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Efficacy of Implantable Cardioverter Defibrillators in Young Patients with Catecholaminergic Polymorphic Ventricular Tachycardia: Success Depends on Substrate

Running title: *Miyake et al.; Efficacy of ICD Therapy in CPVT*

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Abstract:

Background - The effectiveness of implantable cardioverter-defibrillator (ICD) therapy for the management of catecholaminergic polymorphic ventricular tachycardia (CPVT) in young patients is not known. ICD discharges are not always effective and inappropriate discharges are common, both resulting in morbidity and mortality.

Methods and Results - This is a multicenter, retrospective review of young patients with CPVT and ICDs from 5 centers. ICD discharges were evaluated to determine arrhythmia mechanism, appropriateness, efficacy of therapy, and complications. A total of 24 patients were included. Median (IQR) ages at onset of CPVT symptoms and ICD implant were 10.6 (5.0 – 13.8) years and 13.7 (10.7 – 16.3) years respectively. Fourteen patients received 140 shocks. Ten patients (42%) experienced 75 appropriate shocks and 11 patients (46%) received 65 inappropriate shocks. On actuarial analysis, freedom from appropriate shock at 1 year after ICD implant was 75%. Of appropriate shocks, only 43 (57%) demonstrated successful primary termination. All successful appropriate ICD discharges were for ventricular fibrillation (VF). No episodes of polymorphic ventricular tachycardia or bidirectional VT demonstrated successful primary termination. The adjusted mean (95% CI) cycle length of successful discharges was significantly shorter than unsuccessful discharges (168 (152-184) msec vs. 245 (229-262) msec, adjusted p=0.002). Electrical storm occurred in 29% (4/14) and induction of more malignant ventricular arrhythmias in 36% (5/14). There were no deaths.

Conclusions - ICD efficacy in CPVT depends on arrhythmia mechanism. Episodes of VF were uniformly successfully treated whereas polymorphic and bidirectional VT did not demonstrate successful primary termination. Inappropriate shocks, electrical storm and ICD complications were common.

Key words: catecholaminergic polymorphic ventricular tachycardia, implanted cardioverter defibrillator, arrhythmia, pediatric, ventricular tachycardia, electrical storm

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but highly malignant disease with an estimated prevalence of 1:10,000.[1] Early onset of symptoms has been associated with a more malignant clinical course and sudden death rates have been reported to be as high as 25-50% by the age of 30 years. [2-6] Arrhythmias associated with CPVT are classically polymorphic or bidirectional ventricular tachycardias triggered by adrenergic stimulation; however, ventricular fibrillation (VF) and atrial arrhythmias can also be seen.[5, 7-9] While anti-arrhythmic therapy has been the first-line approach to managing these patients, implantable cardioverter-defibrillators (ICDs) are also used as a treatment strategy.

Information regarding the use of ICDs in this patient population is limited and conflicting. High rates of appropriate shocks have been reported but deaths have occurred despite appropriate therapy. [3, 5, 6, 10, 11] Based on small case reports, it appears that ICD discharges are sometimes but not always effective and therefore ICD implantation may not necessarily be life-saving. [12] In fact, ICD implantation may potentially increase mortality risk. Death secondary to lethal arrhythmias triggered by inappropriate discharges has occurred. [9] Despite these concerns, there have been no previous studies evaluating appropriate and effective therapy in these patients.

This study aimed to describe the appropriateness and effectiveness of ICD therapy in young patients with CPVT, with an emphasis on factors associated with effective ICD therapy.

Methods

Study Population

We performed a multicenter retrospective review of young CPVT patients from 5 centers in the United States and Canada who had an ICD placed between January 1999 through September

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2011. This study was conducted under IRB approval obtained separately at each participating institution. Inclusion criteria included: 1) onset of CPVT symptoms before the age of 21 years, 2) diagnosis of CPVT made by genetic testing or clinical history as determined by a pediatric electrophysiologist, and 3) presence of an implanted ICD.

Patient and ICD characteristics

Data collection included demographics, symptoms, dates of presentation and therapy, medical management, length of follow-up and family history. Details regarding exercise testing, genetic testing, and electrophysiology (EP) studies were collected. An exercise test or EP study was considered positive for the purpose of the CPVT diagnosis if it documented a ≥3 beat run of bidirectional (BDVT) or polymorphic ventricular tachycardia (PMVT). Indication for primary or secondary prevention ICD was recorded. Secondary prevention was defined as documented sustained or hemodynamically unstable ventricular tachycardia (VT), VF, or resuscitated cardiac arrest. All ICD-related complications were recorded.

ICD discharge data

Each center submitted all available electrograms for each ICD discharge. Electrograms were available for 119 (85%) of all discharges. A blinded committee reviewed and classified all ICD discharge tracings and each tracing was independently reviewed by at least two pediatric electrophysiologists. If electrograms were not available for an event, the event was classified as reported by the patient's treating electrophysiologist. Evaluation and adjudication of ICD electrograms determined the following: 1) the arrhythmia initiating the ICD event detection (VF, PMVT, BDVT, ventricular ectopy, or a supraventricular rhythm including sinus or atrial tachycardia), 2) appropriate vs. inappropriate ICD discharge, 3) the termination pattern (primary termination, secondary termination, spontaneous termination, or required a subsequent shock),

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and 4) whether the discharge resulted in a more malignant ventricular arrhythmia. A more malignant ventricular arrhythmia was defined as a shock resulting in the conversion of a supraventricular rhythm into a ventricular tachyarrhythmia, or the conversion of ventricular ectopy or slow VT into a more rapid VT or VF (Figure 1A).

Arrhythmia substrate definitions were adapted from prior publications.[13, 14] PMVT was defined as an irregular tachycardia with electrograms demonstrating constant amplitude but shift in morphology or axis and a mean cycle length (CL) >200msec. BDVT was defined as VT with a consistent pattern of alternating QRS axis and morphology. VF was defined as an irregular VT with a mean CL <200msec or if 75% of recorded CLs were <260msec. Mean CL was measured by averaging all CLs used by the device to meet VF detect criteria. If electrograms were not available, mean CL was calculated using the average ventricular rate reported by the device and description of the tachyarrhythmia by the patient's electrophysiologist was used to make the best determination of the arrhythmia.

