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The Relationship between Baseline and Follow-Up Left Ventricular Ejection Fraction with Adverse Events among Primary Prevention ICD Patients

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Abstract

Background—Left ventricular ejection fraction (LVEF) is used to select patients for primary prevention implantable cardioverter defibrillators (ICDs). The relationship between baseline and long-term follow-up LVEF and clinical outcomes among primary prevention ICD patients remains unclear.

Methods—We studied 195 patients with a baseline LVEF $\geq 35\%$ 6 months prior to ICD implantation and follow-up LVEF 1–3 years after ICD implantation without intervening left ventricular assist device (LVAD) or transplant. The co-primary study endpoints were: (1) a composite of time to death, LVAD, or transplant and (2) appropriate ICD therapy. We examined multivariable Cox proportional hazard models with a 3-year post-implant landmark view; the LVEF closest to the 3-year mark was considered the follow-up LVEF for analyses. Follow-up LVEF was examined using 2 definitions: (1) $\geq 10\%$ improvement compared to baseline or (2) actual value of $\geq 40\%$.

Results—Fifty patients (26%) had a LVEF improvement of $\geq 10\%$ and 44 (23%) had a follow-up LVEF $\geq 40\%$. Neither baseline nor follow-up LVEF was significantly associated with the composite endpoint. In contrast, both baseline and follow-up LVEF were associated with risk for long-term ICD therapies, whether follow-up LVEF was modeled as a $\geq 10\%$ absolute improvement (baseline LVEF HR 0.87, CI 0.91–0.93, $p < 0.001$; follow-up LVEF HR 0.18, CI 0.06–0.53, $p = 0.002$) or a $\geq 40\%$ follow-up value (baseline LVEF HR 0.89, CI 0.83–0.96, $p = 0.001$, follow-up LVEF HR 0.26, CI 0.08–0.87, $p = 0.03$).

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Conclusions—Among primary prevention ICD recipients, both baseline and follow-up LVEF were independently associated with long-term risk for appropriate ICD therapy, but they were not associated with time to the composite of LVAD, transplant, or death.

Keywords

Implantable cardioverter defibrillator; left ventricular ejection fraction; heart failure; sudden cardiac death; remodeling

Introduction

The left ventricular ejection fraction (LVEF) is the most widely used measure of LV systolic function among patients with heart failure (HF). The strong association between a reduced LVEF and ventricular arrhythmias led to several randomized trials demonstrating that primary prevention implantable cardioverter defibrillators (ICD) reduce all-cause mortality among patients with HF and an LVEF of $\leq 35\%$.^(1–5) Thus, the LVEF is a crucial prognostic variable that determines the use of approximately 100,000 primary prevention ICDs (73.8% of all ICDs) implanted in the United States on an annual basis.⁽⁶⁾

Current appropriate use criteria describe how LVEF should be incorporated into decision making regarding primary prevention ICD implantation, stating that the LVEF should be reassessed 3 months after initiation of optimal medical therapy or revascularization or 40 days after a myocardial infarction, in order to determine primary prevention ICD candidacy. However, it is well recognized that during longer term follow-up, LV systolic function often changes, with some patients experiencing dramatic improvements and others experiencing dramatic declines in LVEF. There are limited data on the prognostic implications of LVEF change over time, particularly as it pertains to the risk for ventricular arrhythmias, and there are currently no guidelines to aid in clinical decision making.^(7,8) Based on this important evidence gap, we performed an analysis assessing the clinical utility of long-term follow-up LVEF in a primary prevention ICD population to determine the relative clinical value of baseline and follow-up LVEF in estimating the risk for the following adverse clinical outcomes: left ventricular assist device implantation (LVAD), transplant, death, and ICD therapy.

Methods

Patient Population

We performed a retrospective landmark analysis of HF patients in the Duke Echocardiography Laboratory Database (DELD) who underwent primary prevention ICD implantation (EF $\leq 35\%$) without cardiac resynchronization therapy (CRT) at Duke University from 2006–2013 and had a baseline LVEF within 6 months of the ICD procedure and a follow-up LVEF 1–3 years after ICD implantation. The DELD is a comprehensive prospectively recorded echocardiography database that includes all clinical echocardiograms that have been performed within the Duke University Health System since January 1, 1995.⁽⁹⁾ The study was approved by the Duke University Institutional Review Board.

