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Appropriateness of Primary Prevention Implantable Cardioverter Defibrillators at Time of Generator Replacement: Are Indications Still Met?

Running title: Appropriateness of ICD Generator Replacement

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ABSTRACT
OBJECTIVES: We sought to determine how often patients with primary prevention ICDs meet guideline-derived indications at time of generator replacement.
BACKGROUND: Professional societies have developed guideline criteria for the appropriate implantation of an ICD for the primary prevention of SCD. It is unknown whether patients continue to meet criteria when their devices need replacement for battery depletion.
METHODS: We performed a retrospective chart review of patients undergoing replacement of primary prevention ICDs at two tertiary VA Medical Centers. Indications for continued ICD therapy at time of generator replacement included LVEF $\leq$ 35% or receipt of appropriate device therapy.
RESULTS: In our cohort of 231 patients, 59 subjects (26%) no longer met guideline-driven indications for an ICD at time of generator replacement. An additional 79 patients (34%) had not received any appropriate ICD therapies and had not undergone reassessment of their LVEF. Patients with an initial LVEF of 30-35% were less likely to meet indications for ICD therapy at time of replacement (OR 0.52, 95% CI 0.30-0.88; p=0.01). Patients without ICD indications subsequently received appropriate ICD therapies at a significantly lower rate than patients who did (2.8% vs. 10.7% annually, $p < .001$). If ICD generator explants were performed instead of replacements in the patients without ICD indications, the cost savings would be $1.6 million.
CONCLUSIONS: Approximately 25% of patients who receive primary prevention ICDs may no longer meet guideline indications for ICD use at time of generator replacement, and these patients receive subsequent ICD therapies at a significantly lower rate.

Key words: Implantable Cardioverter-Defibrillator, Sudden Cardiac Death, ICD Generator Replacement

Selected Abbreviations
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
SCD = sudden cardiac death
ICM = ischemic cardiomyopathy
NICM = nonischemic cardiomyopathy
CRT (D or P) = cardiac resynchronization therapy with (-D) or without (-P) defibrillator

INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) reduce mortality in patients with reduced left ventricular function in the absence of previous sustained ventricular arrhythmias [1-3], a treatment strategy referred to as primary prevention. Based on the data from several randomized clinical trials, the American College of Cardiology (ACC) / American Heart Association (AHA) / Heart Rhythm Society (HRS) as well as the Centers for Medicare & Medicaid Services (CMS) have developed specific guideline criteria which patients are required to fulfill in order to receive ICDs for the primary prevention of sudden cardiac death (SCD) [4]. These guideline criteria do not distinguish between patients receiving initial devices and those undergoing generator replacement for battery depletion. However, following initial ICD implantation, the clinical characteristics of patients may change. In particular, many patients who receive primary prevention ICDs may experience improvement or recovery of the left ventricular ejection fraction (LVEF) [5,6], and therefore, no longer meet indications for a primary prevention ICD at the time of generator replacement.

It is possible that patients who experience improvement or recovery of LVEF may have no benefit from continued ICD therapy. Furthermore, multiple studies have shown that device replacement is associated with significant morbidity and even mortality [7-9]. Patients with ICDs may also experience inappropriate therapies which have been shown to have detrimental effects including progression of heart failure, psychological well-being and impaired survival [10,11]. Since approximately 30,000 replacement procedures are performed in the United States annually [12], ICD replacement also has a significant healthcare cost [13,14]. For all of these reasons, research examining the appropriateness of ICD replacement is long overdue.

In this study, we sought to determine how often guideline-derived indications for primary prevention ICD therapy are still present when patients undergo elective ICD generator replacement. Additionally, we examined how often patients who no longer have an indication for primary prevention ICD at the time of generator replacement receive ICD therapies compared to patients who meet these indications. Finally, we sought to estimate the differential costs of replacing versus potentially withholding replacement in patients who no longer meet indications for primary prevention ICD at the time of elective generator replacement.

