HHS Public Access

Author manuscript

Circ Arrhythm Electrophysiol. Author manuscript; available in PMC 2016 August 25.

Published in final edited form as:

Circ Arrhythm Electrophysiol. 2016 March ; 9(3): e003283. doi:10.1161/CIRCEP.115.003283.

Outcomes After Implantable Cardioverter-Defibrillator Generator Replacement for Primary Prevention of Sudden Cardiac Death

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Abstract

Background—The effectiveness of implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden death in patients with an ejection fraction (EF) ≤35% and clinical heart failure is well established. However, outcomes after replacement of the ICD generator in patients with recovery of EF to >35% and no previous therapies are not well characterized.

Methods and Results—Between 2001 and 2011, generator replacement was performed at 2 tertiary medical centers in 253 patients (mean age, 68.3±12.7 years; 82% men) who had previously undergone ICD placement for primary prevention but subsequently never received appropriate ICD therapy. EF had recovered to >35% in 72 of 253 (28%) patients at generator replacement. During median (quartiles) follow-up of 3.3 (1.8–5.3) years after generator replacement, 68 of 253 (27%) experienced appropriate ICD therapy. Patients with EF ≤35% were more likely to experience ICD therapy compared with those with EF >35% (12% versus 5% per year; hazard ratio, 3.57; P=0.001). On multivariable analysis, low EF predicted appropriate ICD therapy after generator replacement (hazard ratio, 1.96 [1.35–2.87] per 10% decrement; P=0.001). Death occurred in 25% of patients 5 years after generator replacement. Mortality was similar in patients with EF ≤35% and >35% (7% versus 5% per year; hazard ratio, 1.10; P=0.68). Atrial fibrillation (3.24 [1.63–6.43]; P<0.001) and higher blood urea nitrogen (1.28 [1.14–1.45] per increase of 10 mg/dL; P<0.001) were associated with mortality.

Conclusions—Although approximately one fourth of patients with a primary prevention ICD and no previous therapy have EF >35% at the time of generator replacement, these patients continue to be at significant risk for appropriate ICD therapy (5% per year). These data may inform decisions on ICD replacement.

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Disclosures

The other authors report no conflicts.

Keywords

cardiomyopathy; death, sudden; defibrillators, implantable; follow-up studies; left ventricular ejection fraction; primary prevention; shock

The role of the implantable cardioverter-defibrillator (ICD) for primary prevention of sudden death in patients with low left ventricular ejection fraction (LVEF) caused by coronary or noncoronary heart disease is well established.[1–3] Current guidelines and appropriate use criteria for initial primary prevention ICD implantation are heavily weighted by LVEF and New York Heart Association functional class.[4,5] However, 40% of ICD-related procedures in the United States involve replacement of ICD generators because of battery depletion in pre-existing systems.[6] There are a paucity of data on the ongoing risk and outcomes of patients undergoing generator replacement.

LVEF at the time of ICD generator replacement is, on average, 4% to 5% higher than at the time of initial implant,[6] and patients may have improvement in their LVEF to >35%, the cutoff used to risk stratify the majority of patients at time of initial implant. Furthermore, 75% to 80% of primary prevention ICD recipients remain free of appropriate ICD therapy during the lifetime of their first ICD generator.[6,7] The benefit of extending ICD coverage for primary prevention in recipients who have never received an appropriate therapy after years of follow-up and who no longer meet the LVEF criterion is unclear.[8]

Patients presenting for ICD generator replacement are older and have more cardiac and noncardiac comorbidities than recipients of an initial ICD implant, significantly affecting the potential benefits of ICD replacement.[6,9] ICD replacement is associated with significant healthcare expenditure and greater risk of complications, such as infection and lead damage compared with initial implant.[10,11] Therefore, the time of ICD generator replacement affords a unique opportunity to evaluate the risks and benefits of ongoing ICD therapy, and better characterization of outcome after ICD replacement is essential to informed decision making. We hypothesized that the incidence of appropriate therapy after ICD generator replacement would be low in patients with recovery of LVEF to >35% and no history of appropriate ICD therapy at the time of replacement. To test this hypothesis, we retrospectively analyzed the prospectively collected databases from 2 tertiary referral centers in the United States.

