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# Predictors of Sustained Ventricular Arrhythmias in Cardiac Resynchronization Therapy

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## Abstract

**Background—**Patients undergoing cardiac resynchronization therapy (CRT) are at high risk for ventricular arrhythmias and risk stratification in this population remains poor.

**Methods and Results—**This study followed 269 patients (LVEF < 35%, QRS > 120ms, NYHA III/IV) undergoing CRT with defibrillator (CRT-D) for 553±464 days after CRT-D implantation to assess for independent predictors of appropriate device therapy for ventricular arrhythmias (VAs). Baseline medication use, medical comorbidities, and echocardiographic parameters were considered. The 4-year incidence of appropriate device therapy was 36%. A Cox proportional hazard model identified left ventricular end systolic diameter (LVESD) > 61mm as an independent predictor in the entire population (HR 2.66, p = 0.001). Those with LVESD > 61mm had a 51% 3-year incidence of VA compared to a 26% incidence among those with a less dilated ventricle (p = 0.001). Among patients with LVESD ≤61mm, multivariate predictors of appropriate therapy were absence of beta-blocker therapy (HR 6.34, p<0.001, LVEF < 20% (HR 4.22, p <0.001), and history of sustained VA (2.97, p = 0.013). Early (<180d after implant) shock therapy was found to be a robust predictor of heart failure hospitalization (HR 3.41, p < 0.004) and mortality (HR 5.16 p < 0.001.)

**Conclusions—**Among CRT-D patients, LVESD > 61mm is powerful predictor of ventricular arrhythmias and further risk stratification of those with less dilated ventricles can be achieved based on assessment of EF, history of sustained VA, and absence of beta-blocker therapy.

### Keywords

Cardiomyopathy; tachyarrhythmias; heart failure; pacemakers; risk factors

## Introduction

Cardiac resynchronization therapy (CRT) is an important device treatment for patients with congestive heart failure with systolic dysfunction and dyssynchrony, as evidenced by a

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**Disclosures**

Dr. Singh reports serving as an advisor or consultant for Biotronik, Boston Scientific, Medtronic, Sorin, St. Jude Medical, Respicardia, and CardioInsight; serving as a speaker or a member of a speakers bureau for Biotronik, Boston Scientific, Sorin, and St. Jude Medical; and receiving grants for clinical research from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. Dr. Ruskin reports serving as an advisor or consultant for Astellas/Cardiome, Biosense Webster, CardioFocus, CardioInsight, CryoCath, Medtronic, Pfizer, Portola, and Third Rock Ventures; receiving fellowship support from Biosense Webster, Boston Scientific, Medronic, and St. Jude Medical; receiving honoraria from Med-IQ; and owning equity in Portola. Dr. Heist reports serving as a consultant for Boston Scientific, Sorin, and St. Jude Medical; receiving research grants from Biotronik, Boston Scientific, and St. Jude Medical; and receiving honoraria from Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical. The other authors report no conflicts.

prolonged QRS interval on the surface electrocardiogram. Many randomized trials have demonstrated that CRT is associated with decrease heart failure (HF) symptoms, HF hospitalizations, and all-cause mortality[1–5]. CRT has therefore become an important tool in the treatment of HF.

The relationship between CRT and the incidence of ventricular arrhythmias (VAs) remains controversial. Initial reports regarding CRT therapy and its effect on VAs were conflicting, some suggesting an increased risk of VAs and VT storm[6–8]. More recent analyses have suggested that CRT patients with on-treatment reverse remodeling, as evidenced by increases in the left ventricular ejection fraction (LVEF) or decreases in left ventricular end diastolic volume (LVEDV), have a decreased burden of device treated VAs[9–11].

Although CRT is associated with a decreased arrhythmia burden in echocardiographic responders, the population as a whole remains at elevated risk for incident ventricular tachycardia (VT) and ventricular fibrillation (VF) and little is known about which baseline patient characteristics are able to identify patients at increased and decreased risk for incident arrhythmic events, information that might be useful in assessing need for antiarrhythmic drugs or catheter ablation, and the likelihood of receiving device therapy. In this study, we performed an analysis of a cohort of patients with CRT with defibrillator (CRT-D) to identify pre-implant characteristics that may be useful in the risk stratification for incident VAs.

## Methods

### Patients

All CRT patients followed at our institution are prospectively enrolled in a research database. Patients were selected from this database for inclusion in this study if they were implanted with CRT-D for approved indications during the enrollment period between 2004 and 2010 (NYHA III/IV symptoms class, LVEF < 35%, QRS duration > 120ms) and followed at our clinic. Both ischemic and non-ischemic HF patients were enrolled.

### Baseline Characteristics and Echocardiography

Standard echocardiographic, clinical, and demographic data were considered as potential predictors of VAs. Baseline echocardiography data was available for 87% of patients. LV diameter measurements were made using the parasternal long axis view and LVEF measurement was typically obtained utilizing the Teich method. Left ventricular mass index (LVMI) was defined as $(1.04\ [(IVS+LVEDD+PW)^3-LVEDD^3]-14\ g)$/body surface area. Follow-up echocardiograms were obtained approximately six months after device implantation. Echocardiographic response was defined as either ≥5% absolute increase in LVEF or 10% decrease in left ventricular end systolic diameter. Continuous variables were analyzed as categorical variables using previously accepted partitions or an upper quartile cutoff for initial investigations. Multiple partition values were tested for candidate variables.

### Device Implantation and Programming

CRT-D implantation, programming, and device selection was at the discretion of the treating electrophysiologist. LV lead implantation was preferentially endovascular although epicardial implantation occasionally occurred (5.9%) after failure of an endovascular attempt. Devices were usually programmed to initially treat VT with antitachycardia pacing (ATP), followed by high voltage shocks if ATP was unsuccessful. VF was treated with high voltage shocks. Detection and therapy zones were not standardized and were determined on an individual basis, although generally therapy zones began at 160–190bpm. Recurrent episodes of symptomatic slow VT prompted lowering of therapy zones in certain instances.

### End Points

The primary endpoint of study was first incident sustained VA receiving appropriate device therapy after implantation of CRT-D. Arrhythmias were classified as VT, VF, electric storm (appropriate therapy for 3 VAs within < 24hrs), or pair of arrhythmias (appropriate therapy for 2 VAs within < 24hrs.) Appropriate therapy was defined as device therapy for a VA delivered according to pre-specified parameters and as verified by electrophysiologist review of device electrograms. A single episode of ventricular arrhythmia requiring multiple therapies (ie multiple rounds of ATP, multiple rounds of shock or ATP followed by shock(s) for termination was classified as a single event. This endpoint excluded non-sustained VT and inappropriate therapies for atrial arrhythmias or other factors (i.e. lead fracture, oversensing, etc.) and does not imply that first therapy attempt was successful.

Incident HF (HF) hospitalization, death, and a composite endpoint of death, left ventricular assist device (LVAD) implantation, or heart transplantation were also examined to assess outcomes among patients with and without appropriate therapy and with and without evidence of echocardiographic reverse remodeling.

### Statistical Analysis

All statistical analyses were performed using SPSS, Version 20.0 (Chicago, Ill), or SAS, Version 9.3 (Cary, NC). All continuous variables and were found to be normally distributed based on inspection of histograms and comparison of each variable's mean, median, and 5% trimmed mean. Baseline characteristics of patients are presented as mean ± SD for continuous variables and as proportions for categorical variables. Differences among proportions were assessed using Pearsons's Chi Square or Fisher's Exact test where appropriate, and differences in mean values were compared with student's t-tests. Kaplan-Meier curves were constructed to compare event rates in different subgroups and formally assessed using log rank testing. Univariate and multivariate analyses were performed using Cox proportional hazards models; forward stepwise selection was utilized for multivariate analyses. Significant univariate predictors at the $p<0.10$ level were tested for inclusion in multivariate models unless otherwise specified. For all tests, a p-value of $<0.05$ was required for statistical significance. For the second multivariate analysis assessing predictors of arrhythmia in patients with LVESD ≤ 61mm, all univariate predictors from the primary analysis were considered along with variables that differed among patients when divided by the 61mm LVESD partition.