METHODS

Study Population:

We performed a retrospective chart review of all patients who underwent ICD replacement at the Philadelphia Veterans Affairs Medical Center (PVAMC) and the VA Pittsburgh Healthcare System (VAPHS) over a period of seven years (3/2006-3/2013) to identify subjects who had an initial ICD implanted for primary prevention of SCD based on low LVEF (≤35%). Within this subgroup we further identified patients who underwent ICD replacement for battery depletion manifest by achievement of the device elective replacement indicator (ERI) or end-of-life (EOL) measure. These patients constituted our study cohort. Patients with any other indication for generator change such as lead malfunction or recall, or upgrade to dual chamber or CRT device prior to battery replacement indication were excluded. Patients undergoing their second or greater generator change, or those who were pacemaker-dependent, were also excluded. We also excluded subjects who received the original device based on Multicenter Unsustained Tachycardia Trial (MUSTT) criteria, i.e., LVEF ≤40% and inducible ventricular tachycardia or fibrillation at electrophysiologic study. Clinical records of all veteran patients are maintained in the national VA wide Computerized Patient Records System (CPRS) and we were

able to review the medical records comprehensively for all study patients. The study was approved by the PVAMC and VAPHS Institutional Review Boards.

Data collection and definitions:

Data collection included patient characteristics such as age and race, initial indication for ICD implantation, type of device implanted (cardiac resynchronization therapy with defibrillator: CRT-D, dual chamber ICD, or single chamber ICD), most recent LVEF, and presence or absence of comorbid conditions at baseline and at time of ICD replacement. Comorbid conditions included: chronic kidney disease (stage III or greater), dialysis dependence, cognitive impairment, neoplastic disease, atrial fibrillation, hypertension, diabetes and history of stroke. Pertinent medication usage (beta blockers, ace-inhibitors or angiotensin receptor blockers, and antiarrhythmic drugs) at baseline and at time of ICD replacement was reviewed. Data was also collected from device interrogation records, which included delivery of appropriate therapies (shock or anti-tachycardia pacing for ventricular arrhythmia) and inappropriate therapies (shocks or anti-tachycardia pacing for non-ventricular arrhythmia events). Conventional criteria validated in prior ICD trials [3] were used to categorize patients as having ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy (NICM).

At the time of the generator replacement, patients were classified into one of three groups: 1) ICD therapy was considered to be ***indicated*** for any patient whose LVEF was ≤35% based on assessment within 1 year of undergoing generator replacement, or if the patient had received appropriate therapy (shock or ATP) from their ICD after initial implantation regardless of the LVEF, 2) ICD therapy was considered ***not indicated*** in patients who demonstrated an improvement in their LVEF to ≥40% and had not received any appropriate therapies over the lifetime of the original device, and 3) ICD therapy was considered ***unclear*** in patients who had

not received any appropriate therapies over the lifetime of the original device and had also not had a reassessment of their LVEF within 1 year of undergoing ICD generator replacement. LVEF assessment was based on echocardiogram or nuclear imaging studies.

Cost Analysis:

Three models were considered for the cost analysis: 1) replace all ICD generators regardless of LVEF, 2) explant generators in the group of patients for whom ICD therapy was considered ***not indicated***, and 3) perform echocardiograms in the group of patients with ***unclear*** indications for ICD, assume that the percentage of patients for whom ICD therapy was not indicated would be the same in this group as in our overall cohort, and additionally explant generators in those patients whose LVEFs had improved (≥40%). Costs were estimated using Medicare physician and facility payment rates for procedures and *Current Procedural Technology* (*CPT*) codes. Total cost of ICD generator replacement (*CPT* code 33240) was estimated at $22,891 (physician cost was $379.02 and outpatient facility cost was $22,512). Total cost of ICD generator explant (*CPT* code 33241) was estimated at $1907.55 (physician cost was $224.55 and outpatient facility cost was $1,683). Total cost of an echocardiogram (*CPT* code 93306) was estimated at $580 (physician cost was $189.51 and facility cost was $390.49) [13,14].