We identified primary prevention ICD implantation procedures (single and dual chamber devices) through institutional records that were created for the purposes of reporting ICD procedures to the National Cardiovascular Data Registry (NCDR). Our electrophysiology group reports 100% of all adult ICD implantations to the NCDR, and therefore this institutional record represents a comprehensive list of ICD procedures during the study period. Data reported to the NCDR from our institution are first recorded by a physician or mid-level practitioner and reviewed by dedicated staff to ensure data completeness and accuracy. These records were subsequently cross matched with LVEF assessments obtained via echocardiography, LV angiography, and cardiac magnetic resonance imaging. Patients with a baseline LVEF within 6 months of the ICD procedure and a follow-up LVEF 1–3 years after ICD implantation were selected for further analysis. Patients with an LVEF > 35% had normal or near normal LVEFs and were implanted with primary prevention ICDs due to hypertrophic cardiomyopathy, inherited arrhythmias syndromes, or cardiac sarcoidosis, and were excluded from this study. Since this study employed a 3-year landmark view, patients were required to be alive without incident heart transplantation or implantation of a LVAD at the end of the 3-year landmark period.

ICD Programming

Although ICD therapy zones were not standardized, ICDs were typically programmed with one zone with VF detection beginning at 188bpm until publication of Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT),(10) when VF detection was routinely increased to 200bpm. Monitor only zones were typically programmed beginning at 150bpm.

Outcomes

The co-primary endpoints for our study included a composite endpoint of time to (1) LVAD implantation, cardiac transplant, or death, and (2) incident appropriate ICD therapy [including both anti-tachycardia pacing (ATP) and shock therapy]. Appropriate ICD therapies were determined by the treating electrophysiologist and were defined as therapies delivered for treatment of ventricular tachycardia or ventricular fibrillation. A key secondary endpoint was incident appropriate ICD shock.

All-cause mortality was determined from vital status in DELD and the Duke Database for Cardiovascular Disease, which include information from the Social Security Death Index, the National Death Index, patient surveys, and electronic inpatient hospital files. LVAD and cardiac transplantation were determined based on a billing record query using the Duke Enterprise Data Unified Content Explorer.(11) Incident ICD therapies were determined by chart review of clinically guided device interrogations, which are typically performed quarterly or more frequently based on clinical changes.

Longitudinal LVEF Assessment

We performed a 3-year landmark analysis to compare the prognostic value of baseline and follow-up LVEF. Baseline LVEF was defined as an LVEF obtained 6 months prior to ICD implantation. If multiple LVEFs were available, we prioritized echocardiography (followed by magnetic resonance imaging and LV angiography) to maximize the likelihood that the

baseline vs. follow-up LVEF comparison are performed using the same imaging modality. A follow-up LVEF 1–3 years after ICD implantation was used for the landmark view; if multiple qualifying LVEFs were available, the LVEF closest to the 3-year mark was carried forward and considered the “follow-up” LVEF for all analyses. Change in LVEF was assessed using (1) a 40% absolute threshold to assess prognostic significance of improvement beyond the 35% threshold and (2) a 10% absolute change in LVEF as smaller changes could be attributed to measurement error.

Statistical Analysis

The baseline characteristics of the overall study population, before and after stratification based on the follow-up LVEF classifications, were described using means with standard deviations for continuous variables and proportions for categorical variables. A comparison of baseline characteristics by follow-up LVEF classification group was performed using the appropriate t-test or non-parametric Kruskal-Wallis and Chi-squared tests for continuous and categorical variables, respectively.

Event rates for the incidence of the composite endpoint (LVAD, transplant, and death), appropriate ICD therapy, and appropriate ICD shock, were generated using the Kaplan-Meier method. The event rates for incident LVAD implantation were assessed using the cumulative incidence function, accounting for death and transplantation as competing risks. The event rates for incident heart transplantation were assessed using the cumulative incidence function, accounting for death as a competing risk.

Cox proportional hazard models were employed to assess unadjusted and adjusted associations between selected variables and outcomes. For time to event modeling for the composite endpoint (LVAD, transplant, or death), we included age, follow-up LVEF, and appropriate ICD therapies during the landmark period. For time to ICD therapy modeling, we included baseline LVEF, a follow-up LVEF variable, and appropriate ICD therapy during the landmark period. Due to the relatively small number of subjects and corresponding events with a pre-implantation LVEF<20%, we re-set LVEF values <20% to 20% to satisfy the linearity assumptions for the ICD therapy endpoints. We additionally performed sensitivity analyses handling the follow-up LVEF as a continuous variable.

A p-value of <0.05 was considered statistically significant for all tests. Analyses were performed using SAS (Version 9.4, SAS institute, Cary, NC).

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Results

Cohort Derivation

A total of 1,745 dual or single chamber primary prevention ICD procedures were performed between 2006 and 2015 at Duke University Hospital. After excluding patients with: prior ICD procedures (n=343); no baseline LVEF assessment at Duke within 6 months of index procedure (n=243); a pre-implantation LVEF >35% (n=192); death or loss to follow-up within 3 years of ICD implantation (n=454); and LVAD or cardiac transplant within 3 years of ICD implantation (n=32), a total of 481 patients remained (Figure 1). Of these patients, 41% (n=195) had a follow-up LVEF assessment between 1 and 3 years after the index procedure and were included for analysis. Compared with study patients, ICD recipients without a follow-up EF were more likely to have non-ischemic cardiomyopathy and be treated with warfarin and a statin, and less likely to have a history of diabetes, coronary artery disease, revascularization, or myocardial infarction (Supplemental Table 1).