Appropriate therapy was defined as ICD discharges for VT (PMVT or BDVT) or VF. Discharges were classified as inappropriate if a shock was delivered for noise, over-sensing, sinus or other forms of supraventricular tachycardia, ventricular ectopy, or after spontaneous termination of an arrhythmia (Figure 1A, 1B). A discharge was defined as effective if it resulted in primary termination of the arrhythmia (Figure 2A). For the purposes of this study, if primary termination did not occur but the patient did not have a subsequent shock, this was classified as either 1) secondary termination or 2) spontaneous termination. Secondary termination was arbitrarily defined as persistence of the tachyarrhythmia immediately after the shock, with subsequent termination within 3 seconds after ICD discharge (Figure 2B). Spontaneous termination was defined as arrhythmia termination greater than 3 seconds after the high voltage

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discharge (Figure 2C). A discharge was defined as ineffective if an appropriate shock did not terminate primarily and included shocks demonstrating secondary termination, spontaneous termination or those that required subsequent defibrillation (Figure 1C, 2B, 2C). For the purposes of this study, shock events without electrograms were classified as primary termination if the clinical record described the shock as successful. Electrical storm was defined as ≥ 3 appropriate ICD discharges within 24 hours.

Statistical Analysis

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile ranges (IQR), depending on the normality of their distribution, and were analyzed using the T-test or the Wilcoxon rank sum test. Categorical variables are presented as counts with percentages and were analyzed using the Fisher Exact test or the Chi-square test. A Kaplan-Meier survival curve was constructed in order to examine the time dependent freedom from a first appropriate shock after ICD implantation. The one-year data is reported with 95% confidence intervals (CI). The observed means and CI for successful vs. unsuccessful shock CL ignoring repeated measures as well as the predicted population means and 95% CI from a repeated measures mixed effects model considering multiple measurements for each subject are reported. Data is reported as adjusted P-value. Statistically significant data were defined as a P-value of <0.05. Data analysis was performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics

A total of 24 patients (11 males, 13 female), each from different families, were included in this study. The majority of patients were probands (23/24, 96%). No affected family members met

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inclusion criteria for this study. Demographic data and presenting symptoms are listed in Table 1. Median (IQR) age at onset of symptoms consistent with CPVT was 10.6 (5.0-13.8) years. The majority of patients (67%) presented with a history of exertional or emotionally-triggered syncope consistent with CPVT while 6 patients (25%) presented with aborted sudden cardiac arrest. The median (IQR) time from initial symptoms to diagnosis was 4.0 (0.4-6.4) years. None of the patients had a history of left sympathetic cardiac denervation.

Diagnostic testing

Diagnostic testing varied by center. Exercise stress tests and EP studies were not performed on all patients prior to initiation of beta- blocker therapy or ICD implant. In total, 14 of 24 patients (58%) underwent exercise stress testing prior to initiation of anti-arrhythmic medications and 13 patients (93%) had positive results. The remaining patient had single premature ventricular contractions during exercise. A total of 9 patients underwent an EP study prior to initiation of any anti-arrhythmic medication and 7 (78%) had spontaneous induction of PMVT after infusion of isoproterenol or epinephrine. None of these patients had a pace-inducible ventricular arrhythmia, but in 2 patients atrial tachycardia was pace-induced.

Genetic testing was performed in 16 of 24 (67%) patients and a probable candidate gene mutation was identified in the ryanodine receptor (RyR2) in 10 (63%) patients (Table 2). Among the remaining 6 patients who tested negative for ryanodine receptor defects, 3 patients underwent further testing for Calsequestrin defects and each tested negative. Five patients (21%) had a family history of CPVT.

Antiarrhythmic medications

Seventeen patients (71%) were on beta-blocker therapy prior to ICD placement. Patients not receiving beta-blocker medications at implant either had an initial presentation of aborted cardiac

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arrest (4) and/or the specific diagnosis of CPVT was made after ICD implantation (3). None of the patients were on flecainide prior to ICD implant. All patients received beta-blocker therapy after ICD implant. Antiarrhythmic therapy before and after ICD implantation is shown in Table 2.

ICD Data

The median (IQR) age at ICD implant was 13.7 (10.7-16.3) years. Indications for implantation included aborted cardiac arrest (8 patients), syncope or VT on medical therapy (12 patients), and history of syncope with documented sustained or non-sustained VT prior to medical therapy (4 patients). In total, indication for ICD implantation was primary prevention in 12 patients and secondary prevention in 12 patients.

Single chamber devices were implanted in 14 patients (58%) while the remainder had dual chamber systems. A total of 20 patients (83%) had transvenous and 4 (17%) had epicardial systems. There were no subcutaneous systems. The majority (17 patients, 71%) received single coil ICD leads. All patients underwent successful defibrillation threshold testing without complication. Over a median (IQR) follow up time of 3.3 (1.1-5.8) years, 8 (33%) patients had a total of 15 ICD related complications (8 lead failures/fractures or lead dislodgements, 1 device recall, 1 improper setscrew, 4 pocket revisions and 1 subclavian vein stenosis).

ICD shocks

Among 24 patients, 14 (58%) experienced a total of 140 ICD discharges over a median (IQR) follow-up time of 3.3 (1.1-5.8) years. Median (IQR) number of discharges per patient was 8 (1-29). Three patients received only appropriate discharges and 4 patients received only inappropriate discharges. The remaining 7 patients received both appropriate and inappropriate discharges. Median (IQR) time to first appropriate shock was 1.3 (0.9-3.3) years and

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inappropriate shock 1.7 (0.8-2.6) years.