Statistical Analysis:

The characteristics of patients at time of initial ICD implantation and ICD replacement were compared with McNemar tests for categorical variables and paired t-tests for continuous variables. Characteristics of patients who met or did not meet criteria for an ICD at time of replacement were compared using Chi square tests for categorical variables and t-tests for continuous variables. We also performed a multivariable logistic regression analysis with

selected variables with known or presumed effects on cardiac remodeling and/or risk of ICD therapy, including presence of CRT, etiology of cardiomyopathy, comorbid conditions, medication use, and LVEF at initial implantation to determine if these could predict whether patients would meet primary prevention ICD indications at time of generator change. Patients were divided into tertiles of initial LVEF (<15%, 16-29%, and 30-35%) to facilitate comparisons between groups. Continuous variables are presented as mean ± standard deviation. P value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics:

Our study cohort comprised 231 subjects. The mean time between initial implantation of ICD and generator replacement was 61 ± 11 months. Characteristics and comorbidities of patients at time of initial ICD implantation and at time of ICD replacement are compared in Table 1. Among the co-morbidities, prevalence of chronic kidney disease [51/231 (22%) versus 68/231 (29%); p<0.01], atrial fibrillation [37/231 (16%) versus 56/231 (24%); p<0.01], hypertension [170/231 (74%) versus 189/231 (82%); p<0.01], diabetes [99/231 (43%) versus 107/231 (46%); p<.01], and neoplastic disease [6/231 (3%) versus 33/231 (14%); p<0.001] was significantly greater at time of ICD generator replacement. Among the medications, only the rate of beta blocker use was significantly greater at time of ICD replacement (177/231 (77%) versus 200/231 (87%); p<0.01).

Indications and predictors of continued ICD use at generator replacement:

Of the 231 patients undergoing generator replacement, primary prevention ICD therapy was considered indicated in 93 subjects (40%), not indicated in 59 subjects (26%) and unclear in 79 subjects (34%) (Figure 1). Of the 93 patients who fulfilled guideline criteria for an ICD at

time of generator replacement, 50 patients (54%) continued to meet primary prevention indications, 35 patients (38%) had received appropriate ICD therapy in the intervening years and continued to have an LVEF of ≤ 35%, and 8 patients (8%) received appropriate ICD therapy but demonstrated improvement in LVEF to ≥40% at time of generator replacement.

Characteristics of patients who continued to meet criteria for an ICD at time of replacement versus those that no longer met criteria are compared in Table 2. Except for a significantly higher LVEF (25 ± 11% versus 49 ± 9%; $p < 0.001$), there was no other statistically significant difference between the two groups. Using a multivariable logistic regression analysis (Table 3), baseline LVEF of 30-35% (compared to LVEF of < 30%) was the only significant characteristic associated with a lower likelihood of meeting primary prevention ICD criteria at the time of generator replacement (odds ratio 0.52, 95% CI 0.3-0.88; p=0.01). Patients with ICM tended to be more likely than patients with NICM to meet criteria for ICD at time of generator replacement (odds ratio 1.89, 95% CI 0.90-3.95; p=0.09), but this did not reach statistical significance.

Subsequent ICD Therapies

The 59 subjects who no longer met indications for primary prevention ICD therapy at time of generator replacement (but still underwent the replacement) were followed up for a mean of 3.5 ± 2.0 years (median 3.1 years; total of 177 person years) after generator replacement. Over this time, 5 subjects (8%) received appropriate ICD therapies (4 received shocks for VT or VF and 1 received ATP for VT). Thus the rate of subsequent appropriate ICD therapy in these patients who no longer met primary prevention ICD indications at the time of generator replacement was 2.8% per person-year. In comparison, subjects who continued to meet primary prevention ICD indication at the time of generator replacement had a significantly higher

appropriate ICD therapy rate of 10.7% per person-year (log rank $p < .001$; Kaplan-Meier survival curves are shown in Figure 2).

