Real-World Evidence Demonstrates an Appropriate Atrial Fibrillation Population for Hybrid Convergent Approach versus Stand-Alone Cryoballoon Ablation: A Long-Term Safety and Efficacy Study

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Abstract

Introduction: A hybrid convergent approach (endocardial and epicardial ablation) demonstrated superior effectiveness in a recent randomized study for long-standing persistent atrial fibrillation (LSPAF). Yet, there is a lack of real-world, long-term evidence as to which patients are best candidates for a hybrid convergent approach compared to standard endocardial cryoballoon pulmonary vein isolation (CB PVI). **Methods and Results:** This single-center, retrospective analysis spanning from 2010 to 2015 compared two distinctly different atrial fibrillation (AF) cohorts; one treated with stand-alone cryoablation and one treated with a hybrid convergent approach. Baseline characteristics described candidates for each approach. The following criteria were utilized to determine CB PVI candidacy: 1) paroxysmal AF (PAF) with failed class I/III antiarrhythmic drug (AAD) or 2) persistent/LSPAF with failed class I/III AAD unwilling to undergo hybrid procedure. Selection criteria for the hybrid procedure included: 1) PAF refractory to both class I/III AAD and prior CB PVI or 2) persistent/LSPAF with failed class I/III AAD agreeable to hybrid procedure. Prior sternotomy was excluded. Serial electrocardiograms and continuous monitoring evaluated primary efficacy outcome of time-to-first recurrence of atrial arrhythmia after a 90-day blanking period. Secondary outcomes were procedure-related complications and AAD use (at discharge, 12, and 36 months). Kaplan-Meier methods evaluated arrhythmia recurrence. Of 276 patients, 197 (64.2 ± 10.6 years old; 66.5% male; 74.1% PAF; 18.3% persistent AF; 1.0% LSPAF; 6.6% undetermined) underwent CB PVI and 79 (61.4 ± 8.1 years old; 83.5% male; 41.8% PAF; 45.5% persistent AF; 12.7% LSPAF) underwent hybrid procedure. Arrhythmia freedom through 36 months was 55.2% for CB PVI and 50.4% for hybrid (p =0.32). Class I AAD utilization at discharge occurred in 38 (19.3%) patients in the CB PVI group and 5 (6.3%) patients in the hybrid group (p=0.01). CB PVI class I AAD utilization at 12 months occurred in 14 (9.0) patients versus 0 patients for hybrid convergent (p=0.004). Patients with one or more adverse event were as follows: two (1.0%) in the CB PVI group (both transient phrenic nerve palsy) and three (3.7%) in the hybrid group (two with significant bleeding and one with wound infection) (p=0.14). **Conclusion:** This study demonstrated that patients with more complex forms of AF (PAF refractory to both AAD and index endocardial ablation or persistent/LSPAF) could be well managed with a convergent approach. Moreover, outcomes match safety and efficacy thresholds achieved by patients with an early, less complex AF etiology treated by CB PVI alone.

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Short Title: Real-World Evaluation of Convergent Procedure

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Conclusion: This study demonstrated that patients with more complex forms of AF (PAF refractory to both AAD and index endocardial ablation or persistent/LSPAF) could be well managed with a convergent approach. Moreover, outcomes match safety and efficacy thresholds achieved by patients with an early, less complex AF etiology treated by CB PVI alone.