## Results

### Baseline Characteristics and Incident Device Treated Arrhythmia

Two hundred and sixty-nine patients (mean age 68.2 ±12.5 years, average LVEF 23.9±6.8%) were followed for 553±464 days after CRT-D implantation. Of these patients, 21% were female, 54% had ischemic cardiomyopathy, 8% had NYHA IV symptom status, and 18% had a previous history of sustained VA. Subjects had a prolonged QRS (mean QRS 161±29ms with QRS > 150ms in 60% of individuals) and dilated left ventricle [mean (left ventricular end diastolic diameter) LVEDD of 62.6±8.7mm and (left ventricular end systolic diameter) LVESD of 54.6±8.9mm.] Nearly three quarters (73%) of patients had hypertension, 40% had diabetes, and 62% had coronary artery disease. The majority of patients were on beta-blockers (91%), an ACE or ARB (83%), and a diuretic (85%.) Three of the 85 patients (4%) with chronic atrial fibrillation underwent AV junctional ablation at the time of implantation. The most common antiarrhythmic drug was amiodarone (19% of patients.) Additional baseline characteristics are detailed in table 1.

Of the 269 patients who were followed, 60 (22%) had an appropriate therapy for VT or VF (mean rate 202±39bpm; range 125–333bpm; 21 episodes < 188bpm, 29 episodes between 188–250bpm, 9 episodes >250bpm, 1 episode with missing rate data) during follow-up. Of these first therapies, 44 were for VT, 6 were for VF, 6 were for electrical storms, and 4 were for a pair of VAs within less than 24 hours. Forty-one percent (n=25) of these patients had at least one additional appropriate device discharge and during follow-up and there were a total of 121 arrhythmic events. Kaplan Meier modeling predicts 1, 2, 3, and 4-year incidences of appropriate therapy to be 18%, 25%, 33%, and 36%, respectively in the overall cohort (Figure 1.)

Baseline characteristics of patients with and without appropriate therapy during follow-up are detailed in table 2. Patients with appropriate device therapy were more likely to have a prior history of sustained VA (30% vs. 15%, p = 0.009), previous percutaneous coronary intervention (PCI) (38% vs. 24%, p = 0.033,) and be off of beta-blocker therapy (20% vs. 6%, p = 0.001.) They were also more likely to have a lower LVEF (22.0±6.4% vs. 24.4±6.9%, p = 0.022) and dilated left ventricle (LVESD 58.2±9.7mm vs. 53.6±8.4mm, p = 0.001; LVEDD 66.0±9.9mm vs. 61.6±8.0, p = 0.001.) Patients who did not require device therapy trended towards being more likely to be female (23% vs. 12%, vs. p = 0.050) and NYHA IV (10% vs. 2%, p = 0.053.) There were no differences between groups with regards to medical comorbidities, renal function, QRS duration, age, body mass index, atrial fibrillation, digoxin use, or whether CRT-D implant was performed as an upgrade from ICD. Of note, patients with baseline echocardiograms (87% of population) were less likely to have undergone upgrade from a pacemaker to CRT-D (5% vs. 19%, p = 0.009) but were otherwise similar.

## Predictors of Appropriate Device Therapy

All available baseline characteristics listed in tables 1 and 2 were considered as potential predictors of appropriate device therapy for the primary analysis. An upper quartile cutoff was initially used to evaluate LVESD, LVEDD, and LVMI. Significant univariate predictors of therapy include LVEF< 20%, previous history of sustained VT or VF, absence of beta-blocker therapy, LVESD > 61mm, LVEDD > 68mm, and LVMI > 162g/$m^2$ (Table 3); the partition values for LVESD, LVEDD, and LVMI represent the upper quartile values for the study population. Given that time of study enrollment could impact risk of arrhythmia owing to changes in practice in device implantation and programming, as well as patient selection, we assess the relative hazard of late implantation compared to earlier implantation, and Cox modeling demonstrate a non-significant difference in risk of VA (HR 0.85, CI 0.49–1.49, p = 0.58). Male gender and history of PCI demonstrated a non-significant trend towards increased risk of appropriate device therapy in the univariate analysis, respectively. LVESD, LVEDD, and LVMI were all highly correlated metrics given their dependence on left ventricular dilation; when all three variables were included in a multivariate analysis with forward stepwise selection, LVESD was the only significant predictor and thus it was used for all subsequent analyses. Kaplan Meier analysis was performed to assess arrhythmia risk by quartile of LVESD; the curves representing the lower three quartiles of LVESD were overlapping while the upper quartile remained divergent throughout follow-up further supporting this partition (Figure 2). Other LVESD partitions ($60^{th}$, $80^{th}$, and $90^{th}$ percentile) were tested and found to be inferior to the upper quartile cutoff.

A multivariate model considering LVESD, absence of beta-blocker therapy, history of sustained VA, gender, PCI, and LVEF < 20% identified LVESD > 61mm and history of PCI as the only independent predictors of incident VA (HR 2.66, HR 1.52–4.65, p = 0.001) and (HR 1.92, CI 1.10–3.35, p=0.022), respectively (Table 4). Three year incidence of VA among those with a history of PCI (n=72) was 46% compared to 28% among those without a history of PCI (n=197)(p=0.063). (While the predictive value associated with a history of

PCI may underscore the importance of revascularization for the reduction of arrhythmias, the relationship may be somewhat confounded by the fact that those who underwent PCI may have been too ill to undergo more complete revascularization (e.g. CABG) or underwent PCI as a "salvage" procedure after CABG. Given that the predictive value is likely related to confounding by indication, it was not used in subsequent models.) Three year incidence of VA among those with LVESD >61mm (n=63) was 51% compared to 26% among those with LVESD ≤ 61mm (n=174) (p = 0.001) (Figure 3a). Of note, the rates of first treated VA did not differ based on more or less ventricular dilatation (202bpm vs. 201bpm, respectively, p=0.97). Table 5 describes differences in baseline characteristics between patients with and without LVESD > 61mm; none of these characteristics were univariate predictors of VAs. The rates of HF hospitalization, all-cause mortality, and LVAD, transplant, or death among patients with and without LVESD > 61mm are detailed in figures 3b, 3c, and 3d, respectively. LVESD > 61mm was associated with increased rates of HF hospitalization (p=0.006) and a trend towards increased rates of all-cause mortality and the composite endpoint.

Further risk stratification was pursued with a multivariate analysis of those with LVESD ≤ 61mm (n=174) utilizing significant univariate predictors from the primary analysis. Absence of beta-blocker therapy (HR 6.34, CI 2.28–17.65, p<0.001), LVEF < 20% (HR 4.22, CI 1.88–9.47, p <0.001), and history of previous sustained VA (2.97, CI 1.25–7.02, p = 0.013) were significant multivariate predictors and improved overall risk stratification (Table 4). There was a significant interaction between LVESD > 61mm and LVEF < 20% (p= 0.022), and LVESD > 61mm and absence of beta-blocker therapy (p = 0.013). In contrast, there was no significant interaction between LVESD > 61mm and history of ventricular arrhythmia (p=0.49).