Cost analysis

Using the first model described in the Methods section, the total cost of replacing all ICD generators regardless of LVEF was estimated at $5,287,821. Using the second model, the total cost of replacing ICD generators in all patients except those for whom ICD therapy was considered not indicated (and explanting generators in this group) was estimated at $4,049,797.45. Using the third model, where echocardiograms would be performed in the group of patients with unclear indications for ICD, and assuming that 26% (range: 13% to 39%) of these would be re-categorized to the group for whom ICD therapy was considered not indicated and these generators would then be explanted, the total cost was estimated at $3,654,964.55 (range: $3,839,962.95 to $3,399,310.50), translating to a cost savings of $1,632,856.45 in the latter group.

DISCUSSION

The salient findings of our study are that, 1) 26% patients receiving initial ICD implants for primary prevention in the setting of low LVEF no longer meet guideline-driven indications at the time of elective generator replacement, and 2) these patients subsequently receive appropriate ICD therapies at a significantly lower rate than patients who continued to meet primary prevention ICD indication. These observations, to the best of our knowledge, have never been previously reported.

Our study shows that a significant proportion of patients who receive their initial ICD for primary prevention based on low LVEF undergo generator replacement despite experiencing recovery of LVEF to $\geq$ 40% and not experiencing any ICD interventions in the intervening years.

Although the risk of SCD in patients who experience recovery of LVEF is unknown and may still be higher than the general population, the current guidelines for primary prevention ICD therapy are the same for patients undergoing initial implant or generator replacement. Similarly, the CMS National Coverage Determination (NCD) does not distinguish between first and subsequent implantations [15]. Two recent studies have concluded that ICD pulse generators should be replaced even if there is improvement in LVEF after initial ICD implantation [16,17]. However, both are limited by relatively small sample sizes, retrospective designs, and base their analyses on the delivery of ICD shocks, which may not be an adequate surrogate for SCD [18,19]. Furthermore, the lack of an appropriate control group precludes any possible conclusion of a mortality benefit from these studies. Our study showed that in patients who no longer fulfill primary prevention ICD therapy indications at the time of generator change, the subsequent rate of appropriate ICD therapies is significantly lower that patients who still meet these indications (2.8% versus 10.7% per person-year; log rank $p < .001$). This finding would suggest that generator replacement may not always need to be performed in this population and that the lack of distinction between initial implantation and generator replacement in existing guideline criteria for appropriate use of primary prevention ICDs may be reasonable.

We also found that one-third of patients undergoing elective replacement of devices that were originally implanted for primary prevention had not had a recent assessment of their LV function despite never having received appropriate therapy from their ICD over the lifetime of the device. Possible explanations for this may include lack of awareness on the part of health care providers that guideline criteria for primary prevention ICD need revalidation at time of generator replacement, or perception that once implanted ICD is a life-long therapy. However, in light of the findings of our study that shows significant improvement of LV function in more

than 25% of patients undergoing initial ICD implantation for primary prevention, and that these patients subsequently receive ICD therapies at a significantly lower rate, an echocardiogram at the time when the original device reaches ER indications may be beneficial. This is particularly true for patients undergoing prophylactic ICD implant in the setting of an initial LVEF of 30-35%. Reassessment of LVEF prior to ICD generator replacement may provide patients with more appropriate counseling regarding the risk-benefit profile. Recent studies have shown that patients undergoing ICD replacement may have double the risk of pocket-related infections and / or require twice as many surgical interventions for hematomas compared to those undergoing initial ICD implantation [7,8]. Furthermore, patients who undergo ICD replacement despite recovery of LVEF will continue to be at risk for inappropriate shocks which have been shown to have detrimental effects on mortality, progression of heart failure, and psychological well-being [10,11,20].