Keywords: Atrial Fibrillation, Convergent Procedure, Cryoballoon Ablation

Abbreviations:

AAD = Antiarrhythmic Drug

AF = Atrial Fibrillation

CB = Cryoballoon

EKG = Electrocardiogram

LAA = Left Atrial Appendage

LA = Left Atrium

IVC = Inferior Vena Cava

LSPAF = Long-Standing Persistent Atrial Fibrillation

LVEF = Left Ventricular Ejection Fraction

PAF = Paroxysmal Atrial Fibrillation

PVI= Pulmonary Vein Isolation

SILS = Single Incision Laparoscopic Surgery

Introduction

Atrial fibrillation (AF), a frequently encountered clinical dysrhythmia, accounts for nearly half a million US hospitalizations yearly and has been reported to increase annual US healthcare costs by $26 billion.[1] These detriments have been mitigated by the maintenance of sinus rhythm with innovative, guideline-supported means of catheter and surgical ablation.[2] The convergent hybrid procedure demonstrated safe and superior effectiveness compared to standard catheter ablation for the treatment of persistent and longstanding persistent atrial fibrillation (LSPAF) in the CONVERGE trial.[3] Apart from this assessment by DeLurgio and colleagues, few additional contemporary studies define AF populations who would benefit from the expansion beyond standard pulmonary vein isolation (PVI).

Furthermore, a recent meta-analysis showed that when the hybrid procedure was studied, the longest follow-up assessed thus far was only 24 months. The same publication describes only two major studies that evaluated the use of the hybrid approach utilizing cryoablation; only one of which utilized it exclusively.[4] Clearly, long-term, "real-world" evidence to guide the use of cryotherapy-predominant convergent ablation is lacking. To supplement this deficit, this retrospective study with up to 48-month-follow-up, aims to describe a "real-world" AF patient population that can benefit from hybrid ablation. Furthermore, it will compare the safety and efficacy observed with this group to a cohort of early AF treated with a standard, PVI-alone approach.

Methods

Study Design :

This retrospective, single-center, observational study was conducted with the goal of improvement of patient care and safety at Orlando Health Heart and Vascular Institute. The study was approved by the Orlando Health Institutional Review Board. Data of patients who underwent either conventional cryoballoon pulmonary vein isolation (CB PVI) or hybrid convergent ablation at Orlando Regional Medical Center from January 2010 through December 2015 were recorded at the time of the procedure. Proceduralists included three electrophysiologists and one cardiothoracic surgeon. Patients in the registry consented to the procedure.

Patient Population :

Patients considered for study were adults with all forms of AF, including patients with prior failed CB PVI. At least one outpatient evaluation 90 days post-procedure (blanking period) was required during follow-up. The following criteria were utilized to determine who was treated by convergent procedure: 1) PAF with failed class I/III antiarrhythmic drug (AAD) therapy and previously failed CB PVI ablation or 2) persistent and LSPAF with failed class I/III AAD willing to undergo the hybrid procedure. The following criteria were utilized to determine who was treated by CB PVI: 1) PAF with failed class I/III AAD or 2) persistent and LSPAF with failed class I/III AAD; unwilling to undergo hybrid procedure. Exclusion criteria included valvular disease that, in the opinion of the surgeon, needed surgical correction. Additionally, prior sternotomy was excluded. Previously documented pericarditis was not an absolute contraindication and all of these cases were successfully ablated.

Hybrid Procedure:

The hybrid convergent procedure has been previously described in detail.[3,5,6] To briefly summarize our surgical experience, preoperative evaluation included an echocardiogram and an ischemic evaluation. General anesthesia was used for all cases. Initially, a laparoscopic approach with an upper midline abdominal incision and the placement of a single incision laparoscopic surgery (SILS) Port was used. Insufflation and two working ports (including a grasper and a harmonic scalpel via the SILS port) allowed us to gain access into the pericardial space via the bare area of diaphragm just medial to the falciform ligament, above the left lobe of the liver. After a year or so, our approach changed. We were able to perform a similar subxiphoid incision without laparoscopy (saving time and cost) by packing the stomach and omentum off to the patient's left with a moist sponge and using two appendiceal retractors to expose the bare area of the diaphragm. A long-tipped low-power Bovie was used to divide the diaphragm and access the pericardial space.