Baseline Characteristics

At the time of the index procedure, patients had an average age of 59.5 ± 13.0 years, a severely reduced LVEF ($26 \pm 7\%$), and most had symptomatic HF (19.0% NYHA class I, 59.5% NYHA class II, 21% NYHA class III). Patients were more frequently male (73%) and predominantly white (62.7%) or black (34.7%). Fifty-three percent of patients had ischemic cardiomyopathy, 26.7% had diabetes, 69.2% had hypertension, 27.2% had atrial fibrillation, and 29.7% had an estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/m}^2$. Use of evidence based HF medications was common (95.9% angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, 76.9% beta-blocker use) and diuretics were used in approximately 2/3 of patients. See Table 1 for a summary of baseline characteristics. Of the 188 patients with data on baseline ICD programming parameters, 80.9% (n=152) had a single treatment zone, 17.6% (n=33) had two treatment zones, and 1.6% (n=3) had three treatment zones.

LVEF Change and ICD Therapies During the Landmark Period

At follow-up echocardiography [median 824 days (interquartile range 619–954) after index ICD procedure], the average LVEF increased from $26.0 \pm 6.9\%$ to $30.1 \pm 10.2\%$. Fifty patients (25.6%) had a 10% absolute LVEF improvement and forty-four patients (22.6%) had an LVEF improvement to 40%. Table 2 depicts differences in baseline characteristics among patients who did and did not have LVEF improvement based on the two study definitions. Compared with patients without 10% absolute LVEF improvement, patients with 10% absolute LVEF improvement were more likely to have non-ischemic cardiomyopathy (66.0% vs. 45.4%, $p=0.012$) and accordingly were less likely to have a prior myocardial infarction (24.0% vs. 47.6%, $p=0.004$). Compared with patients with a follow-up LVEF $< 40\%$, patients with a follow-up LVEF 40% had a shorter PR interval ($170 \pm 52 \text{ ms}$ vs. $183 \pm 46 \text{ ms}$, $p=0.038$) and slightly higher baseline LVEF (28.0 ± 6.7 vs. 25.5 ± 6.9 , $p=0.025$). At baseline, there were no differences in LV dimensions, moderate to severe mitral or tricuspid regurgitation, or moderate to severe right ventricular systolic dysfunction among patients with or without eventual LVEF improvement (Supplemental Table 2). Patients with LVEF improvement (by both definitions) demonstrated smaller LV dimensions at follow-up

compared to patients without LVEF improvement. Moderate or severe RV dysfunction was less common at follow-up among patients with LVEF improvement. Within the first 3 years of the index ICD procedure, 18% of patients had an appropriate ICD therapy.

Long Term LVAD, Transplant, or Death by Follow-up LVEF Classification

During a median follow-up of 1079(IQR 579–1712) days after the landmark date, 42(21.5%) patients met the endpoint of LVAD, transplant, or death(8 LVADs, 6 transplants, 33 deaths). Table 3 depicts the 1, 3, and 5 year cumulative incidences of the composite endpoint(LVAD, transplant, or death) and all-cause mortality by follow-up LVEF classifications.

There was no significant association between a 10% absolute LVEF improvement and the composite endpoint in unadjusted (HR 1.08, CI 0.56–2.07, $p = 0.82$;Figure 2a) or adjusted models (HR 1.07, CI 0.53–2.15, $p=0.85$;Table 4). Similarly, there was no association between a follow-up LVEF of 40% and the composite endpoint in unadjusted (HR 0.59, CI 0.26–1.32, $p=0.20$;Figure 2b) or adjusted models (HR 0.60, CI 0.26–1.37, $p = 0.23$;Table 4). In a sensitivity analysis, there was no association between the follow-up LVEF modeled as a continuous variable and the composite endpoint (HR 0.98, CI 0.94–1.01, $p=0.14$;Supplemental Table 3). Across all models assessing the composite endpoint, the only significant association with increased risk of LVAD, transplant, or death, was increasing age.

Long Term ICD Therapy by Follow-up LVEF Classification

During a median follow-up of 977 (IQR 490–1561) days after the landmark date, 34 patients (17.4%) received an appropriate ICD therapy (27 patients with appropriate shocks). Table 3 depicts the 1, 3, and 5 year cumulative incidences of appropriate ICD therapy and appropriate ICD shock by follow-up LVEF classifications.

A 10% absolute LVEF improvement was associated with a significantly lower risk of appropriate ICD therapy in both unadjusted (HR 0.27, CI 0.09–0.76, $p=0.01$;Figure 3a) and adjusted models (HR 0.18, CI 0.06–0.53, $p=0.002$;Table 5). Similarly, a follow-up LVEF of 40% was associated with a significantly lower risk of appropriate ICD therapy in both unadjusted (HR 0.25, CI 0.08–0.81, $p=0.02$;Figure 3b) and adjusted models (HR 0.26, CI 0.08–0.87, $p=0.03$;Table 5). Patients who received one or more appropriate ICD therapies during the landmark period were not at a significantly increased risk of appropriate ICD therapy during long term follow-up in either adjusted model.