Appropriate versus inappropriate shocks

Of 140 shocks, 75 (54%) were appropriate and involved 10/24 (42%) patients, while the remaining 65 (46%) inappropriate discharges involved 11/24 (46%) patients (Figure 4). The first appropriate ICD discharge was delivered for VF (mean±SD CL: 164±17msec) in 7 patients and PMVT (mean±SD CL: 251±34 msec) in 3 patients. All appropriate shocks, including multiple shocks per patient, were delivered for 43 VF (mean±SD CL: 155±21 msec), 29 PMVT (mean±SD CL: 252±21 msec), and 3 BDVT (mean±SD CL: 245±5 msec). On actuarial survival analysis, freedom from the first appropriate shock per patient was 75.0% (95% CI: 49.6-88.8) at 1 year after ICD implantation (Figure 5). The most common reasons for inappropriate discharges were atrial tachycardia (24 events, 36%) and spontaneous termination of a ventricular arrhythmia prior to ICD discharge (22 events, 34%). Spontaneous termination of 3 VF (mean±SD CL: 153±25 msec), 14 PMVT (mean±SD CL: 277±36 msec), 2 BDVT (mean±SD CL: 269±22 msec), and 5 ventricular ectopy (mean±SD CL: 286±19 msec) resulted in inappropriate discharges.

A total of 24 shocks for AT (mean±SD CL: 269 ± 29 msec) occurred among 8 patients, 3 of whom had dual chamber devices. Of the 18 shocks with available electrograms for review, there was spontaneous AT termination prior to shock delivery in 2, primary termination in 5, secondary termination in 3, spontaneous termination after an unsuccessful shock in 4, and in 4 patients subsequent shocks were delivered. Primary termination of 5 AT episodes occurred in 3 patients with single chamber devices; electrograms demonstrated a regular rhythm in 3 episodes and an irregular rhythm in 2 episodes.

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Mechanism of arrhythmia and pattern of termination

Arrhythmia mechanism resulting in ICD detection and discharge included 46 episodes of VF, 43 PMVT, 5 BDVT, 5 ventricular ectopy, and 24 atrial tachycardia. The remaining 17 ICD discharges occurred due to lead fracture and noise (Figure 4 and 5).

Among 75 appropriate discharges, effective primary termination occurred in 43 (57%) (7 patients). All 43 episodes were for VF and therefore 100% of VF episodes that persisted to defibrillation demonstrated primary termination. Electrograms were available for 39 of the 43 VF episodes. In the 4 episodes without electrogams, the primary electrophysiologist reported VF and the mean arrhythmia CL range was 130-160msec. The 3 remaining VF episodes were classified as inappropriate shocks because VF terminated prior to ICD discharge. Ineffective ICD discharges were seen in 32 of the 75 (43%) appropriate discharges (3 patients). All 32 episodes were for PMVT (29) or BDVT (3). Of these 32 ineffective discharges, 5 (16%) demonstrated secondary termination within 3 seconds, 15 (47%) demonstrated spontaneous termination after 3 seconds, and 12 (37%) required one or more subsequent shocks. The adjusted mean (95% CI) CL of ventricular arrhythmias resulting in successful termination was significantly shorter than in those that did not primarily terminate (168 (152-184) msec vs. 245 (229-262) msec, adjusted p=0.002). The observed mean and CI for successful vs. unsuccessful shocks, not taking into account repeated measures, was 163 msec (95%CI: 153-173 msec) and 251 msec (95% CI: 244-260 msec) respectively. Details regarding appropriate, inappropriate, effective and ineffective discharges are listed in Figure 4. One patient exhausted ICD therapy but survived after the VT eventually spontaneously terminated. Interestingly, reported compliance with medical therapy, per shock, was higher in the successful (36/43 (84%)) vs. the unsuccessful shock group (11/32 (34%)).

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Primary versus secondary prevention

Two of 12 (17%) patients in the primary prevention group and 8 of 12 (67%) patients in the secondary prevention group received an appropriate discharge. While none of the primary prevention group had VF or an effective discharge, 7 of 12 (58%) patients who received an ICD for secondary prevention had VF and received an effective shock.

Electrical storm and induction of more malignant arrhythmias

Twelve discharges (in 5 patients) or 8.5% of total shocks resulted in a more malignant ventricular arrhythmia. The arrhythmias responsible for these ICD discharges included 3 PMVT, 8 AT, and 1 ventricular ectopy. In 11 of the 12 discharges, the shock-induced ventricular arrhythmia eventually spontaneously terminated; however 5 discharges resulted in the patient receiving at least 1 inappropriate shock secondary to committed device therapy. In 1 patient, shock for an atrial tachycardia resulted in induction of PMVT and 3 subsequent shocks were delivered with eventual secondary termination. Four of 14 patients (29%) who received ICD therapy suffered electrical storm events secondary to ICD discharges. There were no patient deaths.

Compliance with medications

Patients were thought to be noncompliant with medications at the time of 61 (44%) ICD discharges. In 54 (38%) ICD discharges, patients were thought to be compliant with medications. In the remaining 25 (18%) ICD discharges, compliance with medications could not be determined by medical chart review.

Discussion

Young patients with CPVT are at high risk for life threatening arrhythmias and sudden death.[2-4, 6, 10, 11, 15] Beta-blockers are not always effective[2, 3, 6, 10, 12, 16] and in some patients, ICD and/or

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left cardiac sympathetic denervation are being used as management strategies.[17] However, death can occur despite ICD implantation.[9, 11] Reports have shown that ICD therapy can be ineffective or dangerous[9, 11, 12] but no mechanism for this phenomenon has been established. Furthermore, previous studies have suggested that inappropriate discharges are secondary to supraventricular arrhythmias[3, 5, 6] (Table 1, online supplement). Our study found that 1) the rate of appropriate therapy is high, but only half are effective, 2) effective therapy is likely related to arrhythmia mechanism and 3) inappropriate therapy is due to both supraventricular arrhythmias and spontaneous termination of arrhythmia prior to ICD discharge.

Patients with VF that persisted to defibrillation demonstrated 100% effective primary termination. No episodes of PMVT or BDVT successfully terminated. Previous studies have demonstrated the mechanism of arrhythmia origination for BDVT and PMVT in CPVT to be abnormal calcium regulation and delayed after depolarizations (DADs).[18-20] Modeling studies suggest that origination and alternation of premature beats between the right and left bundle branches of the purkinje system (the "Ping-Pong" mechanism) results in BDVT. When DADs arise from multiple purkinje sites, PMVT ensues.[21] PMVT may spontaneously terminate, possibly explaining the high incidence of secondary or spontaneous termination seen after ICD therapy in this cohort, or may degenerate into VF, the arrhythmia that is likely responsible for sudden cardiac death in CPVT patients. BDVT and PMVT arise from focal DADs and catecholamine surges following ICD discharge can increase further DADs. We therefore speculate that BDVT and PMVT are less amenable to defibrillation, whereas VF is a large wavefront of myocardial depolarization that will respond to ICD therapy. Arrhythmia substrate and mechanism in CPVT patients may explain our findings of 1) successful defibrillation for VF, 2) unsuccessful therapy for BDVT and PMVT, and 3) the incidence of more malignant

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arrhythmias after ICD discharges.