Methods

Study Population

Data from all patients undergoing their first ICD generator replacement between January 2001 and June 2011 at the Mayo Clinic, Rochester, MN, or at Beth Israel Deaconess Medical Center, Boston, MA, were reviewed for the following inclusion criteria: (1) initial ICD implantation for primary prevention of sudden cardiac death and (2) the absence of appropriate ICD therapy for ventricular arrhythmia during the life span of the first pulse generator. Patients with an ICD implanted for sustained ventricular tachycardia/ventricular fibrillation inducible with programmed stimulation and without a history of syncope or spontaneous sustained ventricular arrhythmias were included. Exclusion criteria included patients with a cardiac resynchronization therapy device at initial implantation or upgrade to

a cardiac resynchronization therapy at the time of generator change, hypertrophic cardiomyopathy, cardiac amyloidosis, other infiltrative cardiomyopathy, primary channelopathy, or congenital heart disease. The flowchart of patients in the study is presented in Figure 1. Details of ICD-related procedures and follow-up were maintained in a prospective ICD registry at both institutions. This study was approved by the institutional review boards at both institutions.

Variables

Demographic characteristics, cardiac and noncardiac medical comorbidities, medication use, and laboratory measures, including hemoglobin, creatinine, and sodium levels, were obtained from the medical records at the time of generator replacement. LVEF obtained within 6 months before or 3 months after ICD generator replacement using echocardiography or radionuclide angiography was obtained from the review of medical records. An ongoing indication for ICD therapy was defined as LVEF ≤35%. Patients for whom the LVEF was not available at the time of generator replacement (5/253) were classified as having an ongoing indication for an ICD. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation.[12]

Outcomes

The outcomes of interest were the first appropriate ICD therapy after first generator replacement and mortality. Appropriate ICD therapy was defined as antitachycardia pacing or shock delivery for ventricular tachycardia or ventricular fibrillation. Appropriateness of ICD therapies was adjudicated by an electrophysiologist or specially trained electrophysiology nurse based on the review of stored electrograms. Follow-up for the end point of appropriate ICD therapy was censored if a patient transferred care of the ICD to a different institution. Data on mortality were obtained from the National Death Index. Follow-up for the mortality end point was terminated on the date these data were obtained.

Statistical Methods

Categorical variables are summarized as number (%) and compared using the χ^2 test. Continuous variables are summarized using mean±SD or median (quartiles) and compared using the *t* test or the rank-sum test as appropriate. The risk of overall mortality and appropriate ICD therapy were estimated using the Kaplan–Meier method. Cox proportional hazards models were used to estimate both unadjusted and adjusted hazard ratios (HRs). Covariates for adjustment were selected based on risk factors with $P<0.1$ in the unadjusted analysis, and stepwise selection was used to construct the multivariable models. A 2-tailed $P<0.05$ was considered statistically significant. All analyses were performed independently by the authors using SAS 9.3 (SAS Institute, Cary, NC).

Results

Study Population and Procedure Characteristics

Two hundred and fifty-three primary prevention ICD recipients without appropriate therapy for the life span of their first device who underwent first generator replacement were included in this analysis. The clinical characteristics of the entire cohort stratified by the

presence or the absence of LVEF recovery to >35% are presented in Table 1. The mean age was 68.3 (±12.7) years, 207 (82%) patients were men, and 194 (82%) had coronary artery disease as the cause of their systolic dysfunction. The mean interval between initial ICD implantation and generator replacement was 4.8 (±1.9) years. The generator was replaced because of battery depletion in the majority of patients (70%) with device advisory/malfunction (23.3%), upgrade (4%), and infection (2.4%) constituting the remaining indications for ICD generator replacement. Generator longevity was 5.5 (±1.6) years in patients with battery depletion. Forty-one (16%) patients also underwent revision of ≥1 leads at the time of generator replacement.

EF and Guideline-Based Indication for ICD at Generator Replacement

Mean LVEF before generator replacement in the overall cohort was 32.3±12.4%. LVEF was >35% in 72 of 253 (28%) patients (Table 1). The mean LVEF in the group with EF >35% was 47.7±9.6% compared with 26.0±6.4% in the group with LVEF ≤35% ($P<0.001$). Patients with improvement in LVEF to >35% were more likely to be women and were less likely to have New York Heart Association functional class II or III symptoms. Lower observed rates of therapy with β-blockers, angiotensin-converting enzyme inhibitors, and aldosterone receptor blockers in the group with EF>35% may be attributed to a higher rate of discontinuation of these medications after LVEF improvement. Patients with EF ≤35% were also more likely to have a history of peripheral vascular disease (19.3% versus 6.9%; $P=0.015$) and higher serum creatinine levels (1.5±1.1 versus 1.3±0.7 mg/dL; $P=0.040$). LVEF was >45% in 13% and >50% in 8% of the cohort.