Once access was obtained with the cannula and laparoscope, the ablation was carried out beginning at the pericardial reflection against the medial side of the right superior pulmonary vein (PV). We moved from superior to inferior along the left atrium (LA), medial to the right PV and down to the level of the inferior vena cava (IVC). This movement was repeated on the patient's left. We ablated to the coronary sinus, taking care to overlap lesions. We then moved underneath the left inferior PV and attempted ablation on the left anterior portion of the left PVs. In approximately two-thirds of cases, we could observe catheter placement up to the base of the left atrial appendage (LAA). In one-third of cases, we could not see the anterior portion of the left PVs due to hemodynamic instability. For these cases, we would place three or four lesions blindly.

After left anterior PV ablation, we ablated the anterior portion of the right PVs. With each ablation, we instilled 25 cc of room-temperature saline into the pericardial wall through the cannula to avoid thermal conduction to other mediastinal structures. Once finished, we placed a silastic drain through a separate incision. We infused 500 mg of solumedrol through the drain and let it sit while we closed the incision in a standard manner. The drain was hooked to bulb suction and removed on the day of discharge. After the surgeon completed the epicardial ablation, all chest incisions and drains were covered in a sterile fashion. Then, the endocardial evaluation and intervention by the electrophysiologist commenced.

After baseline intervals and pacing thresholds were measured, RA and RV pacing at fixed incremental cycle lengths were performed. The first half of the initial heparin bolus was then given, and the maintenance infusion was started after the diagnostic catheters were in position. The cryoballoon (CB) process of PV isolation began after transvenous access and transeptal puncture. At that point, an exchange length wire was advanced to the left superior PV to exchange for a 12F FlexCath sheath in place of a SL-1 sheath. The second half of the heparin bolus was given after the left atrium was entered. A preoperative computed tomography scan with contrast of the LA and PVs was used to evaluate LA size, PV anatomy (including any anomalies), and the PV ostium. Depending on the size of the ostium, a 23/28mm Artic Front CB catheter with a spiral 15/20mm Achieve wire was advanced sequentially to all PVs, the anterior and posterior walls of the LA, and the roof of the LA. Using a field filter of 0.1 mV, each area was mapped to evaluate for isolation. Pacing, using the Achieve catheter, was performed to verify non-capture at the antrum/ostium of each PV as well as the posterior wall. Entrance and exit block were confirmed in all pulmonary veins. A 3D anatomical map was performed of the LA (specifically the roof), posterior walls, and all PVs. This was done to verify PV and posterior wall isolation. Posterior wall isolation was homogenous, starting at the level of the superior PVs down to the level of the right and left inferior PVs.

It was generally identified that the anterior/superior turnaround borders of the left and right superior PVs were not completely isolated, especially the ridge between the left superior PV and the LAA. Rarely, the inferior/posterior borders of the left and right inferior PV were also still connected. When the PVs were not completely isolated, cryo-energy was delivered to complete the isolation. Care was taken to verify that the esophageal temperature probe was positioned directly behind the PV we were isolating or the posterior wall we were ablating. The goal was to achieve approximately -40 degrees Celsius for 4 minutes. When PV signals were present on the Achieve catheter, we strove to isolate these signals or eliminate them altogether within the first 60 seconds. If this was not achieved, we would reposition the balloon catheter to find a better fit

and seal. Care was taken to verify that the esophageal temperature did not fall below -30 degrees Celsius.

When delivering cryo-energy along the right-sided PVs, a quadripolar catheter was often positioned in the right subclavian vein to pace the right phrenic nerve. A fetal monitor was placed on the patient's abdomen to audibly monitor right hemidiaphragm contractility. Cryo-energy delivery to the right-sided pulmonary veins was stopped when the intensity of diaphragmatic contractility began to diminish. When the endocardial posterior roof line was not complete, a 4 mm tipped deflectable, irrigated tipped electrode was used to deliver radiofrequency using 20-25 watts for 30-60 seconds. If the esophageal temperature probe temperature rose $>$ 1 degree Celsius, ablation was stopped, and the area was allowed to return to baseline temperature before another ablation lesion was delivered nearby, but not in the same location. The goal was elimination of endocardial signals $>$ 0.1 mV and lack of pacing response from the ablated area.

