0)	4.3 (4.0- 5.0)	0.73
LV ejection fraction by TTE (%)	55 (50 – 60)	55 (50 -60)	55 (50 -60)	0.64

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; therapy; LV, left ventricular; TIA, transient ischemic attack.

Table 2. Procedural characteristics in the amio-failure and amio-success groups.

Characteristics	Total (n=307)	Amiodarone failure (n=124)	Amiodarone Success (n=183)	p-value
Ablation type				**0.02**
RF ablation	251 (81.8)	109 (87.9)	142 (77.6)	
Cryoballoon ablation	56 (18.2)	15 (12.1)	41 (22.4)	
Index ablation	218 (71)	85 (68.5)	133 (72.7)	0.43
Cardioversion pre-ablation	228 (74.3)	105 (84.7)	123 (67.2)	**<0.01**
Time of cardioversion pre-ablation (months)	3 (2–8)	3 (1.7-9.2)	3 (2-8)	0.77
Ablation strategy				**0.03**

Characteristics	**Total (n=307)**	**Amiodarone failure (n=124)**	**Amiodarone Success (n=183)**	**p-value**
PVI only	199 (64.8)	68 (54.8)	131 (71.6)	
PVI and roof line	26 (8.5)	11 (8.9)	15 (8.2)	
PVI and mitral line	3 (1)	2 (1.6)	1 (0.5)	
PVI and focal ablation	10 (3.3)	6 (4.8)	4 (2.2)	
PVI and combo/other	49 (16)	24 (19.4)	25 (13.7)	
PVI with posterior box lesion	20 (6.5)	13 (10.5)	7 (3.8)	
Rhythm at ablation				**<0.01**
Sinus rhythm	183 (59.6)	0 (0)	183 (100)	
Atrial fibrillation	97 (31.6)	97 (78.2)	0 (0)	
Atrial flutter	27 (8.8)	27 (21.8)	0 (0)	
Time to recurrence (months)	5 (3-7)	4 (3-7)	5 (3-7.5)	0.07
AAD after ablation in patients with recurrence	102 (33.2)	43 (34.7)	59 (32.2)	0.92
Cardioversion after ablation in patients with recurrence	80 (26.1)	43 (34.7)	37 (20.2)	**0.02**
Type of recurrence				0.80
Atrial fibrillation	93 (30.3)	34 (27.4)	59 (32.2)	
Atrial flutter	28 (9.1)	12 (9.7)	16 (8.7)	
Atrial tachycardia	1 (0.3)	0 (0)	1 (0.5)	
Atrial fibrillation/ Atrial flutter	8 (2.6)	3 (2.4)	5 (2.7)	
Repeat ablation	111 (36.2)	45 (36.3)	66 (36.1)	0.96

Figure 2. KM curves showing arrhythmia-free survival for all patients, with no difference in outcomes between the amio-success (blue) and amio-failure (green) cohort

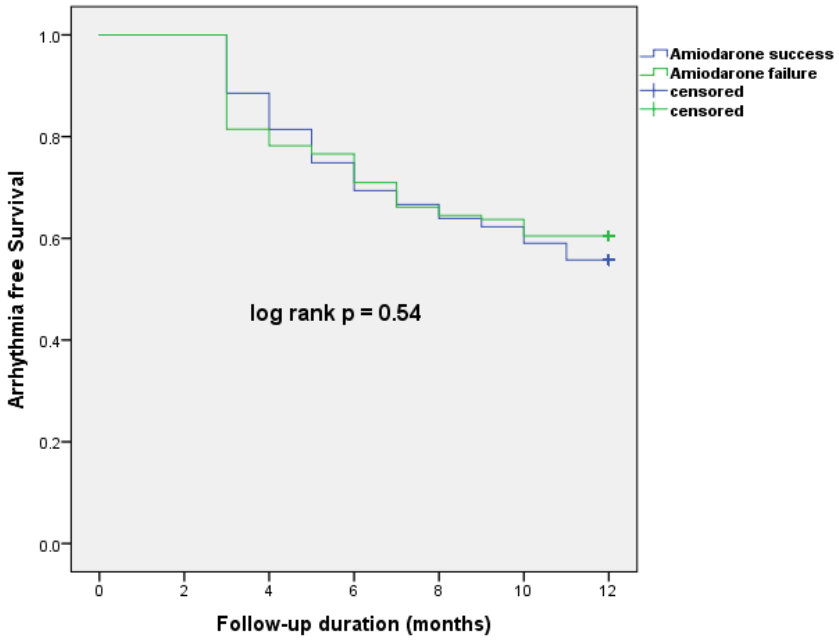

Figure 3(A). KM curves showing arrhythmia-free survival for patients with PAF (A) with no difference in outcomes between the amio-success (blue) and amio-failure (green) cohorts.