An important implication of our study pertains to the healthcare costs of generator replacement in patients who may no longer meet indications for primary prevention ICD therapy. More than 100,000 ICDs are implanted in the United States annually; of these procedures, approximately 30,000 are generator replacements [12]. In our cohort alone, the cost savings of not replacing ICD generators in patients who did not meet criteria for ICD was greater than $1.5 million. In contrast, the cost of performing echocardiograms, which are relatively simple, noninvasive, outpatient tests, for determination of LVEF in patients about to undergo ICD replacement who never received appropriate ICD therapies was less than $50,000. These cost calculations would favor an approach where every patient who receives an ICD for primary prevention and who has not received appropriate ICD therapy over the course of the original device life should undergo an echocardiogram when the battery reaches its ERI or EOL

indicator. It is also worth mentioning that although initial ICD implantations for primary prevention have been shown to be cost-effective for the numbers of lives saved [21,22], the same may not be true following generator replacement, especially among patients with improved LVEF and/or those undergoing multiple (≥2) generator replacements.

Although using LVEF alone as a predictor for arrhythmic death is flawed, population studies have shown quite clearly that patients with an LVEF of less than 30-35% have a much higher mortality, attributable in large part to SCD, than patients with an LVEF > 40% [23,24]. While these studies examined risk of mortality based on initial LVEF, our observations further add to this and suggest that LVEF improvement may impart a similar decrease in the risk of SCD. Although the annual rate of appropriate defibrillator discharge in patients with primary prevention ICDs in major trials is 5.1% [3], CRT responders who experience LVEF improvement to > 45% have an estimated 2-year risk of less than 3% for appropriate ICD therapy, and CRT responders who experience complete recovery of LVEF have a risk of SCD that is comparable to the general population [25,26]. These studies, as well as our observations, make a case for performing ICD explant instead of generator replacement in patients who experience no appropriate therapies and show significant improvement of LVEF when their devices reach ER indications. In the cases where improvement of LVEF has occurred with the original device being CRT-D, a CRT-P device could be used instead of CRT-D for replacement.

Our study found that patients with LVEF of 30-35% at time of initial ICD implantation were significantly more likely to not meet guideline driven indications for primary prevention ICD therapy at time of replacement compared to patients with LVEF ≤ 15%. Interestingly, while patients with ICM were more likely to meet guideline indications at the time of generator replacement compared to patients with NICM (22% versus 33%) this difference did not reach

statistical significance. Similarly, the type of the original device (CRT-D versus single or dual chamber ICDs) was also not a predictor of whether or not patients fulfilled guideline indications at the time of generator change. The lack of significant difference in some of these comparisons may be due to the small sample size of our study.

Limitations:

Our study has some important limitations. This was a retrospective study of male veterans that examined practice patterns at 2 medical centers, and these results may not be able to be extrapolated to the general population. Although the CPRS system comprehensively captures any care that the patients receive within the VA system and non-VA health care records can also be scanned into this system, it is possible that some veterans may have received care outside of the VA system which was not documented in CPRS and these data may have been missed. Due to the retrospective nature of the study, we were unable to provide accurate data regarding the specifics of ICD programming, which may have impacted the rate of appropriate ICD therapies. Our cost calculations were relatively simple and did not take into account the potential cost implications of pursuing incidental findings that may be unmasked in patients undergoing echocardiograms prior to generator change. Furthermore, even though this was a study of veteran patients, we used Medicare physician and facility payment rates for procedures. We used this method because VA health care does not typically generate administrative claims indicating the cost of medical care. Finally, although all patients included in this analysis met guideline derived criteria for primary prevention ICD therapy, the retrospective nature of the study prevented us from being able to determine accurately the time frame between the diagnosis of cardiomyopathy and implantation of the original device, or validate optimization of medical therapy prior to initial ICD implantation.

CONCLUSIONS

Approximately 25% of patients who receive ICDs for primary prevention may no longer meet guideline driven indications for continued ICD use when their original batteries reach elective replacement or end of life indicators. These patients may subsequently receive fewer ICD therapies than those who continue to meet indications. These findings have important implications on health care costs. Large-scale studies and / or prospective randomized trials are needed to determine the mortality benefit and cost-effectiveness of ICD replacement among patients who demonstrate improvement in LVEF following the initial implant.