When all PVs and the posterior wall were isolated and the posterior roofline was completed, we would continue to pace and remap for 20 minutes after the last ablation. Isoproterenol up to 5 mcg/min was often infused during this waiting period. Sometimes intravenous adenosine 6 and 12 mg were used after the 20-minute waiting period. If there was no reconnection of PVs or posterior wall, then the ablation was terminated. Post ablation, no significant signals above 0.1 mV were observed. Likewise, pacing along the line failed to capture atrial tissue. After PVI, RA, and RV incremental pacing and programmed stimulation were performed. No arrhythmias were inducible. Intracardiac echocardiography was used to rule out pericardial effusion as well as to measure PV velocities pre- and post-procedure. Heparin was reversed with intravenous protamine by the anesthesia service.

Patient follow-up and Study Endpoints:

Patient demographics and co-morbidities, including salient details of the patient's AF, baseline left ventricular ejection fraction (LVEF), and medications were recorded. Standard follow-up protocol included a 1-week post-procedure electrocardiogram (EKG) and a 24–48-hour Holter monitor at 1, 3, 6, 12, 24, and 48 months. At minimum, an EKG was obtained on every follow up visit. The primary outcome was defined as freedom of arrhythmia outside of the 90-day blanking period. Secondary outcomes included AAD at discharge, 12, and 36 months as well as the following procedure-related complications: incidence of complications; bleeding requiring $>$2 units PRBCs; wound infection; transient phrenic nerve palsy; and atrioesophageal fistula.

Statistical Analysis

Continuous variables are summarized as mean $\pm$ standard deviation and dichotomous variables are presented as the number and percent of subjects. Baseline and procedural characteristics are summarized as means. Kaplan-Meier methods were used to estimate the 36-month freedom from atrial arrhythmia. Standard error was calculated with Greenwood's formula. Values of p $<$0.05 were considered statistically significant. Statistical analyses were performed with Statistics Kingdom.

Results

The baseline characteristics of the 276 patients (197 CB PVIs with an average age of 64.2 $\pm$ 10.6 years and 79 hybrid procedures with an average age of 61.4 $\pm$ 8.1 years) did have some significant differences among the two subgroups (table 1). Both cohorts were composed of mostly men, representing 66.5% of the CB PVI group and 83.5% of the hybrid group (p=$<$0.01). PAF represented 74.1% of the CB PVI group and 41.8% of the hybrid group (p=$<$0.001) while persistent AF was encountered in 18.3% of the CB PVI group vs. 45.6% of the hybrid group. LSPAF patients composed 1.0% of the CB PVI group and 12.7% of the hybrid group (p=$<$0.001). Generally, the CB PVI group had a much shorter duration of AF (4.4 $\pm$ 4.3 years) when compared to the hybrid group 9.4 $\pm$ 7.9 years (p=$>$0.001).

Both groups, on average had preserved LVEF. CHA_2DS_2-VASc scores were significantly higher in the CB PVI group (2.3 $\pm$ 1.6) when compared to the hybrid group (1.7 $\pm$ 1.3) (p=0.01). The hybrid group more frequently had both prior ablation and prior cardioversions (58.2% and 83.5% respectively) in comparison to the CB PVI group (18.3% and 44.7% respectively) (p = $<$0.001). There was no significant difference in the prevalence of the following comorbidities: heart failure, hypertension, diabetes mellitus, stroke or

transient ischemic attack, and coronary/peripheral artery disease. Regarding primary outcomes, freedom from arrhythmia post-procedure at 6 months (CB PVI: 82.4% vs. hybrid: 85.1%), 12 months (CB PVI: 74.5% vs. hybrid: 66.5%), 24 months (CB PVI: 64.5% vs. Hybrid: 61.4%), and 36 months (CB PVI: 55.2% vs. Hybrid: 50.4%), was similar in both groups. Some patients were able to be followed through 48 months and again, arrhythmia occurrence was similar in both arms (CB PVI: 49.5% vs. Hybrid: 39.2%) (figure 1).