Rates of Appropriate ICD Therapy After Generator Replacement

The first appropriate ICD therapy occurred after generator replacement in 68 of 253 patients during a median (quartiles) follow-up of 3.3 (1.8–5.3) years, with a rate of 7% per year. The Kaplan–Meier estimated cumulative incidence of first appropriate therapy at 1, 2, 3, and 5 years was 15%, 23%, 28%, and 36%, respectively. Patients with EF≤35% were more likely to experience an appropriate therapy than patients without (12% versus 5% per year; HR, 3.57; $P=0.001$). When stratified by LVEF, the 1-, 2-, and 3-year cumulative rates of appropriate ICD therapy for a ventricular arrhythmia increased over time in the group with EF ≤35% (20%, 30%, and 35%, respectively) with a smaller increase in those with EF >35% (7%, 9%, and 14%, respectively). Unadjusted Kaplan–Meier analysis of first appropriate therapy stratified by EF is presented in Figure 2.

ICD programming can affect the rate of appropriate therapy significantly and is summarized here. All patients had a programmed ventricular fibrillation zone at median (minimum–maximum) of 188 (170–316) beats per minute. Detection parameters in this zone were programmed as 12/16 intervals (n=36), 18/24 intervals (n=125), 24/32 intervals (n=3), 30/40 intervals (n=21), or 1 (1–2.5) s (median, minimum–maximum). A second lower zone was programmed in 72 (28%) patients at median (minimum–maximum) of 164 (150–194) beats per minute. Detection parameters in this zone were either median (minimum–maximum) of 16 (16–32) intervals or 2.5 (1.0–12.0) s. ICD programming in the groups stratified by LVEF is summarized in Table 1.

Because the duration from first ICD implantation to generator replacement was variable, the rate of postgenerator replacement ICD therapy was examined in each quartile of time from initial implantation to replacement. There was no statistically significant difference in the probability of receiving ICD therapy after generator replacement as a function of how soon a patient received a generator change after initial implant (36%, 26%, 23%, and 22% in each quartile; P=0.30).

Significant predictors of first appropriate therapy in univariate analysis included lower LVEF, higher New York Heart Association functional class, lower hemoglobin, lower estimated glomerular filtration rate, and higher blood urea nitrogen (Table 2). A trend toward statistical significance was noted for history of stroke or transient ischemic attack, QRS duration, and serum sodium. A multivariable Cox proportional hazards model of risk factors for the first appropriate ICD therapy after ICD generator replacement is presented in Table 3. After multivariable adjustment, lower LVEF (1.96 [1.35–2.87] per 10% decrease; P=0.001), lower hemoglobin (1.21 [1.03–1.42] per decrement of 1 g/dL; P=0.021), and lower serum sodium (HR, 4.31 [1.41–13.16] per decrement of 10 mEq/L; P=0.010) were independently associated with the first appropriate ICD therapy.

Mortality After Generator Replacement

Death occurred in 90 patients over a median (quartile) follow-up of 5.8 (4.2–8.1) years with a mortality rate of 5% per year. The Kaplan–Meier estimated the mortality rate at 1, 2, 3, and 5 years was 5%, 10%, 14%, and 25%, respectively. There was no statistically significant difference in mortality between patients with EF ≤35% and EF >35% (7% versus 5% per year; HR, 1.10; P=0.68). Figure 3 presents the unadjusted Kaplan–Meier analysis of death after first generator replacement stratified by LVEF at generator replacement.

Sixty patients (23.7%) died after first ICD replacement without ever experiencing an appropriate ICD therapy. The cumulative incidence of death without ICD therapy was 4%, 11%, 14%, and 23% at 1, 2, 3, and 5 years of follow-up, respectively.