Individuals without any of these risk factors (LVESD > 61mm, LVEF < 20%, absence of beta-blocker therapy, and a history of VA) demonstrated a 21% three year incidence of VA, versus a 41% three year incidence among those with LVESD ≤ 61mm and at least one additional risk factor (Log Rank 16.4321, p < 0.001). Figure 4 demonstrates that among those with LVESD < 61mm, an increasing number of risk factors is associated with a stepwise increase in risk of VA (overall, p<0.001); those with 0, 1, or 2+ risk factors demonstrated a 3-year VA incidence of 21%, 35%, and 75%, respectively.

## Reverse Remodeling and Relationship to Outcomes

Reverse Remodeling and its relationship to incident VA, HF hospitalization, and a combined endpoint of death, LVAD, or cardiac transplantation were examined in 154 patients with six month follow-up echocardiograms. Echocardiograms occurred 201±41 days after implantation Compared to those with follow-up studies, the group without follow-up studies had more epicardial leads (11% vs. 3%, p = 0.039), ICD upgrades, (46% vs. 32%, p = 0.033), paroxysmal atrial fibrillation (33% vs. 21%, p = 0.046), and lower BMI (mean 27kg/$m^2$ vs. 28kg/$m^2$, p = 0.034). When assessed using proportional hazards modeling, lack of follow-up echocardiographic data was not a marker of increased mortality, HF hospitalization, or VA, and thus lack of follow-up studies were not likely related to early adverse outcomes that precluded follow-up.

Baseline and follow-up echocardiographic measurements of patients divided by LVESD are detailed in table 6. Although both groups of patients experienced reverse remodeling, those with a LVESD > 61mm had a more enlarged left ventricle, depressed LVEF, and more severe mitral regurgitation at both baseline and follow-up. Furthermore, those with baseline LVESD > 61mm demonstrated a lesser degree of post-CRT reverse remodeling.

The relationship between composite echocardiographic response and outcomes are listed in table 7. Although response is associated with a decreased risk of VA (HR 0.51, CI 0.27–0.96, p = 0.037) it is no longer significant when included in a multivariate model with baseline LVESD > 61mm (HR 0.62, 0.32–1.18, p = 0.15), suggesting that while echocardiographic response to CRT is important in assessing prognosis, response is a relative measure and must be interpreted in the context of the severity of the baseline underlying cardiomyopathy. Table 7 also details how response is associated with reduced risk of death, LVAD, or transplant, and a trend towards decreased risk of HF hospitalization and death. The prognostic significance of reverse remodeling in the prediction of other outcomes was also somewhat attenuated after adjustment for LVESD > 61mm: HF Hospitalization (HR 0.70, CI 0.40–1.23, p = 0.21), death (HR 0.57, CI 0.28–1.12, p = 0.13), and death, LVAD, or transplant (HR 0.49, 0.25–0.96, p = 0.038).

We additionally analyzed whether the clinical impact of echocardiographic response varied according to baseline LVESD. Among patients with LVESD > 61mm and follow-up echocardiograms (n=39), echocardiographic evidence of response did not significantly predict decreased risk for arrhythmia (HR 0.646, CI 0.260– 1.607, p = 0.35) as it did in the overall population though the point estimate suggests a possible protective effect. However, this may be related to sample size as the subgroup of patients with LVESD ≤ 61mm and follow-up echocardiograms (n=115) also only demonstrated a trend towards decreased incidence of arrhythmias (HR 0.590, CI 0.241–1.445, p = 0.25).

### Outcomes in Patients with Appropriate Device Therapy

We subsequently examined association between incident VA, modeled as a time varying covariate, and risk of mortality, HF hospitalization, and a composite endpoint of death, LVAD implantation, or cardiac transplant. Events were stratified according to therapy type (ATP, shock, or any therapy) and timing of therapy relative to implant (<180d, >180d, or any time after implant) and the results are detailed in table 8. The results of multivariate adjustment with (age, cardiomyopathy type, LVEF <20%, and gender are detailed in table 9. Shocks were associated with a substantially increased risk of heart failure hospitalization, mortality, and the composite endpoint. Any therapy (ATP or shock) and early therapies were also associated with increased risk for all three endpoints, though this relationship seemed to be largely driven by the impact of shocks.

Given that early shock may be a marker of frequent arrhythmia, we attempted to separate the effect of recurrent arrhythmias from early shock, by repeating a multivariate analysis excluding patients with multiple VAs during follow-up; early shock remained a robust predictor of mortality (HR 4.61, CI 1.94–10.94, p < 0.001 and the point estimate and confidence intervals remained unchanged even when adjusting for >1 of shock delivered for the VA into the model. HF hospitalization was predicted by any shock, early shock, late shock, early electrical therapy (ATP or shock) and any electrical therapy (Table 9). Additionally, there was no difference in incidence of death, heart failure hospitalization, or death, LVAD, or transplant when patients with arrhythmias were divided based on the rate of their first arrhythmia (rate < 180bpm, 180–250bpm, >250bpm).

## Discussion

### Predictors of Appropriate Device Therapy

In this study, we demonstrate that baseline LVESD is a powerful independent predictor of appropriate device therapy in patients undergoing CRT-D, outperforming the conventionally utilized LVEF in risk stratification. To our knowledge, this is the first time LVESD has been identified as a predictor of VA in a population of HF patients undergoing CRT-D. We have

further demonstrated that among patients with LVESD ≤ 61mm, absence of beta blocker therapy, history of sustained VA, and LVEF < 20% are useful for further risk stratification. Other studies [12–14] have identified pre-implantation predictors of appropriate device therapy in a CRT population. Although these studies have demonstrated some variability in results, gender [12], absence of beta-blocker therapy[12], absence of ACE or ARB therapy[12], NYHA IV status[12, 13], LVEF < 20% [14], and history of VA (either sustained [13] or non-sustained [14]) were significant predictors of VA. There were important differences between these and our studies that should be noted. The COMPANION study[12] excluded patients with previous sustained VAs and thus this metric cannot be studied in this cohort. There was less beta blocker utilization in the COMPANION[12] and Ventak CHF/Contak CD[13] analyses than would be expected in a contemporary cohort of HF patients (68% in the COMPANION Cohort and 49% in the Ventak CHF/Contak CD Cohort, compared to 91% in our study), potentially limiting the generalizability of these results to the current era. Furthermore, these previous reports [1213] were analyses of randomized trials that excluded patients with atrial fibrillation, a condition that is highly prevalent and problematic in contemporary CRT cohorts. Notably, the analysis by Soliman and colleagues[14] includes only males with NYHA III symptom status at time of device implant. In contrast, our analysis includes men and women of both NYHA III/IV class on excellent medical therapy, with a variety of arrhythmic comorbidities (i.e. sustained VAs, atrial fibrillation), comprising a real world population.

Although much work has been done on VA risk stratification in patients with HF meeting criteria for ICD implantation, CRT patients are different in many important ways potentially limiting the extent to which results of ICD trials can be generalized to a CRT population. CRT patients are generally sicker than ICD patients based on the traditional implantation requirements for more advanced symptom status and conduction disease (as defined by prolonged QRS). Furthermore, biventricular pacing is a dynamic therapy that has the potential to alter a number of factors including neurohormonal activation (i.e. norepinephrine)[15], wall tension[11], oxygen consumption[16], left ventricular mass[17, 18], and left ventricular size[17, 19], which may be important in the genesis of VAs[20]. Additionally, biventricular pacing decreases conduction delays and pauses which are important for macroreentrant and pause dependent arrhythmias, respectively [21].