CPVT patients are known to have atrial tachyarrhythmias[5, 7, 8 9] but therapy for these supraventricular arrhythmias has not been studied. Studies have demonstrated DADs in atrial myocytes and decreased conduction velocities due to defects in RYR2 which can lead to atrial arrhythmias and potential atrial fibrillation.[22] A total of 8 patients received 24 shocks for AT. Interestingly, 5 of these episodes (in 3 pts) demonstrated primary termination, 2 of which were irregular tachycardias and 3 regular tachycardias. Primary termination seen in irregular ATs may be explained by atrial fibrillation. Reasons for primary termination of regular AT seen in this cohort are not clear and further studies are needed. Since each of these 3 patients had single chamber devices, we cannot exclude the possibility of a reentrant supraventricular tachycardia.

A high rate of inappropriate therapy due to spontaneous rhythm termination prior to ICD discharge was seen throughout this cohort. Overall, 46% of patients experienced an inappropriate discharge, a significantly higher percentage than the published rates of 25-30% in other pediatric device patients.[23] Our study confirmed high rates of inappropriate discharge for supraventricular arrhythmias, as previously reported [3, 5, 6] however, we also found that spontaneous termination of ventricular arrhythmias accounted for an equally high rate of inappropriate discharge. This has not been previously reported and is an important consideration in terms of ICD programming for these patients.

Changes in ICD programming may help prevent unnecessary discharges and specific ICD programming details (which vary among devices) need to be considered in this patient population. In this study, all inappropriate shocks due to spontaneous termination prior to ICD discharge may have been avoided. To avoid shocks secondary to ventricular ectopy and nonsustained brief runs of PMVT after VT/VF termination, setting a single VF zone to a

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substantially shorter CL (range 200-260msec) would have decreased reconfirmation intervals and along with increasing redetect duration may have also helped limit shocks to sustained VF episodes. While in this cohort of patients, the above programming adjustments may have limited inappropriate shocks, device selection and programming should be individualized to each specific patient.

Preventing inappropriate ICD shocks may particularly be important among CPVT patients as we found that device therapy may be harmful. Among the 14 patients who received device therapy, 5 (36%) suffered more malignant arrhythmias and 4 (29%) suffered electrical storm. We suspect that ICD discharge results in catecholamine surges that potentiate further DADs. These findings are quite concerning as patients with CPVT are sensitive to catecholaminergic surges and hypothetically these surges could result in death. Despite these potential concerns, as well as relatively high rates of defibrillation failure and inappropriate device therapies, none of these events led to death in this cohort.

ICD therapy, while potentially life-saving, comes at a heavy cost in this patient population. Compliance with medications is paramount and use of flecainide and/or left sympathetic cardiac denervation may decrease the need for ICDs in the future; however, if ICDs are implanted, programming needs to be adjusted to reduce the risks of inappropriate shocks and mortality from therapy exhaustion. Extending detection times and altering reconfirmation rates (to account for frequent spontaneous termination and ventricular ectopy) as well as adjusting ICD detection rates to shorter CLs (for detection of VF rather than VT) may improve outcomes for these patients. Specific rates and detection periods will need to be individually adjusted. The authors found atrial arrhythmias to be frequent (57%) among patients who received shocks and that dual chamber devices were often helpful in discriminating atrial versus ventricular

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arrhythmias; however further studies are needed in order to better understand atrial arrhythmias in this population and determine if there is evidence to support the extra atrial lead burden.

Limitations

This is a retrospective study with a small patient population. Although 63% of patients who underwent genetic testing were positive, only 42% of our patients had genetic confirmation of their CPVT diagnosis. Electrograms at the time of ICD discharge were not available for all events. Since some unknown electrograms were classified as successful on the basis of the treating electrophysiologist's note, without independent review of the tracings, we may have overestimated the rate of successful discharges. The clinical definitions of arrhythmia mechanism (VF, PMVT, BDVT) were based on prior published ICD studies, but there may be a continuum in these mechanisms and this classification may not accurately reflect the cellular arrhythmia substrate. Alternatively, the rate of the tachycardia may be important to successful defibrillation. Although a mean CL of 163 msec during tachycardia could be rapid PMVT susceptible to defibrillation, we felt that the electrograms and rate of tachycardias were most consistent with VF. Rhythms suspected to be atrial tachycardia were based on identical electrograms in arrhythmia and during sinus rhythm but a majority of patients had single chamber ICDs. This limited our ability to distinguish atrial from ventricular tachycardias and we may have misclassified certain arrhythmia mechanisms.

Conclusion

ICD efficacy in young patients with CPVT depends on arrhythmia substrate or tachycardia cycle length. ICD therapy, while potentially life-saving for VF, may be ineffective for PMVT or BDVT and pro-arrhythmic in a significant subset. Atrial arrhythmias and spontaneous termination of ventricular arrhythmias prior to ICD discharge contribute to high rates of

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inappropriate discharges. The risks and benefits of ICD therapy in patients with CPVT should be carefully considered prior to implantation, particularly for primary prevention. Identifying those at highest risk, as well as optimizing ICD configuration and programming may help improve effectiveness and decrease related comorbidities. Left sympathetic cardiac denervation may also be an important and alternative treatment strategy for these patients.[17] A comparative evaluation of different such strategies may prove clinically valuable.

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Table 1. Characteristics of the entire cohort and a comparison of primary vs. secondary prevention: data is presented as median ± IQR or count with (%).