As listed in table 2, there were two procedure-related perioperative complications in the CB PVI group and three in the hybrid group (p=0.14). AAD utilization is listed in table 3. Class I AAD utilization at discharge occurred in 38 (19.3%) patients in the CB PVI group and 5 (6.3%) in the hybrid convergent group (p=0.01). CB PVI Class I AAD utilization at 12 months occurred in 14 (9.0) patients versus 0 patients for hybrid convergent (0.004). There was no additional AAD utilization difference noted at discharge, 12, or 36 months.

Discussion

This retrospective study showed that despite a longer duration of AF and a more frequent prevalence of prior AF ablation, prior cardioversions, and persistent/LSPAF, the hybrid convergent cohort demonstrated success similar to the results seen in a much less complex cohort of primarily PAF treated with early, stand-alone cryoballoon ablation. This was not at the expense of more frequent perioperative complications. Moreover, the hybrid cohort received significantly less class I AAD prescriptions at 12 months when compared to the cryoballoon group.

At the time of study initiation, there were no efficacy data from large, randomized, multicenter clinical trials using cryoablation in AF. Many of the non-randomized clinical trials using radiofrequency or cryo-energy in patients with PAF reported outcomes between 38% to 78% for a single ablation and one-year success rates of 54% to 80% for multiple ablations[7]. The experience at our center using first generation cryoablation catheters for PAF was similar, with success rates of greater than 70%. We found recurrence of PAF was generally due to difficult pulmonary vein anatomy (i.e., large common PV on the left or large ovoid PV ostium) or more likely extrapulmonary vein triggers (i.e., posterior wall or carina). To minimize multiple procedures, we collaborated with our cardiovascular surgical colleagues on the hybrid convergent ablation technique to address extrapulmonary vein triggers and substrate modification to improve efficacy after a second ablation procedure.

On the contrary, non-randomized persistent AF trials from that time demonstrated single procedure efficacy of 22 to 45%. The majority of centers reported efficacy rates of less than 30%[7]. In line with these results, our single procedure success rate for persistent AF using a first generation cryoballoon catheter to only isolate the pulmonary veins was also approximately less than 50% at one year. Consequently, to minimize repeat ablations and maximize outcomes in this patient population, we collaborated with our surgeons on the hybrid/convergent ablation technique as an initial approach.

While an atrial fibrosis-guided AF ablation approach showed theoretical promise, the negative DECAAF2 trial illuminates the importance of PVI.[8] Despite different explored ablation strategies for persistent AF, none have previously proven superior effectiveness over PVI.[9–11] Recently however, in patients with persistent and LSPAF, DeLurgio et al showed superior effectiveness over endocardial ablation with the convergent approach.[3]Moreover, Makati and colleagues summarize these techniques, describing "best practices.[5]" Nevertheless, there is still a lack of real-world, long-term evidence on the convergent approach; especially with the utilization of cryotherapy ablation. In fact, many of the long-term follow-up data in "real-world," community settings, are either for PVI in early AF disease or demonstrate PVI in advanced AF disease with room for efficacy improvement.

In comparison to a meta-analysis which included 551 patients across six studies, our cohort was noted to have a similar rate of freedom from atrial arrhythmia occurrence (67% vs 69%) but less class I/Class III AAD utilization at one year (39% vs 50%). In alignment with the six major studies, we shifted from a transdiaphragmatic surgical approach to a subxiphoid, pericardial approach early in our study. Similarly, our hybrid ablation was performed in the same setting as opposed to two separate visits. Importantly, only three studies specify inclusion of patients with prior PVI, whereas in our study, these patients composed the

majority of the hybrid cohort. Our hybrid patients notably had a longer preprocedural mean duration of AF (9.4 years vs 2-5.1 years). Monitoring methods for arrhythmia detection such as serial EKGs and continuous monitoring were comparable to the majority of previously published studies[4]. A key distinguishing factor is that we present a study with two intentionally different cohorts with different complexities across the AF spectrum.