Statistically significant predictors of mortality on univariate analysis included age, history of atrial fibrillation, hypertension, peripheral vascular disease, stroke or transient ischemic attack, higher New York Heart Association functional class, prolonged QRS duration, reduced estimated glomerular filtration rate, elevated blood urea nitrogen, and reduced hemoglobin (Table 4). The use of angiotensin-converting enzyme inhibitor or aldosterone receptor blocker showed a trend toward lower mortality, and lower serum sodium showed a trend toward higher mortality although these did not meet statistical significance. Statistically significant predictors of mortality in multivariable analysis using stepwise selection included a history of atrial fibrillation (HR, 3.24 [1.63–6.43]; P<0.001) and higher blood urea nitrogen (HR, 1.28 [1.14–1.45] per increment of 10 mg/dL; P<0.001; Table 5).

Discussion

This study describes mortality and appropriate ICD therapy after ICD replacement in primary prevention recipients without a previous history of appropriate ICD therapy. Twenty-eight percent of patients had an LVEF of >35% at the time of replacement, no

longer meeting the initial implant criteria. Although persistently depressed EF predicted future therapies, even in the subgroup of patients whose EF had increased to >35% at the time of generator replacement, ventricular arrhythmias requiring appropriate therapies were relatively common—5% per year. These data suggest that the risk of ventricular arrhythmia associated with LV systolic dysfunction does not completely abate even with functional recovery such that great care should be taken in discontinuing ICD therapy.

Professional society guidelines classify primary prevention ICD indications based on randomized trials of first-time ICD implantation.[4] However, clinical trials have not been performed to assess the benefit of ICD replacement after first pulse generator depletion when the device did not discharge and the cardiac condition seems to have improved. This study addressed this gap in the current evidence base.

We found that the first ever ICD therapy for ventricular arrhythmia occurred in 23% of patients within 2 years of generator replacement. This figure is comparable with rates reported after first device implantation in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) randomized trial (24% during 2 years).[13] Our cohort, however, had a higher incidence of ICD therapy than that reported in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (22% during 4 years), likely reflecting the higher percentage of patients with infarct-related cardiomyopathy (82%) in our study compared with SCD-HeFT (48%).[1,14] The incidence of appropriate ICD therapy for ventricular arrhythmia was significantly higher in patients with persistently low LVEF, with continued divergence of Kaplan–Meier curves in the years after device replacement. The risk of ventricular arrhythmias has previously been reported to remain elevated and constant for several years after initial ICD implantation in patients with low EF.[15] This persistent risk seems to extend to patients after generator replacement in our study. Moreover, observations from the MADIT II trial demonstrate that the survival benefit with ICD therapy increases with time in patients with a remote myocardial infarction, so that in patients with EF ≤30% even 15 years after an myocardial infarction, substantial benefit remains.[16]

A significant number of patients with LVEF to >35% received appropriate ICD therapy for ventricular tachyarrhythmias after generator replacement. These findings reinforce the limitations of using LVEF alone for prediction of sudden cardiac death.[17,18] Additional markers, such as inducibility of ventricular tachycardia or magnetic resonance imaging, to identify and quantify fibrosis may be useful and should be investigated. Our data support the replacement of ICD generator in patients who continue to have a reduced LVEF of ≤35% even in the absence of previous appropriate therapy. In patients who have LVEF >35%, the observed rate of appropriate therapy of 4% per year is in the range for which guidelines recommend ICD therapy for many conditions.[14,19,20] In the absence of other significant patient factors or preferences, it would, therefore, seem reasonable to proceed with generator replacement in these patients.

This study provides the most comprehensive assessment of the role of repeat EF measurement before ICD replacement to date. Similar to findings in this study, Zhang et al have reported improvement in EF to >35% in 25% of primary prevention ICD recipients with a reduced incidence of ICD therapies in patients with EF improvement.[21] Kini et al[22]

also reported a lower incidence of ICD therapy after ICD replacement in patients with improvement in EF to >40% (2.8% versus 10.7% per person-year). In contrast to these observations, LVEF improvement during follow-up was not predictive of reduced appropriate ICD therapy in primary prevention recipients in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE) and in a cohort of ICD replacement patients.[23,24] These studies are, however, limited by the absence of EF measurement in a significant proportion of patients, potentially introducing bias in the assessment of outcomes.