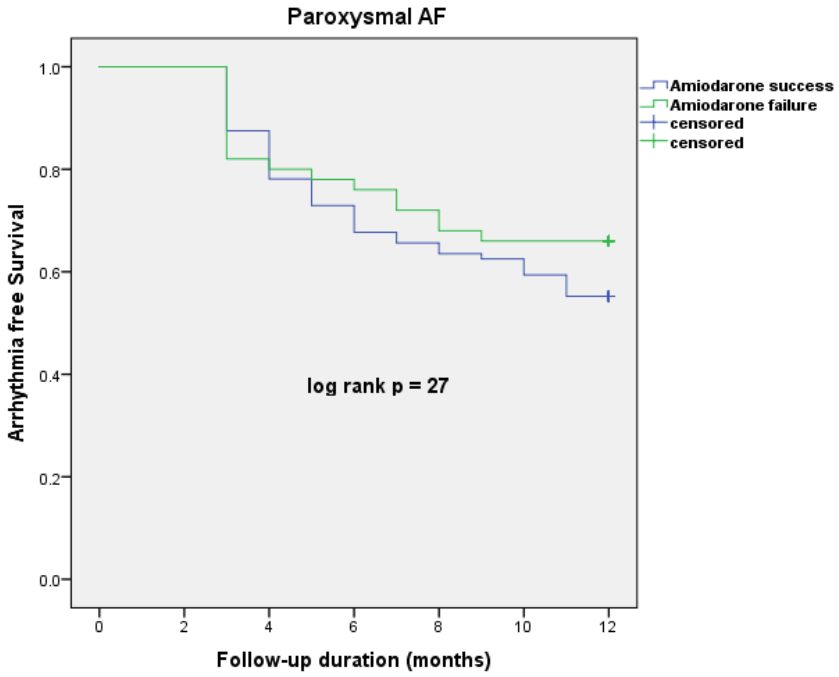

Figure 3(B). KM curves showing arrhythmia-free survival for patients with persAF with no

difference in outcomes between the amio-success (blue) and amio-failure (green) cohorts.

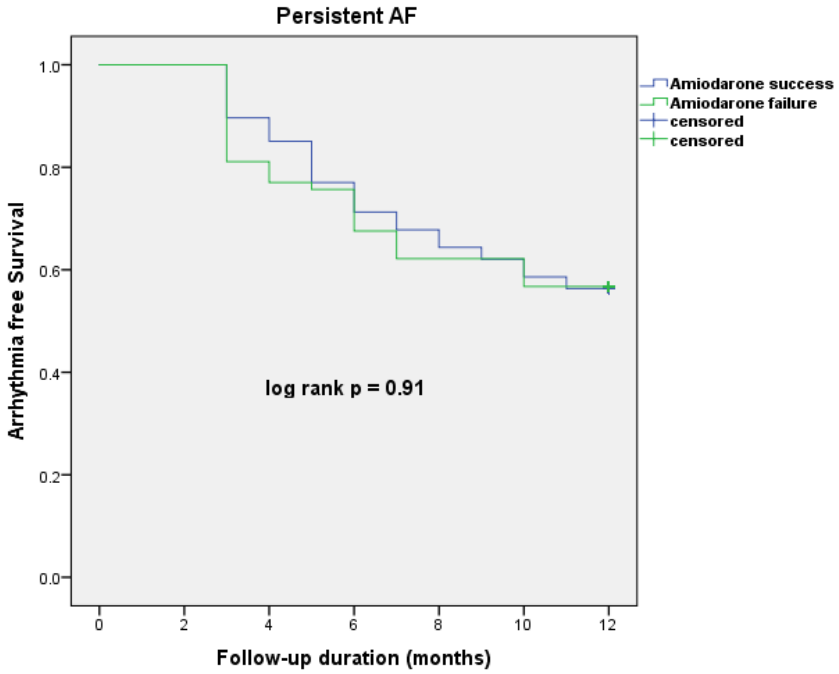

Table 3: Procedural complications for all patients and by amiodarone failure vs. amiodarone success cohorts

Complications	Total (n=307)	Amiodarone failure (n=124)	Amiodarone Success (n=183)	p-value
Overall, n (%)	9(2.9)	2(0.6)	7(3.8)	0.06
Cardiac tamponade, n (%)	5 (1.6)	1 (0.8)	4 (2.2)	0.41
Vascular complications, n (%)	2 (0.7)	0	2 (1.2)	0.41
Aspiration pneumonia n (%)	1 (0.3)	1 (0.8)	0	0.41
Pulmonary embolism, n (%)	1 (0.3)	0	1 (0.5)	0.41