Isolating comparison to the only study which utilized cryoballoon exclusively (Makati et al), our hybrid group included much more PAF patients (41.8% vs 1.5%), a similar amount of persistent AF patients (45.5% vs 38.1%) and less LSPAF patients (12.7% vs 60.4%). Age, sex, and CHADS2VASc scores were comparable (table 1). Our hybrid cohort had a higher prevalence of prior cardioversions (83.5% vs 58%) and we reported similar periprocedural complication rates (3.7 % vs 6%). Notably, our study provides longer follow up (up to 48 months vs up to 24 months). Freedom from atrial arrhythmia at designated follow up intervals is compared between our study and the study performed by Makati et al as follows: 6 month (85.1% vs 91.1); 12 month (66.5% vs 82.4%); 24 months (61.4% vs 51.7%).[12]

A major limitation to our study includes selection bias. The high prevalence of PAF in the hybrid cohort may lead to possible improved outcomes given a lower complexity of AF. However, patients selected for study needed to have previously failed both class I/III AAD and CB PVI ablation. This study intentionally evaluated cohorts with different complexities of AF and therefore should not be seen as a traditional, "standard of care vs novel intervention" study. The retention rate in this longitudinal cohort study gradually declined over the course of 48 months however this pattern has also been appreciated in previously published projects. Future studies in this field would be those designed to elucidate the differences in patient characteristics and clinical outcomes in patients undergoing hybrid ablation who have had prior PVI ablation vs not. Findings would likely uncover additional insight into the reasons for AF recurrence therefore add clinical utility to the provider.

Conclusion

A recently completed randomized clinical trial demonstrated the safety and efficacy of the convergent approach.[3] Yet, real-world, long-term evidence is generally lacking. This study demonstrated that patients with more complex forms of AF (PAF refractory to both AAD and index cryoballoon ablation and persistent/LSPAF) could be well managed with a convergent approach. Moreover, outcomes match safety and efficacy thresholds achieved by patients with an early, less complex AF etiology treated by cryoballoon PVI-alone.

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Figure Legend

Table 1. Baseline Demographic Characteristics

Characteristic	CB PVI (N=197)	Hybrid (N=79)	P-Value
Age, years	64.2 ± 10.6	61.4±8.1	0.017
Sex, male	131 (66.5)	66 (83.5)	0.005
Atrial Fibrillation type			
Paroxysmal	146 (74.1)	33 (41.8)	<0.001
Persistent	36 (18.3)	36 (45.5)	<0.001
Long-standing Persistent	2 (1.0)	10 (12.7)	<0.001
Unknown or Undetermined	13 (6.6)	0 (0)	0.023
Duration in Atrial Fibrillation Disease, years	4.4 ± 4.3	9.4 ± 7.9	<0.001
Left Ventricular Ejection Fraction, %	56.3 ± 7.6	53.5 ± 8.8	0.017
CHA_2DS_2-VASc Score	2.3 ± 1.6	1.7± 1.3	0.008
Prior Arrythmia Catheter Ablation	36 (18.3)	46 (58.2)	<0.001
Prior Cardioversion	88 (44.7)	66 (83.5)	<0.001
Past Medical History			
Heart Failure	13 (6.6)	13 (16.5)	0.014
Hypertension	132 (67.0)	60 (75.9)	0.151
Diabetes	23 (11.7)	10 (12.7)	0.839
Stroke or Transient Ischemic Attack	16 (8.1)	3 (3.8)	0.293
Coronary/Peripheral Artery Disease	41 (20.8)	9 (11.4)	**0.083**