Patients undergoing replacement of devices that are infected or under advisory had device replacement sooner after implantation compared with those with battery depletion. These patients were included in this study because they are at particularly high risk of procedural complications and hence need a thorough discussion of the risks and benefits.[25,26] The variable period of time between implantation and replacement, however, may bias the results because of varying opportunity to have experienced an appropriate therapy or have improvement in EF. The rate of appropriate ICD therapy stratified by the quartile of time from implantation to replacement, however, was comparable in this study. Lead revision was undertaken at the time of generator replacement in 16% of the cohort. Because lead revision carries a higher risk for periprocedural complications, knowledge of the effect of LVEF on incidence of future therapies is important to the discussion of the risks and benefits of such a procedure.

Significant predictors of mortality in our study were atrial fibrillation and elevated blood urea nitrogen. LVEF, however, was not significantly associated with mortality. Although definition of the cause of death in these patients may provide insights into this finding, these data were not reliably available in this cohort. Previous studies have consistently shown the importance of cardiac diseases, such as atrial fibrillation and heart failure, and noncardiac comorbidities, including renal dysfunction, peripheral vascular disease, cerebrovascular disease, and pulmonary disease in predicting mortality after initial ICD implantation and generator replacement.[27–31] Our data reinforce the importance of considering both cardiac and noncardiac comorbidities in the decision to replace an ICD generator.

Limitations

Our study has the limitations of a retrospective observational study. The decision to replace an ICD may be biased by several clinical factors and patients who opted not to undergo ICD replacement were not included in this study. The effects of the ICD replacement procedure itself could have influenced the results although these effects would be expected to be balanced between the comparison groups in this study. Moreover, factors associated with improvement in LVEF may also directly influence the outcomes of interest. Although we adjusted for known confounders using statistical methods, there may be unknown confounders that we could not account for. The lack of a control population without ICD replacement also limits our ability to draw definitive conclusions on the mortality benefit of ICD replacement. Hence, large multicenter prospective controlled studies are needed to determine factors associated with benefit from ongoing ICD therapy. Because of the retrospective nature of the study, the time frame between the diagnosis of cardiomyopathy,

first ICD implantation, and subsequent improvement in EF could not be ascertained. The adequacy of medical therapy before ICD implantation was also not available. However, only patients who were judged to have a primary prevention indication by the implanting physician, including previous adequate medical therapy and no recent revascularization, were included. The lower rates of therapy with β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker in the group with EF >35% could have influenced the rate of appropriate therapy noted in this group. Finally, ICD therapy for ventricular arrhythmia does not equate to aborted sudden death and is influenced by device programming.[32] Device programming was noted to vary between patients and was reflective of clinical practice at the time of the study. More recently, a reduction in the rate of ICD therapy and mortality was shown with programming of higher rate zone and longer detection interval in primary prevention ICD recipients.[33] Future studies are required to evaluate the outcomes with the newer programming parameters. The occurrence of ICD therapies is, however, indicative of the continued presence of a substrate for ventricular arrhythmias despite improvement in EF.

Conclusions

Among primary prevention ICD recipients who have never received appropriate ICD therapy and require ICD generator replacement, the degree of LV systolic dysfunction modulates the risk of future ICD therapy. In patients with LVEF >35%, the risk of ventricular arrhythmia is sufficiently high (5% per year) to reasonably consider ICD replacement. LVEF was, however, not correlated with survival after generator replacement. Future prospective research on stratification of likelihood of benefit from ICD replacement should focus on identifying factors that clearly identify an increased risk of arrhythmic death out of proportion to overall mortality.

Acknowledgments

Dr Kramer was supported by a Paul Beeson Career Development Award in Aging Research (K23AG045963). Dr Buxton was supported by a research grant from Medtronic, Inc, with no personal compensation. Dr Friedman serves on advisory boards for Medtronic and Boston Scientific. He has served on a clinical trial steering committee for St. Jude Medical.

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WHAT IS KNOWN

- Implantable cardioverter-defibrillator (ICD) implantation for primary prevention of sudden cardiac death improves survival in patients with left ventricular ejection fraction (EF) ≤35%.
- Generator changes of existing ICDs now account for 40% of ICD procedures. Outcomes in patients who do not experience appropriate ICD therapy during the lifetime of the first generator and have subsequent improvement in left ventricular EF to >35% could inform the decision to replace the ICD.