A significant relationship between baseline LVEF and long term ICD therapies was observed in all time to event models, even after adjustment for follow-up LVEF; these findings were consistent regardless of whether follow-up LVEF was modeled as a categorical(Table 5) or a continuous variable(Supplemental Table 3). Results were similar when assessing the association between baseline and follow-up LVEF and appropriate ICD shocks (i.e. excluding appropriate ATP) (see Supplemental Table 4 and Supplemental Figure 1).

Discussion

Our study sought to define the comparative prognostic utility of baseline versus long-term follow-up LVEF among primary prevention ICD patients. It provides several clinically

relevant findings. First, neither baseline nor follow-up LVEF were found to have significant relationships with risk of LVAD, transplant or death. Second, baseline and follow-up LVEF were associated with appropriate ICD therapies. Third, although LVEF improvement is associated with a significantly lower probability of having a ventricular arrhythmia during long-term follow-up, the cumulative risk of ventricular arrhythmias appears clinically significant over time. Finally, appropriate ICD therapies during the initial 3 years of ICD implantation were not independently associated with subsequent ICD therapies.

Given that the LVEF is a measure of LV function, it is intriguing that neither baseline nor follow-up LVEF were significant predictors of a composite of LVAD, transplant, or death in our study. Several recent studies have demonstrated LVEF improvement after ICD implantation is associated with improved survival,(12–14) although data are conflicting.(15) A recently published meta-analysis assessing the association between LVEF improvement to >35% and ICD therapies and all-cause mortality demonstrated LVEF improvement was associated with a lower rate of ICD therapy and death.(16) Interestingly, the association between LVEF improvement and mortality was not significant among the subset of primary prevention ICD patients *without* cardiac resynchronization therapy. Notably, there appeared to be significant publication bias with underreporting of studies where LVEF improvement was *not* significantly associated with outcomes, based on funnel plot assessment.(16)

There are many potential explanations for why LVEF does not have a strong relationship with all-cause mortality in ICD patients, particularly compared with CRT therapy patients. It is possible that the effect size of LVEF improvement is relatively small, making it difficult to detect a statistically significant difference except with large sample sizes. The unreliability of the LVEF assessment (high intra- and inter-reader variability) may be an important factor, although this problem would be expected to impact CRT and non-CRT patients equally. Overall, the LVEF may simply be a poor estimate of systolic function. Other measures, like stroke volume, cardiac output, and global longitudinal strain, may be complimentary or superior measures of systolic performance. Additionally, LVEF does not reflect diastolic function. Differential risk for non-cardiac death across various studies (and among CRT vs. ICD only patients) could very reasonably modulate the extent to which EF assessment can predict all-cause mortality. Finally, it is interesting to consider that LVEF improvement in ICD only patients may be more transient compared to CRT patients, rendering LVEF improvement a less reliable predictor of long term all-cause mortality. An explanatory hypothesis is that CRT may be more effective than the ICD in leading to sustained improvements in cardiac function change compared to optimal medical therapy.

Consistent with most other studies on the topic, our study identified LVEF improvement during follow-up to be significantly associated with a lower rate of appropriate ICD therapies.(16) Additionally, among patients with LVEF improvement, the risk for ventricular arrhythmias accumulates over time, reaching a clinically significant incidence over just a few years (>10% cumulative incidence of appropriate therapies by 5 years using either LVEF improvement definition). The current study makes an important contribution to the literature by identifying that baseline and follow-up LVEF are *both* independently associated with appropriate ICD therapy. This key finding suggests that the pre-implantation LVEF includes important information about the myocardial substrate than cannot be gleaned

through follow-up echocardiography alone. Specifically, it is likely that a lower pre-implant LVEF often indicates increased myocardial scar, reflecting a larger quantity of a potentially arrhythmogenic substrate that would persist even if the LVEF improves. Our findings suggest that, although follow-up LVEF assessment can be an important tool for risk stratification in ICD patients, it should be considered in the context of the pre-implant LVEF.

It is notable that, in our study, appropriate ICD therapies during the landmark period were not associated with long-term appropriate ICD therapy (ATP or shocks) or appropriate shocks in either unadjusted or adjusted analyses. Although the poor negative predictive value of no prior ICD therapies has been well established, early ICD therapies are typically predictive of later ICD therapies.^(17–19) The lack of independent association between early ICD therapies and late ICD therapies in our study may reflect aggressive management of risk factors after a first ICD therapy, statistical under powering, or changes in ICD programming strategies (longer delays with increased detection intervals) during the course of the study. The use of a landmark view, which necessitated excluding patients who died within 3 years of ICD implant, may have selected for healthier patients in whom early ICD therapies did not carry a negative prognosis. Regardless of the explanation, our study emphasizes the important observation that the presence or absence of an early tachyarrhythmia should not be used as a sole factor when predicting risk for long-term ventricular arrhythmias.