## Clinical Implications

The metric LVESD is a simple, widely available, reproducible, and physiologically relevant tool for the risk stratification of VAs among patients with systolic dysfunction, that integrates elements of both ventricular size and function because its measurement occurs during systole, the time of maximal myocardial contraction. Ventricular dilatation is proportional to wall stress potentially explaining the relationship between dilated ventricles and risk for ventricular arrhythmias. LVESD may be clinically useful for identifying CRT patients at particularly high risk for incident ventricular arrhythmias. Though absence of beta-blocker therapy, history of sustained VA, and LVEF < 20% are all markers of increased risk among patients with less dilated ventricles (LVESD ≤ 61mm), those without any of the 4 identified risk factors remain at substantial risk for incident VA (21% over three years) and thus should continue to be considered for defibrillator implantation at the time of CRT implantation.

Whether prophylactic defibrillators should be considered among CRT patients receiving devices for newer indications is an interesting and relevant question as a number of trials are assessing or have suggested CRT efficacy in patients with only moderately depressed ejection fractions in situations requiring permanent RV pacing. Scenarios include RV pacing in AV block (Block HF, study ongoing[22]; COMBAT [23] and HOBIPACE[24], both completed) and AV nodal ablation in atrial fibrillation (PAVE[25], APAF[26]). Whether LVESD may be

useful in risk stratification in these populations or populations with similar systolic dysfunction but less severe symptoms (i.e MADIT-CRT[4], RAFT[5]) is an intriguing but untested hypothesis.

## Relationship Between ICD Therapy and Outcomes

Our study further demonstrates that while ICD therapy is associated with worsened clinical outcomes, the relationship is influenced by both the timing and type of electrical therapy, with early therapy (<180 days post-implant) and shock therapy generally being associated with worsened outcomes. Our findings are in contrast with a previous study[12] that demonstrated that appropriate shocks (irrespective of timing) are not significantly predictive of all-cause mortality in a CRT population. The results in our study are however consistent with previous analyses examining the relationship between defibrillator shocks and mortality in ICD patients[27, 28].

Controversy exists regarding whether arrhythmia and subsequent appropriate ICD therapy is a marker of worsened overall cardiovascular status, if these arrhythmias are drivers of worsened outcomes, or both. Both scenarios are plausible given ventricular arrhythmias and other unfavorable cardiovascular outcomes share risk factors and ventricular arrhythmias may precipitate HF events and ischemia, both of which have the potential to lead to death (both sudden and otherwise). Perhaps even more intriguing is the potential relationship between device therapy (namely shock therapy) and cardiovascular status. Studies have demonstrated that shock therapy can lead to decreased ejection fraction and cardiac output [29, 30] with shocks of increasing voltage being associated with increasing degree of cardiac dysfunction [30]. Notably, an analysis by Sweeney and colleagues [31] demonstrated that shock therapy was associated with increased mortality compared to antitachycardia pacing among ICD (without CRT) patients receiving device therapy for fast VT (188–250 bpm.)

## Study Limitations

This study was a retrospective analysis of a prospectively acquired cohort and thus was subject to all of the inherent limitations of such studies. It is additionally a single center study including patients followed at a multidisciplinary CRT clinic at a tertiary care academic medical center and thus the results may not be immediately applicable to all CRT patients. Though the LVESD partition utilized in multivariate analyses was chosen *a priori*, it was ultimately validated in a *post hoc* analysis and as such requires replication in an independent dataset to verify that if it is in fact the most optimal partition value. Device programming, including therapy zones, was not uniform and was left to the discretion of the treating electrophysiologist. Only appropriate device therapies for VAs were included in this analysis and we did not investigate a number of other related events that might have prognostic importance, including slower VT, atrial fibrillation, non-sustained VT, and inappropriate device therapies. We did not have access to post mortem device interrogation reports for patients and were thus unable to assess the incidence of first events manifesting as device refractory ventricular arrhythmias causing sudden cardiac death[32]. This could have led to an underestimate of the incidence of appropriate therapy in certain high-risk populations, although these patients are included in analyses of overall mortality. Finally, our echocardiographic measurements of left ventricular size were restricted to internal diameter measures (i.e. LVESD and LVEDD), rather than volumes, which are often reported in the CRT literature.

## Conclusion

Among CRT-D patients, LVESD > 61mm is powerful predictor of VA. Further risk stratification of CRT-D patients with less dilated ventricles can be achieved based on assessment of ejection fraction, history of sustained VA, and absence of beta-blocker therapy. The relationship between ICD therapy and adverse outcomes is impacted by both the timing and type of electrical therapy with early therapy and shocks generally predicting worsened outcomes.

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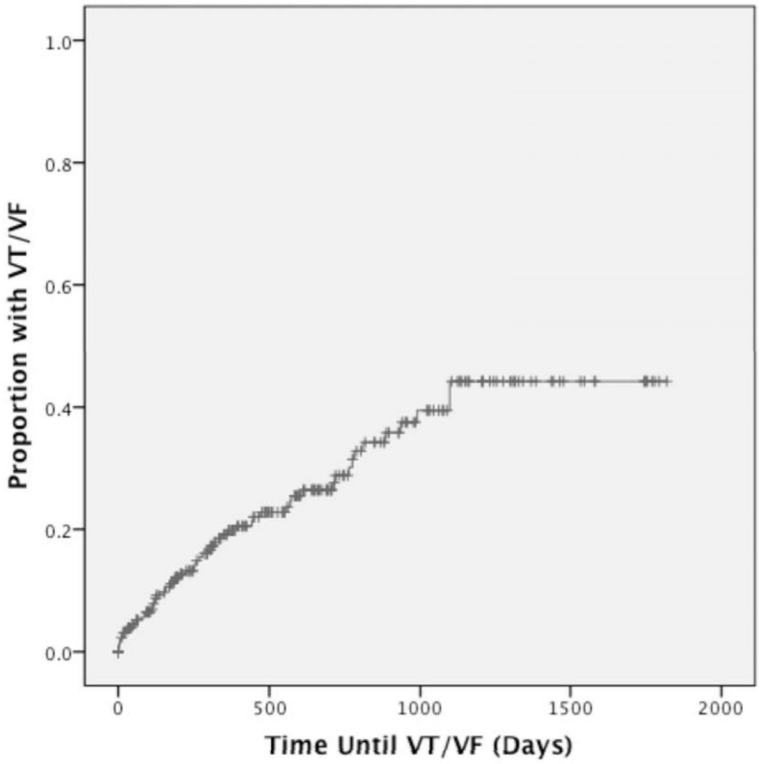