Variables	Total Cohort N=24	Primary prevention N=12	Secondary prevention N=12	*P
Sex (male)	11 (46%)	4 (33%)	7 (58%)	0.414
Age at first CPVT symptom (yrs)	10.6 (5.0-13.8)	11.6 (5.0-13.3)	10.0 (4.5-14.6)	0.862
Symptoms				0.007
Aborted cardiac arrest	6 (25%)	-	6 (50%)	
Exertional syncope	12 (50%)	6 (50%)	6 (50%)	
Emotional syncope	4 (17%)	4 (33%)	0	
Other	2 (8%)	2 (17%)	0	
Positive EST	13/14 (93%)	10/10 (100%)	3/4 (75%)	0.286
Positive EP study	7/9 (78%)	5/6 (83%)	2/3 (67%)	0.999
Genetic testing positive for RyR2	10/16 (63%)	4/7(57%)	6/9 (67%)	0.999
Medications prior to ICD				0.613
Beta-blocker (single agent)	12 (50%)	7 (58%)	5 (42%)	
Mixed anti-arrhythmics	5 (21%)	2 (17%)	3 (25%)	
None	7 (29%)	3 (25%)	4 (33%)	
Total follow up (yrs)	6.1 (3.3-8.3)	6.1 (4.0-7.9)	6.2 (2.1-9.4)	0.840
Age at ICD implant (yrs)	13.7 (10.7-16.3)	13.7 (12.3-16.0)	13.3 (8.7-16.3)	0.707
Single chamber	14 (58%)	5 (42%)	9 (75%)	0.214
Follow up post-ICD (yrs)	3.3 (1.1-5.8)	3.7 (1.0-6.4)	3.2 (1.8-5.7)	0.885
Type of ICD shock				0.040
Appropriate only	3 (13%)	1 (8%)	2 (17%)	
Inappropriate only	4 (17%)	4 (33%)	0	
Appropriate & Inappropriate	7 (29%)	1 (8%)	6 (50%)	
None	10 (42%)	6 (50%)	4 (33%)	
Medications after ICD				0.268
Beta-blocker (single agent)	16 (67%)	6 (50%)	10 (83%)	
Mixed anti-arrhythmics	8 (33%)	6 (50%)	2 (17%)	

*P-values compare primary vs. secondary prevention.
CPVT – catecholaminergic polymorphic ventricular tachycardia; VT – ventricular tachycardia; ICD – implantable cardioverter defibrillator; EST – exercise stress test; Mixed anti-arrhythmics – more than one beta blocker or beta blocker and other class of antiarrhythmic

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Table 2. Patient

Patient	Sex	Age at first sx (yrs)	Reason for ICD	Meds pre-ICD	Meds post -ICD	Follow up since ICD (mo)	Total #shocks	Types of shocks	Gene Testing
1	F	5	P	Bisoprolol	Bisoprolol	13	0	-	RYR2
2	M	14	S	Nadolol Propranolol Mexilitine Sotalol	Nadolol	68	4	Both	-
3	M	9	S	Nadolol	Nadolol	30	8	App	Neg
4	F	10	S	-	Metoprolol	68	8	Both	RYR2
5	M	12	P	Nadolol	Nadolol Verapamil	56	2	Inapp	-
6	M	14	P	Metoprolol	Metoprolol	97	18	Both	-
7	M	16	P	-	Atenolol	37	8	App	Neg*
8	F	5	P	Atenolol	Atenolol	11	0	-	RYR2
9	F	6	P	Atenolol	Atenolol	4	0	-	RYR2
10	F	11	P	-	Metoprolol Nadolol Diltiazem Verapamil Digoxin	71	5	Inapp	Neg*
11	M	16	S	-	Atenolol	6	0	-	RYR2
12	M	3	S	-	Propranolol	43	18	Both	RYR2
13	F	4	P	Atenolol	Atenolol	51	1	Inapp	-
14	F	13	P	Atenolol Mexilitine	Atenolol Flecainide	82	0	-	-
15	F	13	P	-	Nadolol Mexilitine	104	0	-	-
16	M	13	S	-	Nadolol Verapamil	34	3	Both	Neg*
17	F	16	P	Atenolol Mexilitine	Atenolol Flecainide	7	0	-	Neg
18	M	3	P	Atenolol	Atenolol Flecainide	29	3	Inapp	RYR2
19	M	16	S	Atenolol	Atenolol	12	0	-	RYR2
20	F	5	S	Atenolol Mexilitine	Atenolol Mexilitine	89	29	Both	RYR2
21	F	10	S	Atenolol	Atenolol	65	16	App	RYR2
22	M	4	S	Atenolol Sotalol Digoxin	Nadolol	33	0	-	-
23	F	2	S	Atenolol	Atenolol	89	17	Both	-
24	F	15	S	Atenolol	Atenolol	1	0	-	Neg

M – male; F – female; sx – symptoms; yrs – years; P – primary prevention; S – secondary prevention; mo – month; App – appropriate shocks; Inapp – inappropriate shocks; Both – appropriate and inappropriate shocks; Neg – negative; * – Calsequestrin was tested and result was negative

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Figure Legends:

Figure 1: A) Inappropriate shock due to atrial tachycardia resulting in a more malignant ventricular arrhythmia. Top EGM: RVtip to RVring, Bottom EGM: HVA to RVring, B) Inappropriate shock due to spontaneous termination prior to ICD discharge. Top EGM: RVtip to RVring, Bottom EGM: Can to RV coil, C) Appropriate but unsuccessful shock for polymorphic ventricular tachycardia. Top EGM: RVtip to RVring, Bottom EGM: Can to RVcoil.

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Figure 2: A) Appropriate shock for ventricular fibrillation with successful primary termination. Top EGM: RVtip to RVring, Bottom EGM: Can to RVcoil, B) Unsuccessful shock with secondary termination (termination <3 seconds of high voltage discharge). Top EGM: RVtip to RVring, Bottom EGM: HVA to RVring. C) Unsuccessful shock of PMVT with spontaneous termination following ICD discharge (termination > 3seconds after shock) results in device redetection and inappropriate shock due to device commitment despite arrhythmia termination. Top EGM: Atip to Aring, Bottom EGM: RVtip to RVcoil.