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Figure legends

FIGURE 1: ICD Indications at Elective Generator Replacement – In our cohort of 231 patients, an ICD was indicated in 93 subjects (40%), not indicated in 59 subjects (26%), and indications were unclear in 79 subjects (34%).

FIGURE 2: Subsequent ICD Therapies after Elective Generator Replacement – Patients with no ICD indication at the time of generator replacement subsequently receive significantly fewer ICD therapies compared to patients with an ICD indication (2.8% vs. 10.7% per person-year, $p < .001$).

TABLE 1: Characteristics of Patients at Initial ICD Implantation and at Time of ICD Replacement

	Initial Implant N = 231	**Generator Replacement** N = 231	**p value**
Characteristics			
Age (mean ± SD, median)	65 ± 10 years 66 years	70 ± 9 years 70 years	<.01
White race	184 (80%)	-	-
Ischemic cardiomyopathy	159 (69%)	-	-
Nonischemic cardiomyopathy	72 (31%)	-	-
LVEF (mean ± SD, median)	23 ± 6% 25%	33 ± 14% 30%	<.01
CRT-D	86 (37%)	-	-
Comorbidities			
Chronic kidney disease (stage III or greater)	51 (22%)	68 (29%)	<.01
Hypertension	170 (74%)	189 (82%)	<.01
Diabetes	99 (43%)	107 (46%)	<.01
Atrial fibrillation	37 (16%)	56 (24%)	<.01
History of stroke	33 (14%)	37 (16%)	.13
Dialysis dependent	1 (<1%)	2 (1%)	.50
Neoplastic disease	6 (3%)	33 (14%)	<.01
Cognitive impairment	5 (2%)	9 (4%)	.13
Nursing facility resident	1 (<1%)	2 (1%)	.50
Medication Usage			
ACE-inhibitor or Angiotensin receptor blocker	198 (86%)	194 (84%)	.39
Beta-blocker	177 (77%)	200 (87%)	<.01

Anti-arrythmic drug	29 (13%)	37 (16%)	.10

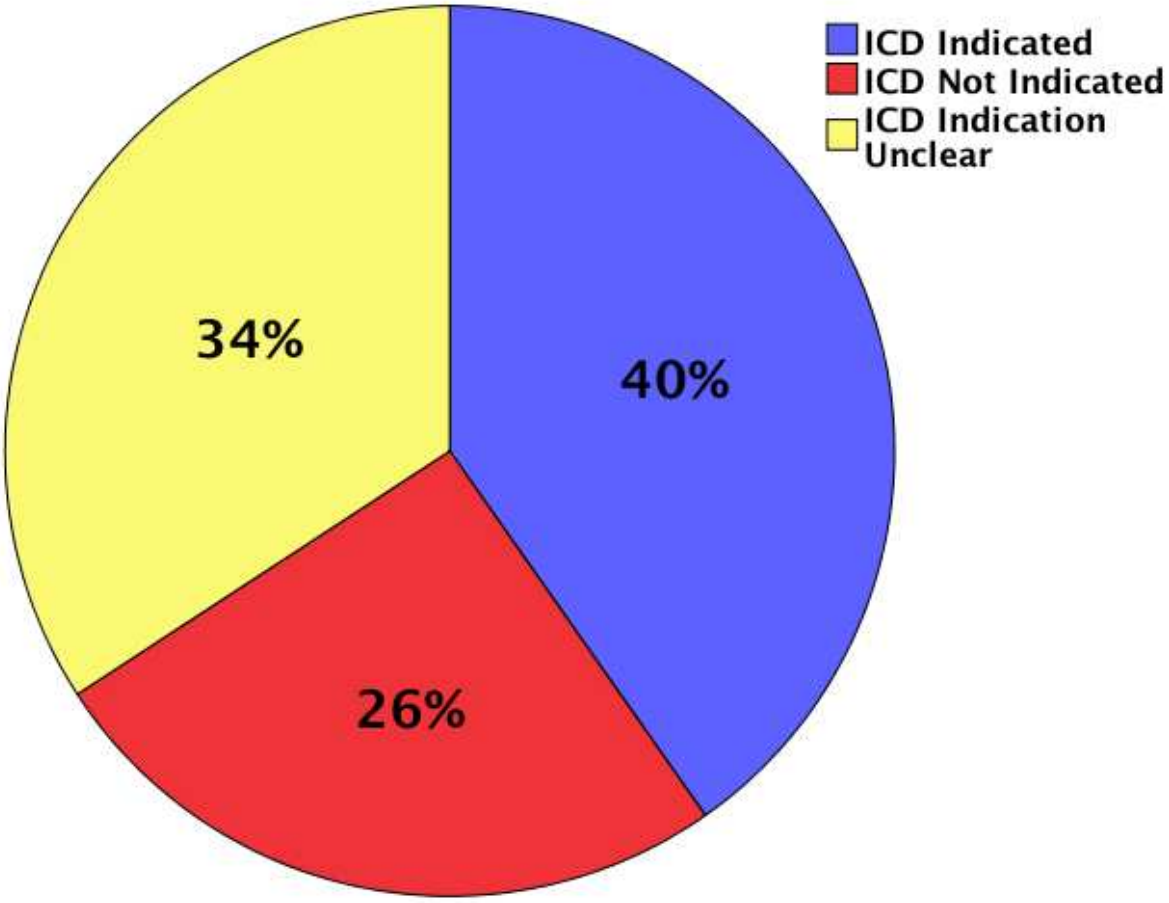
TABLE 2: Characteristics of Patients Who Met or Did Not Meet Criteria for Primary Prevention ICD at Time of Generator Replacement