**Figure 1.**
Incidence of appropriate device therapy for VT or VF among all patients.

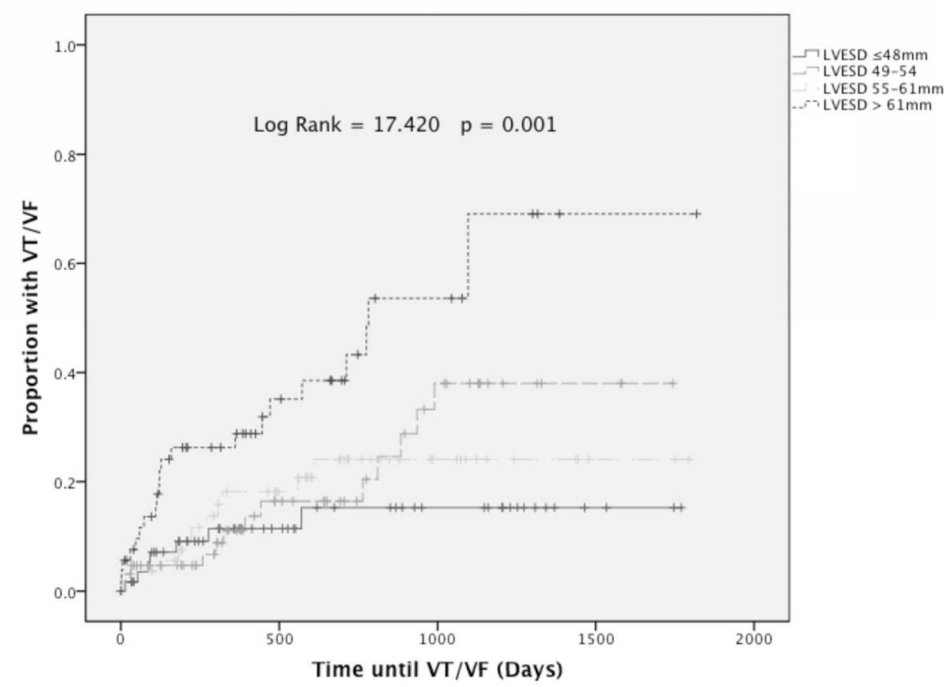


**Figure 2.**
Incidence of appropriate device therapy for VT or VF when patients are divided based on LVESD quartile.

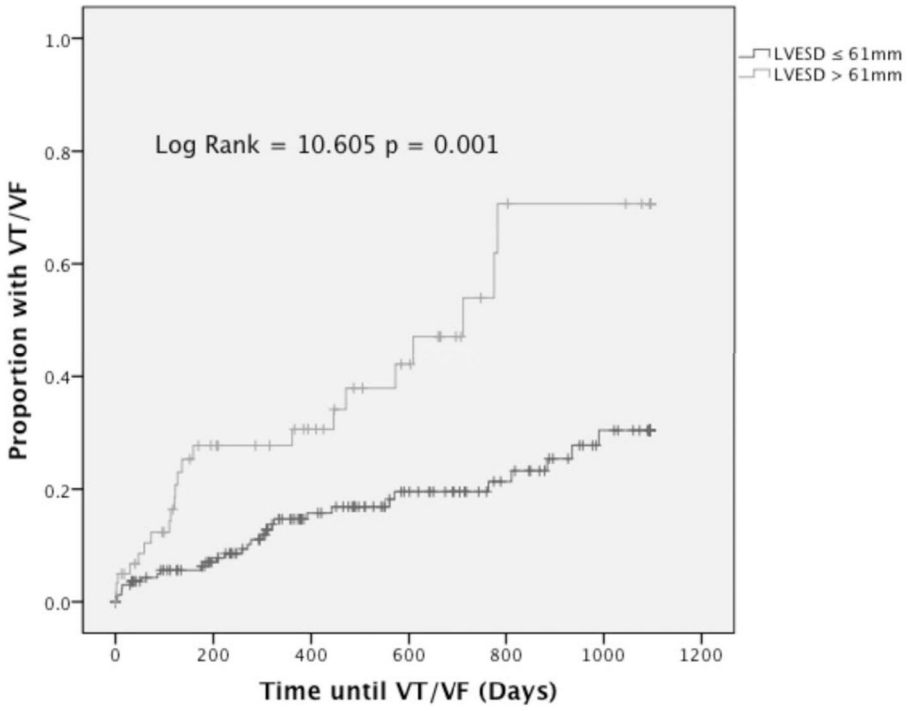


Figure 3a

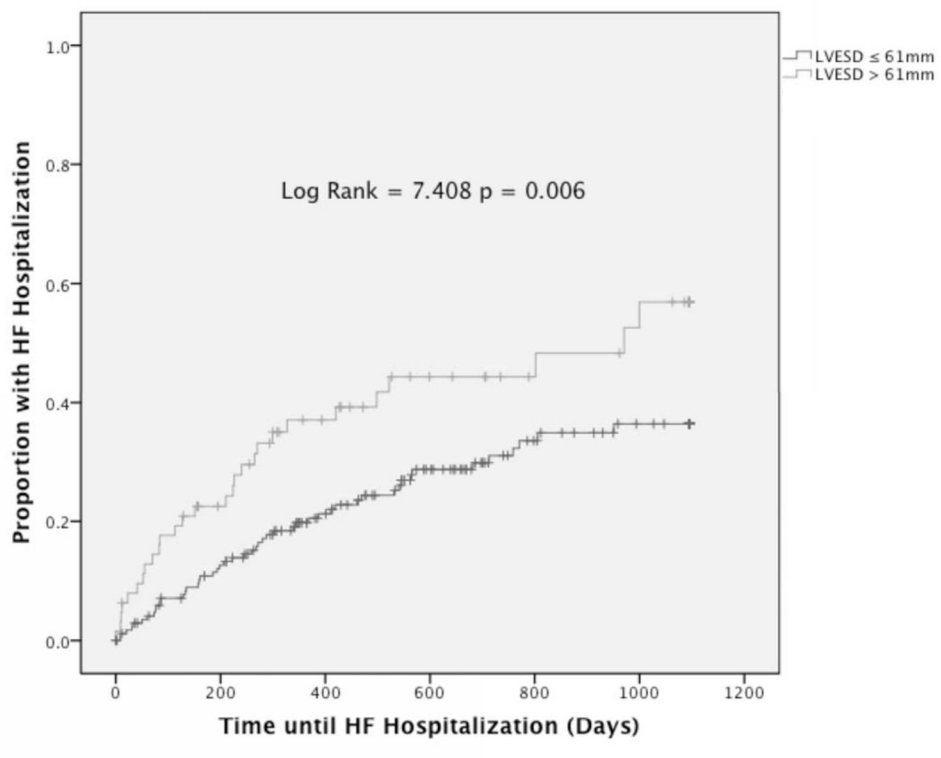


Figure 3b

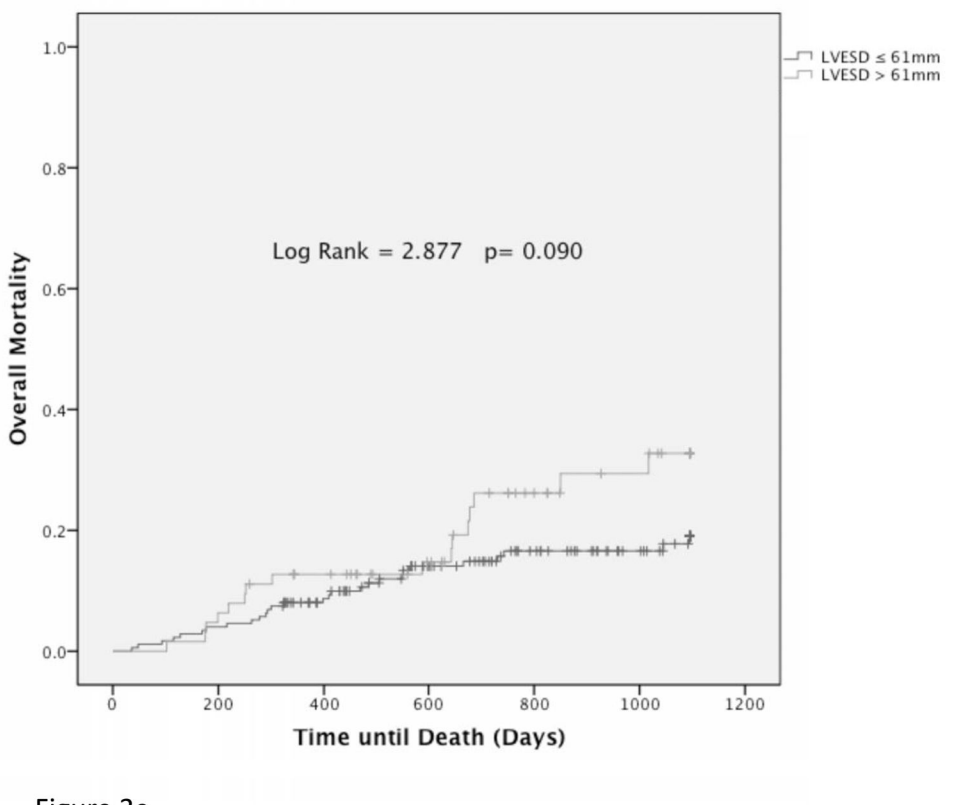


Figure 3c

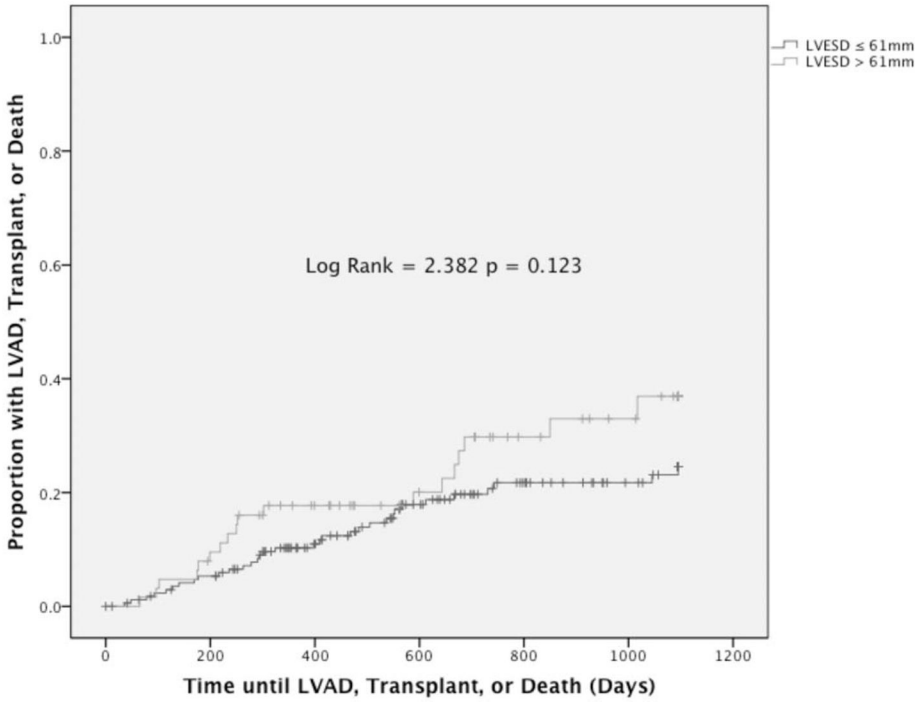


Figure 3d

**Figure 3.**

Incidence of (a) appropriate device therapy for VT or VF, (b) heart failure hospitalization, (c) mortality, and (d) death, LVAD, or cardiac transplant among all patients when stratified by LVESD with a 61mm (upper quartile) partition.

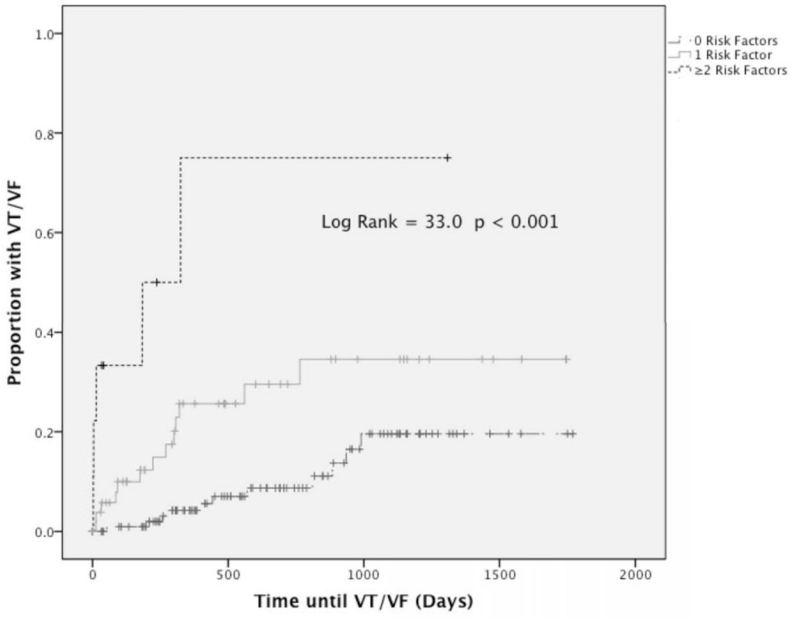


**Figure 4.**

Incidence of appropriate device therapy for VT or VF among patients with LVESD ≤ 61mm when stratified by number of additional risk factors (LVEF < 20%, absence of beta-blocker therapy, or previous history of VT or VF.)

**Table 1**

Baseline characteristics of all study patients.

| Characteristic | Frequency or Mean |
|---|---|
| Age | 68.2(12.5) |
| Female, % | 20.4 |
| NYHA IV, % | 7.8 |
| BMI, kg/m$^2$ | 27.9(5.1) |
| Baseline QRS, ms | 161 (29) |
| QRS > 150ms, % | 60 |
| Transvenous LV Lead, % | 94.1 |
| ICD Upgrade, % | 38.9 |
| Pacemaker Upgrade, % | 6.3 |
| *Medical Comorbidities* | |
| CABG, % | 35.9 |