WHAT THE STUDY ADDS

- At ICD generator replacement, EF was >35% in 28% of patients without previous appropriate ICD therapy.
- Patients with EF >35% continue to experience appropriate ICD therapy after generator replacement (5% per year) although at a lower rate than patients with a persistently low EF (12% per year).

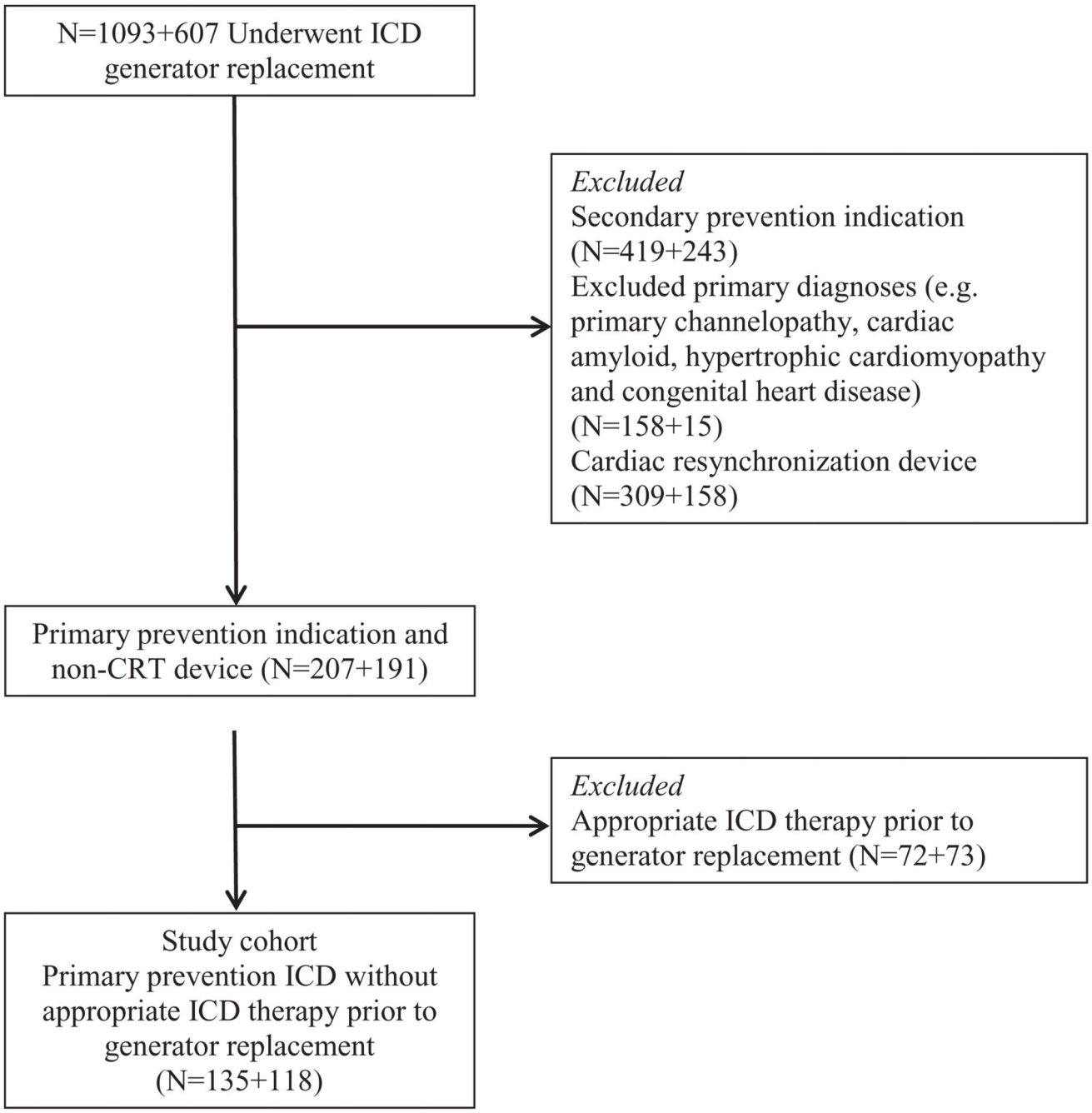

Figure 1.
Flowchart of patients in this study. CRT indicates cardiac resynchronization therapy; and ICD, implantable cardioverter-defibrillator.