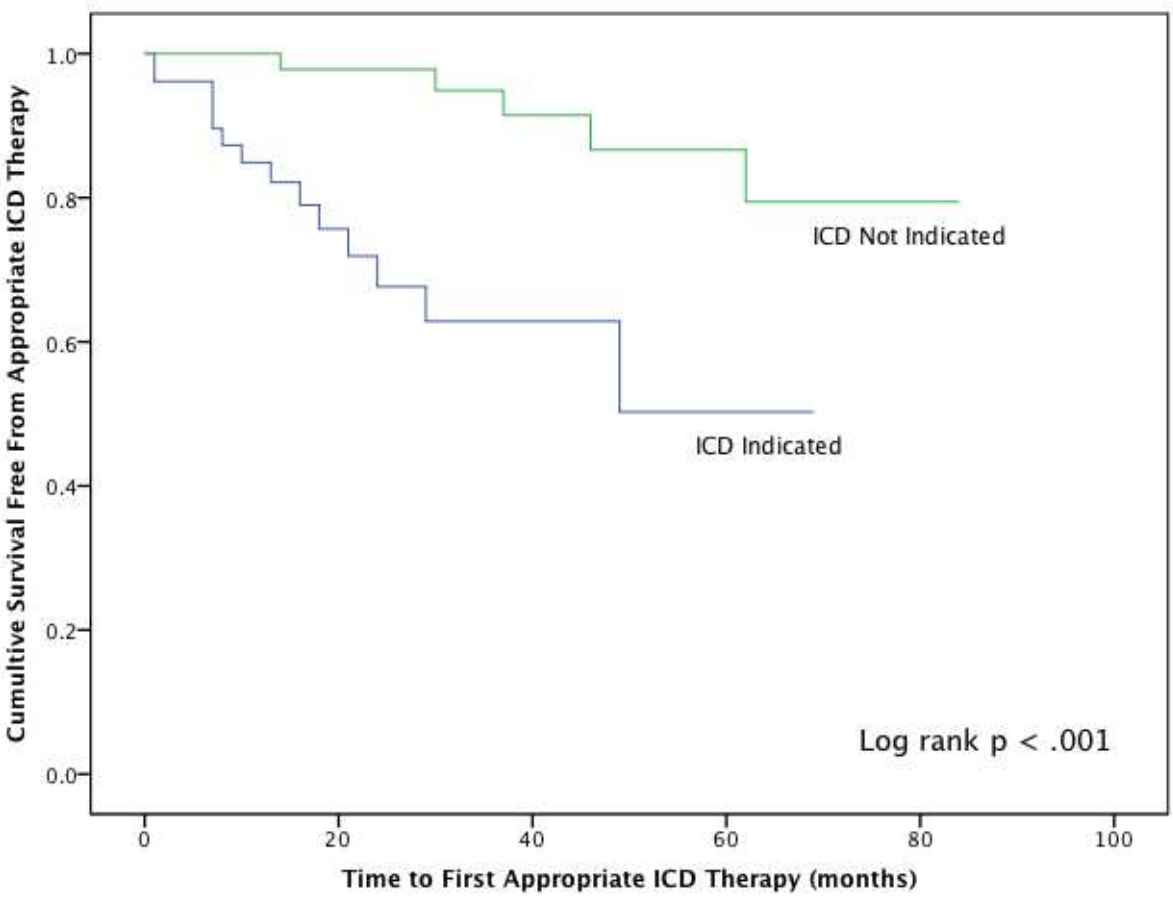
	Met guideline criteria for ICD N = 93	**Did not meet guideline criteria for ICD** N = 59	**p value**
Characteristics			
Age (mean ± SD, median)	67 ± 9 years 65 years	69 ± 9 years 67 years	0.88
White race	68 (73%)	46 (78%)	0.63
Single or dual chamber ICD	61 (66%)	41 (69%)	0.75
CRT-D	32 (34%)	18 (31%)	0.75
LVEF (mean ± SD, median)	25 ± 11% 25%	49 ± 9% 45%	<.001
Ischemic cardiomyopathy	54 (58%)	35 (59%)	0.88
Comorbidities			
Chronic kidney disease (stage III or greater)	28 (30%)	20 (34%)	0.76
Hypertension	65 (70%)	42 (71%)	0.86
Diabetes	48 (52%)	27 (46%)	0.59
Atrial fibrillation	30 (32%)	13 (22%)	0.24
History of stroke or Transient ischemic attack	17 (18%)	9 (15%)	0.79
Dialysis dependent	1 (1%)	1 (2%)	0.74
Neoplastic disease	7 (8%)	8 (14%)	0.35
Cognitive impairment	6 (6%)	0 (0%)	0.12
Nursing facility resident	3 (3%)	1 (2%)	0.96
Medication Usage			
ACE-inhibitor or Angiotensin receptor blocker	81 (87%)	46 (78%)	0.21