| CAD, % | 62.2 |
| Chronic Atrial Fibrillation, % | 31.5 |
| Cr >2, % | 15.1 |
| Diabetes, % | 40.4 |
| Hypertension, % | 73 |
| Ischemic CM, % | 54.4 |
| Paroxysmal Atrial Fibrillation, % | 24.2 |
| PCI, % | 27 |
| Previous VT/VF, % | 18.1 |
| Valve Surgery, % | 17.4 |
| *Echocardiographic Characteristics* | |
| Grade 3–4 MR | 46.9 |
| IVS > 11mm, % | 27.4 |
| Left Atrial Size (AP) > 38, % | 88.1 |
| LVEDD (mm) (n=235) | 62.6(8.7) |
| LVEF (%) | 23.9 (6.8) |
| LVEF < 20%, % | 27.8 |
| LVESD (mm) | 54.6(8.9) |
| LVEDD > 53mm, % (n=246) | 87.4 |
| PWT > 11mm, % | 20.2 |
| RVSP > 35mmHg, % (n=189) | 75.7 |
| RVSP, mmHg | 45.5(12.0) |
| *Medications* | |
| ACE/ARB, % | 83 |
| Aldosterone Antagonist, % | 37.4 |
| Beta Blockers, % | 91.1 |
| Digoxin, % | 35.2 |
| Diuretics, % | 84.8 |

| Characteristic | Frequency or Mean |
|---|---|
| Amiodarone, % | 18.5 |
| Mexiletine, % | 2.2 |
| Sotalol, % | 2.6 |

NYHA, New York Heart Association Symptom Class; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; Cr, creatinine; CM, cardiomyopathy; PCI, percutaneous coronary intervention; MR, mitral regurgitation; IVS, intraventricular septum; PWT, posterior wall thickness; RVSP, right ventricular systolic pressure; ACE/ARB, angiotensin converting enzyme / angiotensin receptor blocker

## Table 2

Differences in baseline characteristics between patients with and without incident ventricular arrhythmia.