Values are presented as mean ± standard deviation (SD) or N (%)

Table 2. Procedure-Related Perioperative Complications

Complication	CB PVI (N=197)	Hybrid (N=79)	P-Value
Total Number of Adverse Events	2 (1.0)	3 (3.7)	0.143
Bleeding Requiring >2 units PRBCs*	0	2 (2.5)	0.082
Wound Infection#	0	1 (1.3)	0.286
Transient Phrenic Nerve Palsy	2 (1.0)	0	0.999
Atrioesophageal Fistula	0	0	0.999

Values are presented as N (%);
*Transfusion of packed red blood cells; # Mediastinitis/deep sternal infection

Table 3. Antiarrhythmic Medication at Discharge, 12 Months, and 36 Months Post-Procedure

	Discharge			12 Months			36 Months		
Antiarrhythmic	CB PVI (N=197)	Hybrid (N=79)	P-Value	CB PVI (N=156)	Hybrid (N=59)	P-Value	CB PVI (N=133)	Hybrid (N=43)	P-Value
Total Class I	38 (19.3)	5 (6.3)	**0.009**	14 (9.0)	0 (0)	**0.025**	10 (7.5)	1 (2.3)	0.299
Flecainide	28 (14.2)	2 (2.5)	**0.004**	8 (5.10)	0 (0)	0.110	4 (3.0)	1 (2.3)	0.999
Propafenone	10 (5.1)	3 (3.8)	0.764	6 (3.8)	0 (0)	0.192	6 (4.5)	0 (0)	0.338
Total Class II	106 (53.8)	46 (58.2)	0.593	85 (54.5)	32 (54.2)	0.999	78 (58.6)	21 (48.8)	0.291
Atenolol	9 (4.6)	3 (3.8)	0.999	3 (1.9)	1 (1.7)	0.999	5 (3.8)	1 (2.3)	0.999
Metoprolol	60 (30.5)	24 (30.4)	0.999	50 (32.1)	14 (23.7)	0.248	50 (37.6)	12 (27.9)	0.275
Propranolol	2 (1.0)	1 (1.3)	0.999	3 (1.9)	1 (1.7)	0.999	2 (1.5)	1 (2.3)	0.999
Carvedilol	8 (4.1)	5 (6.3)	0.530	6 (3.8)	6 (10.2)	0.094	8 (6.0)	3 (7.0)	0.999
Other	27 (13.7)	13 (16.5)	0.573	23 (14.7)	10 (16.9)	0.832	14 (10.5)	4 (9.3)	0.999
Total Class III	141 (71.6)	64 (81.0)	0.128	56 (35.9)	23 (39.0)	0.752	42 (31.6)	18 (41.9)	0.267
Amiodarone	30 (15.2)	19 (24.1)	0.116	13 (8.3)	3 (5.1)	0.565	14 (10.5)	4 (9.3)	0.999
Dofetilide	38 (19.3)	20 (25.3)	0.327	18 (11.5)	11 (18.6)	0.184	11 (8.3)	7 (16.3)	0.151
Sotalol	39 (19.8)	18 (22.8)	0.699	21 (13.5)	8 (13.6)	0.999	11 (8.3)	5 (11.6)	0.544
Dronedarone	32 (16.2)	7 (8.9)	0.129	4 (2.6)	1 (1.7)	0.999	6 (4.5)	2 (4.7)	0.999
Other	2 (1.0)	0 (0)	0.999						
Total Class IV	21 (10.7)	3 (3.8)	0.096	22 (14.1)	6 (10.2)	0.505	20 (15.0)	3 (7.0)	0.204
Diltiazem	21 (10.7)	3 (3.8)	0.096	21 (13.5)	6 (10.2)	0.647	19 (14.3)	2 (4.7)	0.109

Values are presented N (%)

Figure 1. Kaplan-Meier Curves demonstrating time-to-first atrial arrhythmia recurrence