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Figure 3: Appropriate versus inappropriate shocks and successful versus unsuccessful termination. VF – ventricular fibrillation, PMVT – polymorphic ventricular tachycardia, BDVT – bidirectional ventricular tachycardia, AT – atrial tachycardia, VEctopy – ventricular ectopy, Spont Term – spontaneous termination of arrhythmia prior to ICD discharge, CL – cycle length, Lead Fx – lead fracture.

Figure 4: Kaplan-Meier estimate of freedom from the first appropriate shock after ICD

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implantation.

Figure 5: Arrhythmia mechanisms resulting in 140 ICD discharges. VF – ventricular fibrillation, PMVT – polymorphic ventricular tachycardia, BDVT – bidirectional ventricular tachycardia, AT – atrial tachycardia, Noise – noise on electrogram secondary to lead fracture, VE = ventricular ectopy.

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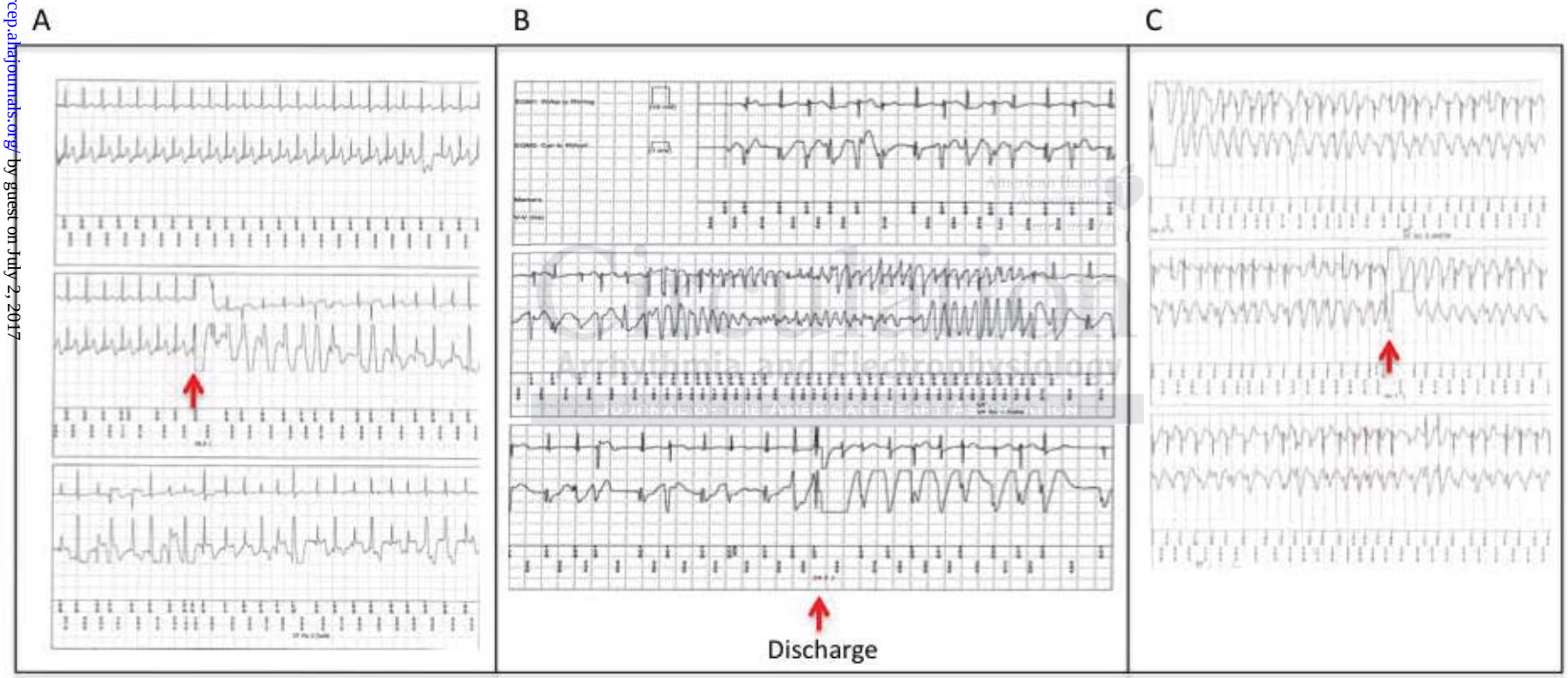

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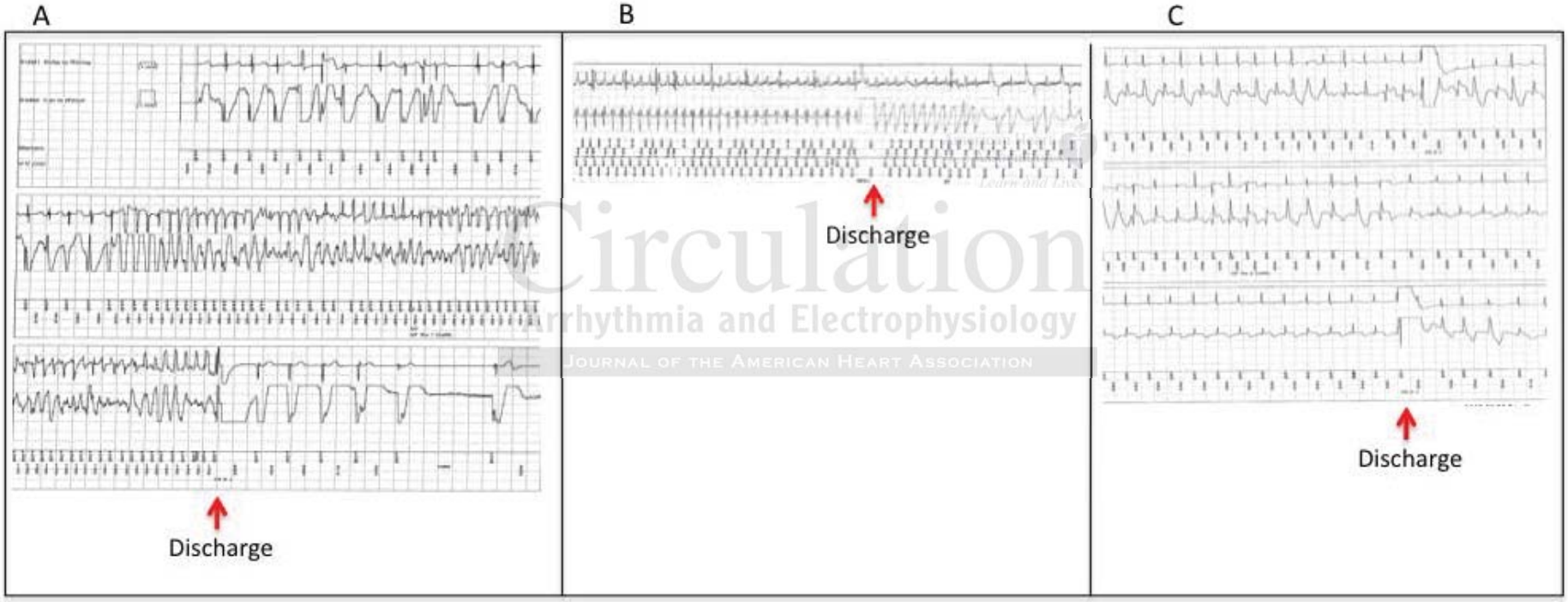