| Characteristic | Incident VT/VF | No VT/VF | p-value |
|---|---|---|---|
| Age | 66.5(12.0) | 68.7(12.6) | 0.23 |
| Female, % | 11.5 | 23.0 | 0.050 |
| NYHA IV, % | 1.8 | 9.9 | 0.053 |
| BMI, kg/m$^2$ | 28.2(4.9) | 27.8(5.2) | 0.61 |
| Baseline QRS, ms | 157.4(28.8) | 162.2(28.6) | 0.26 |
| QRS > 150ms, % | 54.1 | 61.7 | 0.29 |
| Transvenous LV Lead, % | 91.8 | 95.2 | 0.34 |
| ICD Upgrade, % | 37.7 | 39.4 | 0.81 |
| Pacemaker Upgrade, % | 6.7 | 6.2 | 1.00 |
| *Medical Comorbidities* | | | |
| CABG, % | 39.3 | 34.9 | 0.53 |
| CAD, % | 63.9 | 61.7 | 0.75 |
| Chronic Atrial Fibrillation, % | 27.9 | 32.5 | 0.49 |
| Cr >2, % | 10.5 | 16.5 | 0.27 |
| Diabetes, % | 42.6 | 39.7 | 0.68 |
| Hypertension, % | 80.3 | 70.8 | 0.14 |
| Ischemic CM, % | 60.7 | 52.6 | 0.27 |
| Paroxysmal Atrial Fibrillation, % | 19.7 | 25.8 | 0.32 |
| PCI, % | 37.7 | 23.9 | 0.033 |
| Previous VT/VF, % | 29.5 | 14.8 | 0.009 |
| Valve Surgery, % | 14.8 | 18.2 | 0.53 |
| *Echocardiographic Characteristics* | | | |
| Grade 3–4 MR | 45.5 | 47.3 | 0.81 |
| Left Atrial Size (AP), | 47.4(8.7) | 45.2(7.1) | 0.10 |
| LVEDD (mm) | 66.0(9.9) | 61.6(8.0) | 0.001 |
| LVEF (%) | 22.0(6.4) | 24.4(6.9) | 0.022 |
| LVEF < 20%, % | 41.4 | 23.7 | 0.008 |
| LVESD (mm) | 58.2(9.7) | 53.6(8.4) | 0.001 |
| LVESD > 61mm, % | 44.4 | 21.2 | 0.001 |
| RVSP > 35mmHg, % | 79.1 | 74.7 | 0.55 |
| RVSP, mmHg | 47.5(10.9) | 44.9(12.3) | 0.21 |
| *Medications* | | | |
| ACE/ARB, % | 82.0 | 83.3 | 0.81 |
| Aldosterone Antagonist, % | 36.1 | 37.8 | 0.81 |
| Beta Blockers, % | 80.3 | 94.3 | 0.001 |
| Digoxin, % | 34.4 | 35.4 | 0.89 |
| Diuretics, % | 86.9 | 84.2 | 0.61 |
| Amiodarone, % | 21.3 | 17.8 | 0.53 |
| Mexiletine, % | 3.3 | 1.9 | 0.62 |

| Characteristic | Incident VT/VF | No VT/VF | p-value |
|---|---|---|---|
| Sotalol, % | 3.3 | 2.4 | 0.66 |

NYHA, New York Heart Association Symptom Class; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; Cr, creatinine; CM, cardiomyopathy; PCI, percutaneous coronary intervention; MR, mitral regurgitation; IVS, intraventricular septum; PWT, posterior wall thickness; RVSP, right ventricular systolic pressure; ACE/ARB, angiotensin converting enzyme / angiotensin receptor blocker

## Table 3

Univariate predictors of appropriate device therapy among all patients, with p<0.10.

| Variable | HR | CI | P |
|---|---|---|---|
| Previous VT/VF | 1.97 | 1.12–3.46 | 0.018 |
| Female Gender | 0.46 | 0.21–1.01 | 0.054 |
| PCI | 1.64 | 0.97–2.78 | 0.066 |
| Absence of BB | 3.23 | 1.67–6.24 | <0.001 |
| LVEF < 20% | 2.41 | 1.42–4.08 | 0.001 |
| LVMI top quartile | 1.90 | 1.07–3.36 | 0.027 |
| LVESD > 61mm | 2.69 | 1.56–4.63 | <0.001 |
| LVEDD > 68mm | 2.02 | 1.19–3.44 | 0.010 |

BB, beta-blocker

## Table 4

Multivariate model among all patients and among patients with LVESD ≤ 61mm.

| Variable | HR | CI | P |
|---|---|---|---|
| *Among all patients* (n=237)* | | | |
| LVESD > 61mm | 2.66 | 1.52–4.65 | 0.001 |
| PCI | 1.92 | 1.10–3.35 | 0.022 |
| *Among patients with LVESD ≤ 61mm (n= 174)* | | | |
| Previous VT/VF | 2.97 | 1.25–7.02 | 0.013 |
| Absence of BB | 6.34 | 2.28–17.65 | <0.001 |
| LVEF < 20% | 4.22 | 1.88–9.47 | <0.001 |

* with baseline echocardiograms

BB, beta-blocker

## Table 5

Differences in baseline characteristics between patients with and without LVESD > 61mm.

| Characteristic | LVESD > 61mm (n=63) | LVESD ≤ 61mm (n=174) | p-value |
|---|---|---|---|
| Age | 65.3(12.5) | 69.5(11.9) | 0.0197 |
| Female, % | 14.3 | 20.7 | 0.27 |
| NYHA IV, % | 11.1 | 6.6 | 0.27 |
| BMI, kg/m$^2$ | 27.6(6.6) | 27.5(5.3) | 0.91 |
| Baseline QRS, ms | 155.1(29.1) | 163.1(27.9) | 0.057 |
| QRS > 150ms, % | 47.6 | 63.8 | 0.025 |
| Transvenous LV Lead, % | 88.9 | 95.4 | 0.069 |
| ICD Upgrade, % | 39.7 | 35.6 | 0.57 |
| Pacemaker Upgrade, % | 1.6 | 5.8 | 0.30 |
| *Medical Comorbidities* | | | |
| CABG, % | 25.4 | 42.0 | 0.021 |
| CAD, % | 47.6 | 67.2 | 0.006 |
| Chronic Atrial Fibrillation, % | 20.6 | 33.9 | 0.0497 |
| Cr >2, % | 17.2 | 14.4 | 0.60 |
| Diabetes, % | 38.1 | 42.5 | 0.54 |
| Hypertension, % | 69.8 | 74.7 | 0.45 |
| Ischemic CM, % | 44.4 | 56.9 | 0.090 |
| Paroxysmal Atrial Fibrillation, % | 25.4 | 24.7 | 0.91 |
| PCI, % | 27.0 | 25.3 | 0.79 |
| Previous VT/VF, % | 22.2 | 16.7 | 0.33 |
| Valve Surgery, % | 12.7 | 20.1 | 0.19 |
| *Echocardiographic Characteristics* | | | |
| Grade 3–4 MR | 67.7 | 40.5 | <0.001 |
| Left Atrial Size (AP), mm | 46.8(7.8) | 45.4(7.3) | 0.19 |
| LVEDD (mm) | 72.9(6.0) | 59.0(5.8) | <0.001 |
| LVEF (%) | 18.9(5.5) | 25.6(6.2) | <0.001 |
| LVEF < 20%, % | 50.8 | 19.0 | <0.001 |
| LVESD (mm) | 66.0(5.4) | 50.6(5.9) | <0.001 |
| LVESD > 61mm, % | - | - | N/A |
| RVSP > 35mmHg, % | 79.6 | 74.1 | 0.42 |
| RVSP, mmHg | 45.8(12.1) | 45.4(12.1) | 0.87 |
| *Medications* | | | |
| ACE/ARB, % | 85.7 | 82.8 | 0.59 |
| Aldosterone Antagonist, % | 34.9 | 39.1 | 0.56 |
| Beta Blockers, % | 87.3 | 93.7 | 0.11 |
| Digoxin, % | 39.7 | 33.9 | 0.41 |
| Diuretics, % | 77.8 | 86.8 | 0.092 |
| Amiodarone, % | 25.4 | 17.8 | 0.37 |
| Mexiletine, % | 6.4 | 1.2 | 0.045 |

| Characteristic | LVESD > 61mm (n=63) | LVESD ≤ 61mm (n=174) | p-value |
|---|---|---|---|
| Sotalol, % | 3.2 | 2.3 | 0.71 |