Beta-blocker	80 (86%)	52 (88%)	0.90
Anti-arrythmic drug	19 (20%)	8 (14%)	0.39

Table 3: Selected Predictors of Meeting Indications for an ICD at Time of Generator Replacement

	OR (95% CI)	**P value**
Age, per 10 years	0.98 (0.94-1.02)	0.30
White race vs. other	0.87 (0.39-1.90)	0.73
Initial LVEF 30-35% vs. < 30%	0.52 (0.30-.88)	0.01
Ischemic vs. Nonischemic Cardiomyopathy	1.89 (0.90-3.95)	0.09
CRT-D	0.95 (0.45-2.03)	0.90
Chronic Kidney Disease (stage III or greater)	0.90 (0.37-2.22)	0.82
Hypertension	1.00 (0.47-2.16)	0.99
Atrial Fibrillation	0.58 (0.26-1.27)	0.17
ACE-I or ARB prescribed	0.47 (0.16-1.41)	0.18
Beta Blocker prescribed	1.34 (0.49-3.89)	0.54


ICD Indicated
ICD Not Indicated
ICD Indication Unclear
40%
26%
34%


Cumultive Survival Free From Appropriate ICD Therapy
1.0
0.8
0.6
0.4
0.2
0.0
ICD Not Indicated
ICD Indicated
Log rank p < .001
0
20
40
60
80
100
Time to First Appropriate ICD Therapy (months)