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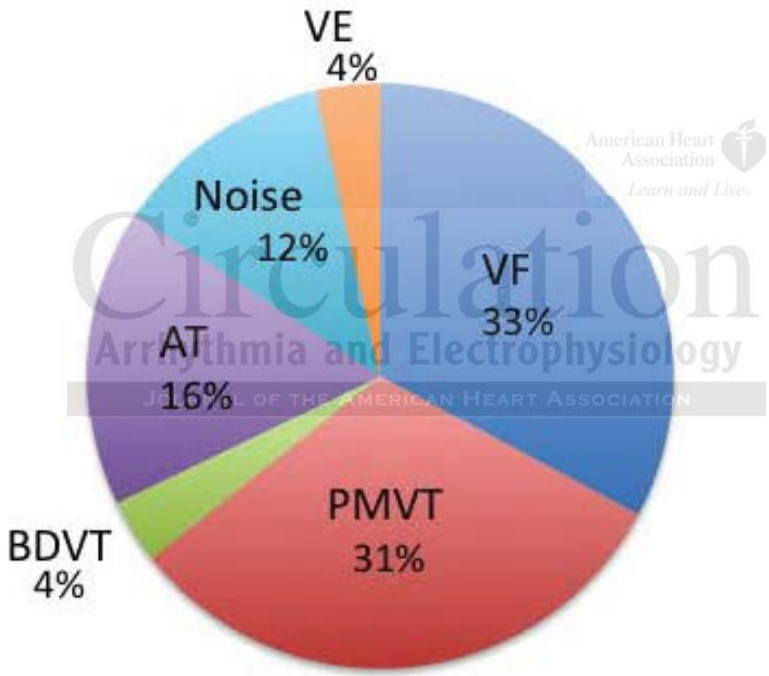

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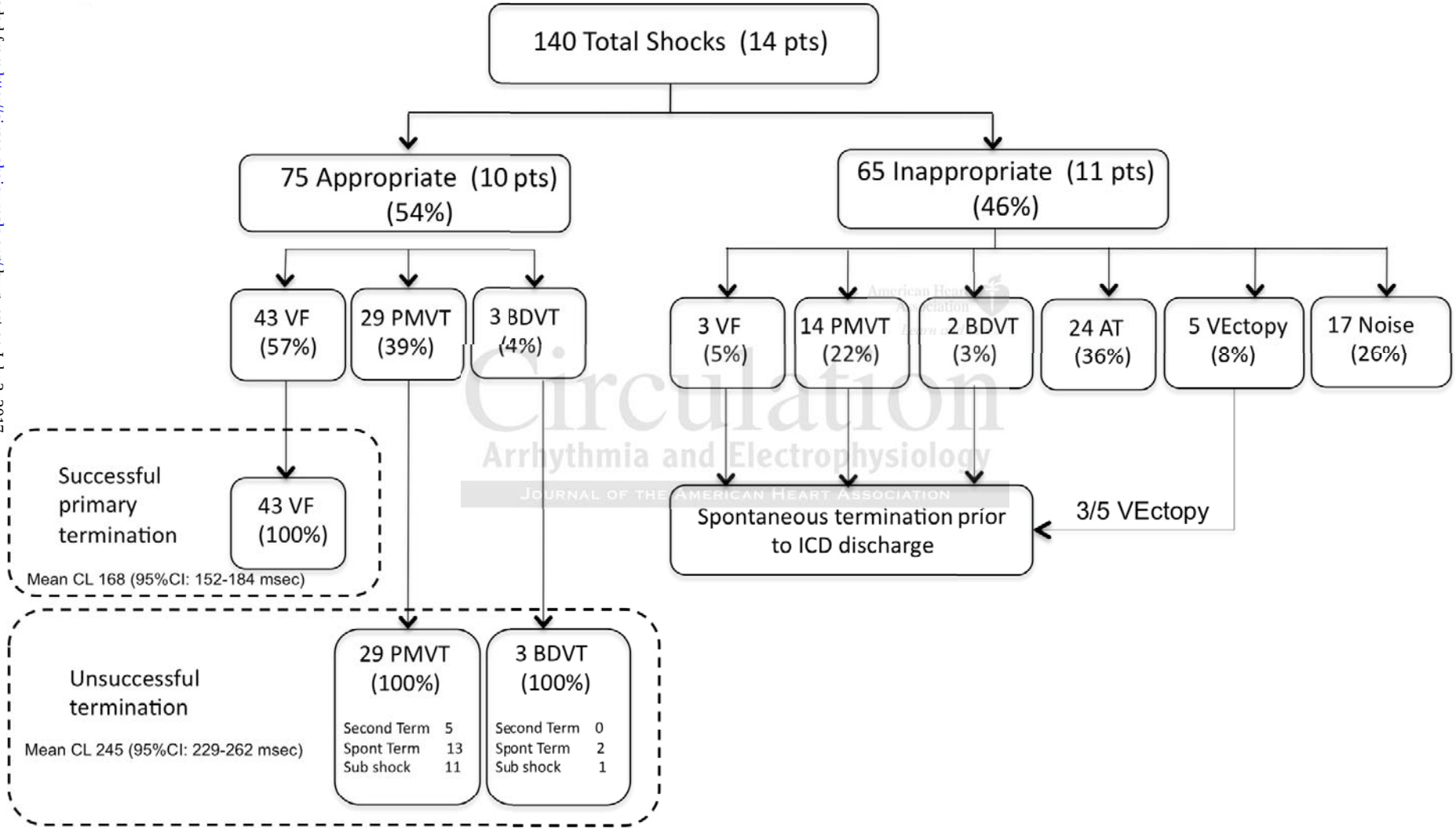