Clinical Implications

Our study has several important clinical implications. First, baseline and follow-up LVEF were observed to have significant relationships with risk for long term ventricular arrhythmias. Thus, patients with a very low pre-implantation LVEF may remain at increased risk for ventricular arrhythmias, even in the presence of significant LVEF improvement after ICD implantation. Therefore, pre-implant LVEF may be a useful tool for assessing likelihood of ongoing ICD benefit for patients with battery depletion or ICD system malfunction or infection. Second, although LVEF improvement is associated with a significantly lower probability of having a ventricular arrhythmia requiring ICD therapy during long-term follow-up, the cumulative risk of ventricular arrhythmias, even in this “low risk” group, may favor ongoing ICD therapy in most instances. Third, the presence or absence of an early ICD therapy was not associated with long-term risk for a ventricular arrhythmia (and by extension, likelihood of ICD benefit).

Limitations

This study has several important limitations. The retrospective nature of study makes it prone to several types of bias, and the single center nature limits generalizability. Since our hospital is a tertiary care center, the patients in this study may be higher than average risk, limiting generalizability to lower risk patients and those at non-tertiary care centers. Our study focused on primary prevention ICD patients who were implanted due to a severely reduced LVEF (< 35%) and therefore may not be generalizable to patients with normal or less depressed LVEFs who underwent primary prevention ICD implantation due to hypertrophic cardiomyopathy, infiltrative cardiomyopathy, or an inherited arrhythmia syndrome. Repeat LVEF assessment was not standardized after ICD implantation and was

sometimes obtained due to a change in clinical status, potentially leading to bias. Although our study demonstrates an association between long term LVEF improvement and appropriate ICD therapies, we are unable to determine whether the time course of LVEF improvement is associated with outcomes. LVEF assessments were performed clinically and not via a dedicated core laboratory. Although ICD therapy zones were not standardized, devices were typically programmed with one zone with VF detection beginning at 188bpm until the publication of MADIT-RIT,(10) when VF detection was routinely increased to 200bpm. Monitor only zones were typically programmed beginning at 150bpm. ICD therapies were classified based on the clinical interpretation and not through blinded core lab adjudication. We do not have comprehensive data on coronary revascularization during follow-up and this could be an important driver of the relationship between LVEF and outcomes among patients with a history of coronary artery disease. Right ventricular pacing burden, an important determinant of LVEF, was not available for the majority of the patients in this study. Our study size was relatively small and given the relatively small number of patients with EF normalization, we could not perform an analysis of this important subgroup. Finally, we do not have data on inappropriate ICD therapies.

Conclusions

Among primary prevention ICD recipients, both baseline and follow-up LVEF were independently associated with long-term risk for appropriate ICD therapy, but they were not associated with increased risk of LVAD, transplant, or death. Although follow-up LVEF assessment can be an important tool for risk stratification of ventricular arrhythmias in ICD patients, it should be used in conjunction with the pre-implantation LVEF, as both measures have independent predictive value.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Among primary prevention ICD patients, baseline and follow-up LVEF were associated with long-term risk for appropriate ICD therapy, but not LVAD or transplant free survival.
- Early ICD therapies were not associated with long-term risk for ventricular arrhythmias.
- Among patients with LVEF improvement by either study definition, the risk for ventricular arrhythmias accumulates over time, reaching a clinically significant incidence over time (>10% cumulative incidence 5 years)

Figure 1.
Consort diagram depicting inclusion and exclusion criteria.

Figure 2.

The rates of LVAD, transplant, or death are depicted using the Kaplan-Meier plots with stratification by EF recovery groups: **(a)** an absolute EF improvement of 10% vs. not and **(b)** an absolute follow-up EF of $\geq 40\%$ vs. $< 40\%$. Unadjusted and adjusted associations between EF recovery group and outcomes were tested using Cox proportional hazards models.

Figure 3.

The rates of appropriate ICD therapy are depicted using the Kaplan-Meier plots with stratification by EF recovery groups: (a) an absolute EF improvement of 10% vs. not and (b) an absolute follow-up EF of 40% vs. <40%. Unadjusted and adjusted associations between EF recovery group and outcomes were tested using Cox proportional hazards models.