NYHA, New York Heart Association Symptom Class; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; Cr, creatinine; CM, cardiomyopathy; PCI, percutaneous coronary intervention; MR, mitral regurgitation; IVS, intraventricular septum; PWT, posterior wall thickness; RVSP, right ventricular systolic pressure; ACE/ARB, angiotensin converting enzyme / angiotensin receptor blocker

## Table 6

Baseline and follow-up echocardiographic measurements for patients with and without LVESD > 61mm (n=154)

| | LVESD > 61mm (n=39) | LVESD ≤ 61mm (n=115) | p-value (between group) |
|---|---|---|---|
| Baseline LVEF | 20 (5) | 26 (6) | <0.001 |
| Follow-up LVEF | 23 (7) | 33 (10) | <0.001 |
| p-value (within group, over time) | 0.002 | <0.001 | |
| Mean Change EF, % | 3 (6) | 7 (9) | 0.002 |
| % with 5% increase in EF | 33 | 60 | 0.004 |
| % with 10 % increase in EF | 13 | 38 | 0.003 |
| Baseline LVESD | 66 (6) | 51(6) | <0.001 |
| Follow-up LVESD | 62 (9) | 48 (8) | <0.001 |
| p-value (within group, over time) | <0.001 | <0.001 | |
| Mean Change LVESD, mm | −5 (8) | − 3 (7) | 0.33 |
| % with >10% decrease LVESD | 33 | 41 | 0.38 |
| Baseline LVEDD | 74 (7) | 59 (6) | <0.001 |
| Follow-up LVEDD | 70 (7) | 57 (7) | <0.001 |
| p-value (within group, over time) | 0.001 | <0.001 | |
| Mean Change LVEDD, mm | −4 (7) | −2 (6) | 0.16 |
| Baseline LA size | 46 (7) | 45 (7) | 0.59 |
| Follow-up LA size | 44 (8) | 44 (7) | 0.78 |
| p-value (within group, over time) | 0.073 | 0.015 | |
| Baseline MR | 2.8 (1.0) | 2.2 (0.9) | <0.001 |
| Follow-up MR | 2.1 (1.0) | 1.5 (0.9) | 0.003 |
| p-value (within group, over time) | <0.001 | <0.001 | |
| Echo Response*, % | 51 | 70 | 0.039 |

* ≥5% absolute increase in LVEF or 10% decrease in LVESD

**Table 7**

Association between reverse remodeling* and outcomes (unadjusted)

| Outcomes | HR | CI | p |
|---|---|---|---|
| VA | 0.51 | 0.27–0.96 | 0.036 |
| HF Hospitalization | 0.69 | 0.38–1.17 | 0.16 |
| All cause mortality | 0.54 | 0.27–1.08 | 0.082 |
| Death, LVAD, or transplant | 0.45 | 0.23–0.88 | 0.019 |

* ≥5% absolute increase in LVEF or 10% decrease in LVESD

## Table 8

Relationship between first incident electrical therapy as a time varying covariate and outcome.

| | Timing | HR | CI | p |
|---|---|---|---|---|
| **Risk of HF Hospitalization** | | | | |
| **ATP or shock** | < 180d | 2.25 | 1.27–4.00 | 0.006 |
| | ≥180d | 1.56 | 0.90–2.73 | 0.16 |
| | Any | 2.02 | 1.30–3.15 | 0.002 |
| **ATP** * | < 180d | 0.93 | 0.29–2.95 | 0.90 |
| | ≥180d | 1.07 | 0.43–2.67 | 0.89 |
| | Any | 1.01 | 0.48–2.13 | 0.97 |
| **Shock** † | < 180d | 3.83 | 1.91–7.67 | <0.001 |
| | ≥180d | 2.66 | 1.47–4.84 | 0.001 |
| | Any | 3.14 | 1.94–5.10 | <0.001 |
| **Risk of Death** | | | | |
| **ATP or shock** | < 180d | 3.37 | 1.73–6.60 | <0.001 |
| | ≥180d | 3.43 | 1.42–8.26 | 0.006 |
| | Any | 3.67 | 2.05–6.63 | <0.001 |
| **ATP** * | < 180d | 2.66 | 0.94–7.52 | 0.064 |
| | ≥180d | 3.01 | 0.88–10.3 | 0.079 |
| | Any | 2.87 | 1.26–6.60 | 0.012 |
| **Shock** † | < 180d | 4.93 | 2.21–11.0 | <0.001 |
| | ≥180d | 2.55 | 0.88–7.38 | 0.0835 |
| | Any | 3.86 | 1.96–7.62 | <0.001 |
| **Risk of Death, LVAD, or transplant** | | | | |
| **ATP or shock** | < 180d | 3.12 | 1.69–5.78 | <0.001 |
| | ≥180d | 0.96 | 0.45–2.06 | 0.72 |
| | Any | 1.79 | 1.05–3.05 | 0.031 |
| **ATP** * | < 180d | 2.54 | 1.00–6.43 | 0.050 |
| | ≥180d | 0.83 | 0.26–2.70 | 0.76 |
| | Any | 1.43 | 0.67–3.06 | 0.36 |
| **Shock** † | < 180d | 4.49 | 2.13–9.48 | <0.001 |
| | ≥180d | 1.04 | 0.41–2.62 | 0.929 |
| | Any | 1.98 | 1.07–3.66 | 0.030 |

Comparison group used in analysis of risk associated with late events excludes patients with early (<180d events).

*Patients with a shock at any time during follow-up were excluded

†Comparison group includes patients with ATP only or no electrical therapy

## Table 9

Multivariate analysis assessing the relationship between first incident electrical therapy as a time varying covariate and outcome

| | Timing | HR | CI | P |
|---|---|---|---|---|
| **Risk of HF Hospitalization** | | | | |
| **ATP or shock** | < 180d | 2.06 | 1.06–4.02 | 0.033 |
| | Any | 2.56 | 1.48–4.42 | <0.001 |
| **Shock**† | < 180d | 3.41 | 1.48–7.86 | 0.004 |
| | ≥180d | 6.59 | 2.86–15.17 | <0.001 |
| | Any | 4.71 | 2.58–8.63 | <0.001 |
| **Risk of Death** | | | | |
| **ATP or shock** | < 180d | 3.13 | 1.59–6.15 | 0.001 |
| | Any | 3.52 | 1.91–6.49 | <0.001 |
| **ATP*** | Any | 3.16 | 1.38–7.25 | 0.007 |
| **Shock**† | < 180d | 5.16 | 2.30–11.58 | <0.001 |
| | Any | 3.19 | 1.55–6.57 | 0.002 |
| **Risk of Death, LVAD, or transplant** | | | | |
| **ATP or shock** | < 180d | 3.25 | 1.74–6.07 | <0.001 |
| | Any | 3.61 | 2.04–6.38 | <0.001 |
| **Shock**† | < 180d | 5.18 | 2.44–11.00 | <0.001 |
| | Any | 3.82 | 1.98–7.36 | <0.001 |

Comparison group used in analysis of risk associated with late events excludes patients with early (<180d events).

Patients with a shock at any time during follow-up were excluded

†Comparison group includes patients with ATP only or no electrical therapy