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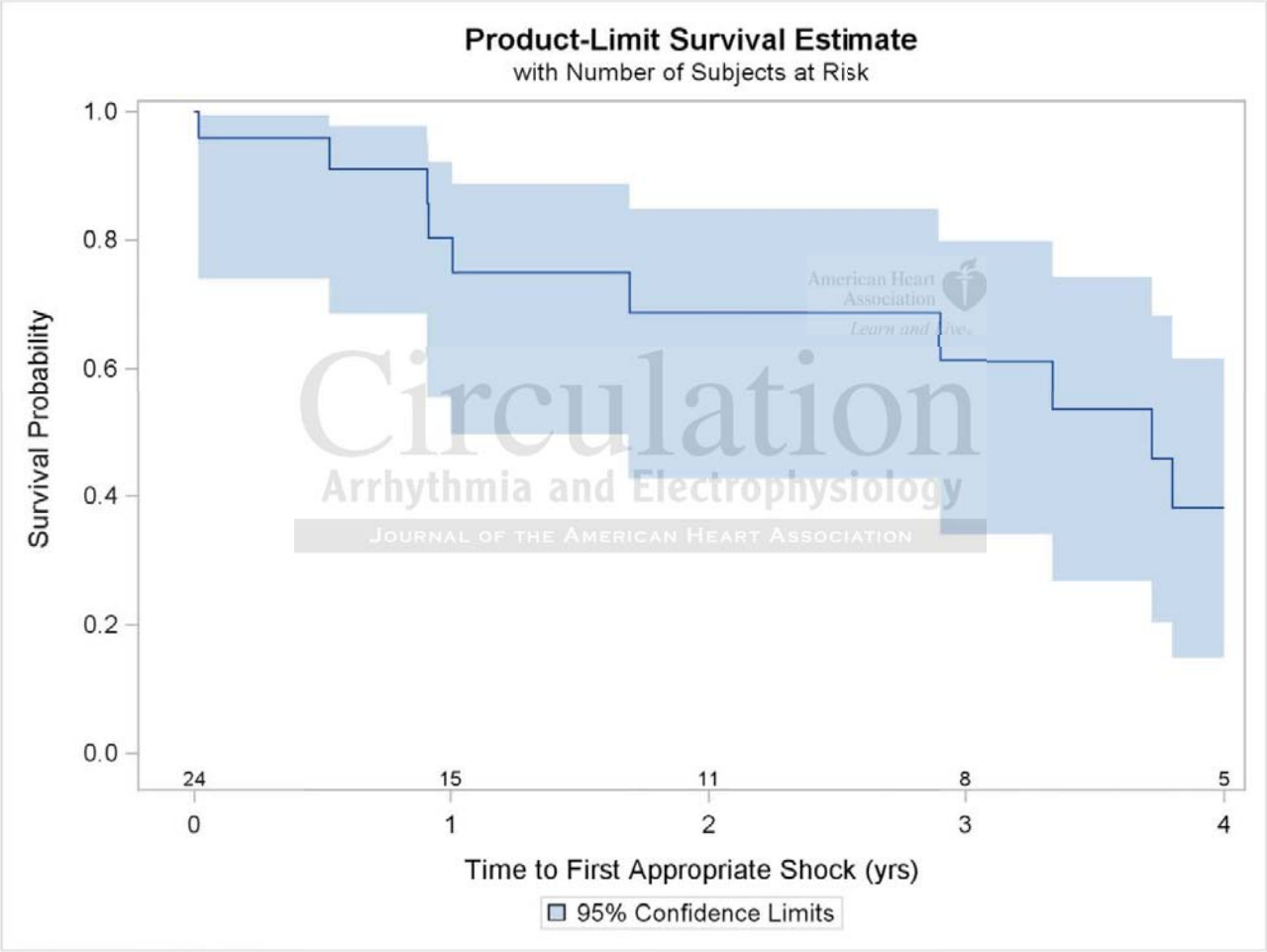

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Efficacy of Implantable Cardioverter Defibrillators in Young Patients with Catecholaminergic Polymorphic Ventricular Tachycardia: Success Depends on Substrate

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SUPPLEMENTAL MATERIAL

Table 1. Previous studies of CPVT patients with ICDs

	# pts with ICD	Age at onset of symptoms	# pts with appropriate shocks	# pts with inappropriate shocks	Reason for inappropriate shocks	# pts with ineffective shocks
Celiker et al Cardiol Young 2009	4	All children	3/4 (75%)	3/4 (75%)	TWO Incr HR Lead fracture	Not reported
Marai et al Am J Cardiol 2009	6	Not reported	4/6 (67%)	Not reported	-	2/4 (50%)
Priori et al Circulation 2002	12	7 pts <21 yrs 4 pts >21 yrs	6/12 (50%)	Not reported	-	Not reported
Sy et al Heart Rhythm 2011	15	Not reported	4/15 (27%)	5/15 (33%)	SVT	Not reported
Hayashi et al Circulation 2009	16	20 +/- 11 yrs	4/16 (25%)	6/38 (38%)	Sinus tach Lead fracture	Not reported
Miyake et al	24	10 yrs (2-16 yrs)	10/24 (42%)	11/24 (46%)	Atrial tach Spont term Vectopy Lead fracture	8/14 (57%)

TWO – T wave oversensing; Incr HR – increase heart rate; tach – tachycardia; spont term – spontaneous termination of arrhythmia prior to ICD discharge