Table 1

Baseline characteristics of the overall study population

Characteristic (n=195).	Mean or Proportion
Age (years)	59.5(13.0)
Female	54/195(27.7%)
Race	
White (non-Hispanic)	121/193(62.7%)
Black (non-Hispanic)	67/193(34.7%)
Hispanic	3/193(1.6%)
Other	2/193(1.0%)
PR Interval	180.3(47.0)
QRS Duration (ms)	110.9(24.5)
Intraventricular Conduction	
LBBB	17/17(100.0%)
Non-LBBB	37/37(100.0%)
Paced	4/4(100.0%)
QRS Duration < 120ms	140/140(100.0%)
Non-Ischemic Cardiomyopathy	99/195(50.8%)
Ischemic Heart Disease	103/195(52.8%)
Atrial Fibrillation/Atrial Flutter	53/195(27.2%)
Ventricular Tachycardia	32/195(16.4%)
NYHA Class	
I	37/195(19.0%)
II	116/195(59.5%)
III	41/195(21.0%)
IV	1/195(0.5%)
Previous PCI	51/195(26.2%)
Previous CABG	47/195(24.1%)
Diabetes	52/195(26.7%)
Previous myocardial infarction	81/195(41.5%)
Chronic Lung Disease	34/195(17.4%)
Cerebrovascular Disease	22/195(11.3%)
Hypertension	135/195(69.2%)
HF Duration	
No	20/195(10.3%)
3 months	24/195(12.3%)
3 to 9 months	93/195(47.7%)
>9 months	58/195(29.7%)
eGFR (mL/min/1.73m ²)	
<15	2/195(1.0%)

Characteristic (n=195).	Mean or Proportion
15–29	8/195(4.1%)
30–59	48/195(24.6%)
>60	137/195(70.3%)
Pre-ICD LVEF %	26.0(6.9)
Post-ICD LVEF %	30.1(10.2)
Dialysis	6/195(3.1%)
BUN	
20	130/195(66.7%)
20–40	54/195(27.7%)
>40	11/195(5.6%)
Sodium Level	
135	25/195(12.8%)
135–145	170/195(87.2%)
ACE inhibitor or ARB	187/195(95.9%)
Amiodarone	19/195(9.7%)
Hydralazine	25/195(12.8%)
Aspirin	183/195(93.8%)
Beta-blocker	150/195(76.9%)
Warfarin	39/195(20.0%)
Diuretic	132/195(67.7%)
Long acting nitrate	68/195(34.9%)
Statin	179/195(91.8%)

ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, BUN=blood urea nitrogen, CABG=coronary artery bypass grafting, HF=heart failure, GFR=glomerular filtration rate, ICD=implantable cardioverter defibrillator, LBBB=left bundle branch block, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, PCI=percutaneous coronary intervention

Table 2
A comparison of baseline characteristics among patients when stratified by the follow-up LVEF.

Characteristic	Improved LVEF (10%) (N=50)	Stable or Worsened LVEF (N=145)	P-value	LVEF 40% (N=44)	LVEF <40% (N=151)	P-value
Age (years)	57.3(12.8)	60.3(13.0)	0.160	60.5(13.2)	59.2(13.0)	0.553
Female	17/50(34.0%)	37/145(25.5%)	0.248	16/44(36.4%)	38/151(25.2%)	0.144
Race			0.432			0.135
White (non-Hispanic)	27/48(56.3%)	94/145(64.8%)		24/43(55.8%)	97/150(64.7%)	
Black (non-Hispanic)	19/48(39.6%)	48/145(33.1%)		16/43(37.2%)	51/150(34.0%)	
Hispanic	1/48(2.1%)	2/145(1.4%)		2/43(4.7%)	1/150(0.7%)	
Other	1/48(2.1%)	1/145(0.7%)		1/43(2.3%)	1/150(0.7%)	
PR Interval	174.7(50.1)	182.0(46.1)	0.166	170.2(51.6)	182.8(45.7)	0.038
QRS Duration (ms)	110.6(25.6)	111.0(24.2)	0.757	113.3(27.9)	110.2(23.5)	0.732
Intraventricular Conduction						
LBBB	6/50(12.0%)	11/145(7.6%)	0.385	5/5(100.0%)	12/12(100.0%)	
Non-LBBB	8/50(16.0%)	29/145(20.0%)	0.534	8/8(100.0%)	29/29(100.0%)	
Paced	1/50(2.0%)	3/145(2.1%)	1.000	2/2(100.0%)	2/2(100.0%)	
QRS Duration<120ms	38/50(76.0%)	118/145(81.4%)	0.412	31/31(100.0%)	109/109(100.0%)	
Non-Ischemic	33/50(66.0%)	66/145(45.5%)	0.012	24/44(54.5%)	75/151(49.7%)	0.569
Ischemic Heart Disease Cardiomyopathy	17/50(34.0%)	86/145(59.3%)	0.002	22/44(50.0%)	81/151(53.6%)	0.670
Atrial Fibrillation/Atrial	17/50(34.0%)	36/145(24.8%)	0.209	16/44(36.4%)	37/151(24.5%)	0.120
Flutter						
Ventricular Tachycardia	9/50(18.0%)	23/145(15.9%)	0.725	9/44(20.5%)	23/151(15.2%)	0.410
NYHA Class			0.065			0.594
I	11/50(22.0%)	26/145(17.9%)		10/44(22.7%)	27/151(17.9%)	
II	23/50(46.0%)	93/145(64.1%)		23/44(52.3%)	93/151(61.6%)	
III	16/50(32.0%)	25/145(17.2%)		11/44(25.0%)	30/151(19.9%)	
IV	0/50(0.0%)	1/145(0.7%)		0/44(0.0%)	1/151(0.7%)	
Previous PCI	9/50(18.0%)	42/145(29.0%)	0.128	12/44(27.3%)	39/151(25.8%)	0.848
Previous CABG	7/50(14.0%)	40/145(27.6%)	0.053	10/44(22.7%)	37/151(24.5%)	0.808
Diabetes	14/50(28.0%)	38/145(26.2%)	0.805	10/44(22.7%)	42/151(27.8%)	0.502

Characteristic	Improved LVEF (10%) (N=50)	Stable or Worsened LVEF (N=145)	P-value	LVEF 40% (N=44)	LVEF <40% (N=151)	P-value
Previous MI	12/50(24.0%)	69/145(47.6%)	0.004	17/44(38.6%)	64/151(42.4%)	0.657
Chronic Lung Disease	10/50(20.0%)	24/145(16.6%)	0.579	6/44(13.6%)	28/151(18.5%)	0.450
Cerebrovascular Disease	6/50(12.0%)	16/145(11.0%)	0.852	6/44(13.6%)	16/151(10.6%)	0.591
Hypertension	32/50(64.0%)	103/145(71.0%)	0.353	26/44(59.1%)	109/151(72.2%)	0.098
HF Duration			0.880			0.615
No	4/50(8.0%)	16/145(11.0%)		4/44(9.1%)	16/151(10.6%)	
3 months	6/50(12.0%)	18/145(12.4%)		3/44(6.8%)	21/151(13.9%)	
3 to 9 months	26/50(52.0%)	67/145(46.2%)		23/44(52.3%)	70/151(46.4%)	
>9 months	14/50(28.0%)	44/145(30.3%)		14/44(31.8%)	44/151(29.1%)	
eGFR (mL/min/1.73m ²)			0.338			0.131
<15	0/50(0.0%)	2/145(1.4%)		0/44(0.0%)	2/151(1.3%)	
15–29	2/50(4.0%)	6/145(4.1%)		0/44(0.0%)	8/151(5.3%)	
30–59	8/50(16.0%)	40/145(27.6%)		7/44(15.9%)	41/151(27.2%)	
>60	40/50(80.0%)	97/145(66.9%)		37/44(84.1%)	100/151(66.2%)	
Pre-ICD LVEF %	24.4(6.7)	26.6(6.9)	0.056	28.0(6.7)	25.5(6.9)	0.025
Post-ICD LVEF %	42.0(7.9)	26.0(7.3)	<.001	44.9(5.0)	25.8(6.6)	<.001
Dialysis	3/50(6.0%)	3/145(2.1%)	0.177	3/44(6.8%)	3/151(2.0%)	0.130
BUN			0.111			0.172
20	37/50(74.0%)	93/145(64.1%)		32/44(72.7%)	98/151(64.9%)	
20–40	13/50(26.0%)	41/145(28.3%)		12/44(27.3%)	42/151(27.8%)	
>40	0/50(0.0%)	11/145(7.6%)		0/44(0.0%)	11/151(7.3%)	
Sodium Level			0.435			0.854
135	8/50(16.0%)	17/145(11.7%)		6/44(13.6%)	19/151(12.6%)	
135–145	42/50(84.0%)	128/145(88.3%)		38/44(86.4%)	132/151(87.4%)	
ACE inhibitor or ARB	48/50(96.0%)	139/145(95.9%)	1.000	41/44(93.2%)	146/151(96.7%)	0.383
Amiodarone	6/50(12.0%)	13/145(9.0%)	0.582	6/44(13.6%)	13/151(8.6%)	0.385
Hydralazine	6/50(12.0%)	19/145(13.1%)	0.841	3/44(6.8%)	22/151(14.6%)	0.176
Aspirin	48/50(96.0%)	135/145(93.1%)	0.734	41/44(93.2%)	142/151(94.0%)	0.735
Beta-blocker	36/50(72.0%)	114/145(78.6%)	0.338	31/44(70.5%)	119/151(78.8%)	0.247

Characteristic	Improved LVEF (10%) (N=50)	Stable or Worsened LVEF (N=145)	P-value	LVEF 40% (N=44)	LVEF <40% (N=151)	P-value
Warfarin	9/50(18.0%)	30/145(20.7%)	0.682	9/44(20.5%)	30/151(19.9%)	0.932
Diuretic	34/50(68.0%)	98/145(67.6%)	0.957	25/44(56.8%)	107/151(70.9%)	0.080
Long acting nitrate	18/50(36.0%)	50/145(34.5%)	0.846	14/44(31.8%)	54/151(35.8%)	0.629
Statin	44/50(88.0%)	135/145(93.1%)	0.248	39/44(88.6%)	140/151(92.7%)	0.364

ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, BUN=blood urea nitrogen, CABG=coronary artery bypass grafting, HF=heart failure, GFR=glomerular filtration rate, ICD=implantable cardioverter defibrillator, LBBB=left bundle branch block, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, PCI=percutaneous coronary intervention

Table 3

Cumulative incidence of study endpoints by follow-up LVEF classification

	Improved LVEF (10%)* (N=50)		Stable or Worsened LVEF* (N=145)		Follow-up LVEF 40% (N=44)		Follow-up LVEF<40% (N=151)	
	Events	Incidence, % [†]	Events	Incidence, % [†]	Events	Incidence, % [†]	Events	Incidence, % [†]
Death without censoring								
1 Year	1	2.0(0.2–9.3)	6	4.4(1.8–8.7)	1	2.3(0.2–10.5)	6	4.2(1.7–8.4)
3 Years	7	16.2(7.0–28.9)	19	16.8(10.5–24.5)	4	11.5(3.5–24.8)	22	18.2(11.8–25.7)
5 Years	10	25.8(12.9–40.8)	23	23.6(15.0–33.3)	7	23.8(9.9–41.0)	26	24.4(16.1–33.7)
LVAD, Transplant, or Death								
1 Year	1	2.0 (0.2–9.3)	11	7.8(4.1–13.0)	1	2.3(0.2–10.5)	11	7.5(4.0–12.5)
3 Years	8	18.5(8.5–31.5)	25	21.5(14.3–29.6)	4	11.5(3.5–24.8)	29	23.4(16.2–31.4)
5 Years	13	34.2(19.1–49.9)	29	27.5(18.7–37.0)	7	23.8(9.9–41.0)	35	31.3(22.3–40.6)
Appropriate Therapy[‡]								
1 Year	1	2.3(0.2–10.7)	12	10.6(5.8–17.1)	1	2.7(0.2–12.3)	12	10.0(5.5–16.2)
3 Years	1	2.3(0.2–10.7)	26	28.6(19.3–38.7)	1	2.7(0.2–12.3)	26	26.7(18.0–36.1)
5 Years	4	16.3(4.4–34.7)	30	38.1(25.6–50.5)	3	14.0(2.9–33.5)	31	37.3(25.3–49.4)
Appropriate Shock[‡]								
1 Year	1	2.3(0.2–10.7)	8	7.1(3.3–12.8)	1	2.7(0.2–12.3)	8	6.7(3.1–12.2)
3 Years	1	2.3(0.2–10.7)	19	21.1(13.0–30.4)	1	2.7(0.2–12.3)	19	19.6(12.1–28.4)
5 Years	4	16.3(4.4–34.7)	23	30.7(19.0–43.1)	3	14.0(2.9–33.5)	24	30.4(19.1–42.4)

* Improved EF is defined by a 10% absolute EF improvement. All other patients were classified as stable or worsened

[†] Cumulative incidence with 95% confidence intervals[‡] After the 3 year landmark date

Table 4

Multivariable models relating follow-up LVEF and cardiac transplant, LVAD, or death

Follow-up LVEF model	10% Absolute LVEF Improvement [*]			LVEF 40% at Follow-up [†]		
	HR	CI	P-value	HR	CI	P-value
Age	1.04	1.01–1.07	0.006	1.04	1.02–1.07	0.003
Baseline LVEF	0.97	0.92–1.01	0.15	0.97	0.92–1.01	0.15
Follow-up LVEF variable	1.07	0.53–2.15	0.85	0.60	0.26–1.37	0.23
ICD therapy during landmark period	0.84	0.36–1.94	0.67	0.86	0.38–1.98	0.73

^{*} Improved LVEF is defined by a 10% absolute EF improvement. All other patients (reference) were classified as stable or worsened.

[†] Patients with follow-up LVEF<40% constituted the reference group.

Table 5

Multivariable models relating follow-up LVEF and appropriate ICD therapy

Follow-up LVEF model	10% Absolute LVEF Improvement [*]			LVEF 40% at Follow-up [†]		
	HR	CI	P-value	HR	CI	P-value
Baseline LVEF	0.87	0.81–0.93	0.0001	0.89	0.83–0.96	0.001
Follow-up LVEF variable	0.18	0.06–0.53	0.002	0.26	0.08–0.87	0.03
ICD therapy during landmark period	1.14	0.48–2.69	0.77	0.96	0.41–2.25	0.92

^{*} Improved LVEF is defined by a 10% absolute EF improvement. All other patients (reference) were classified as stable or worsened.

[†] Patients with follow-up LVEF<40% constituted the reference group.