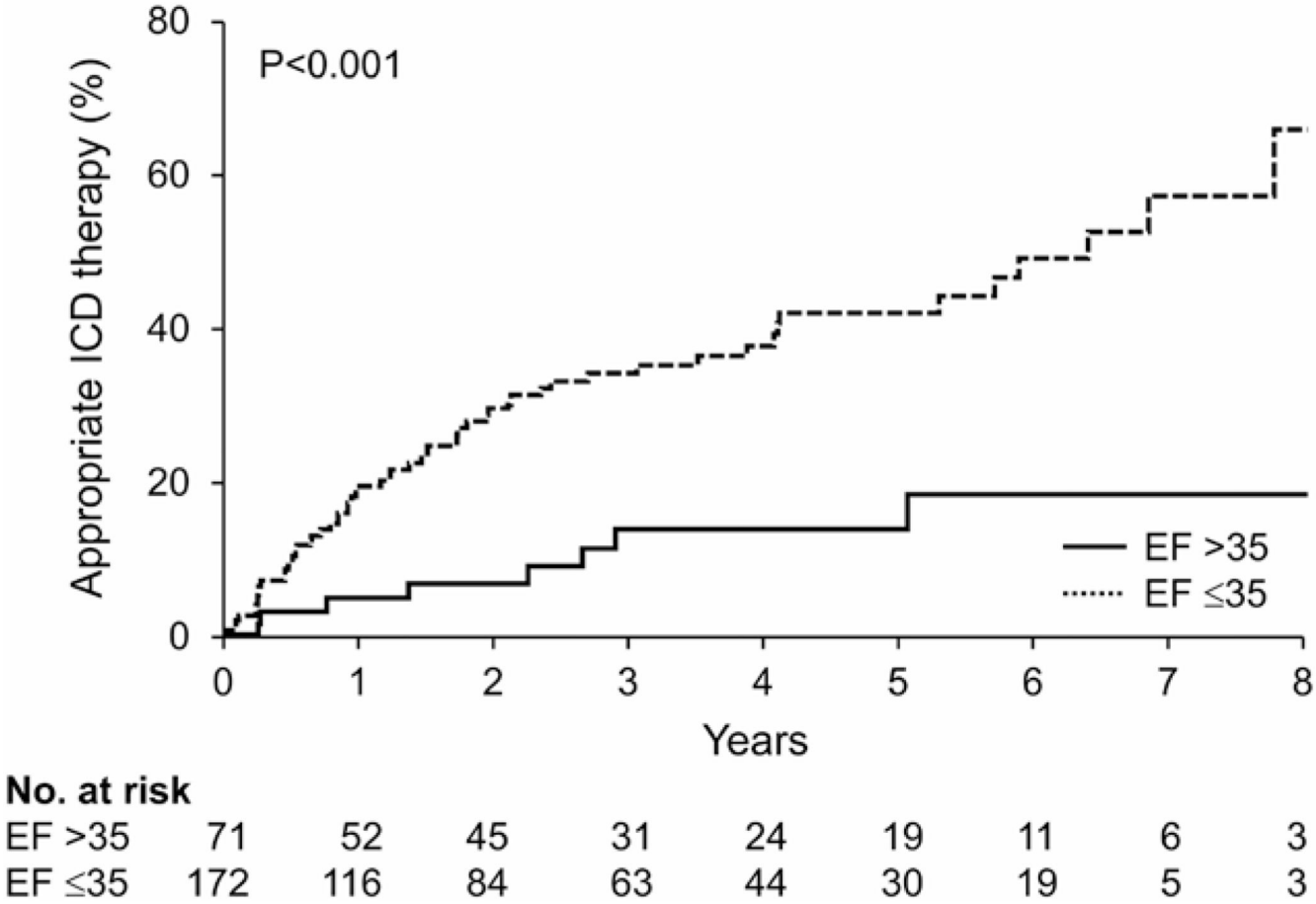

Figure 2.

Unadjusted Kaplan–Meier analysis of appropriate implantable cardioverter-defibrillator (ICD) therapy after generator replacement stratified by the presence or the absence of continuing indication for ICD therapy. EF indicates ejection fraction.

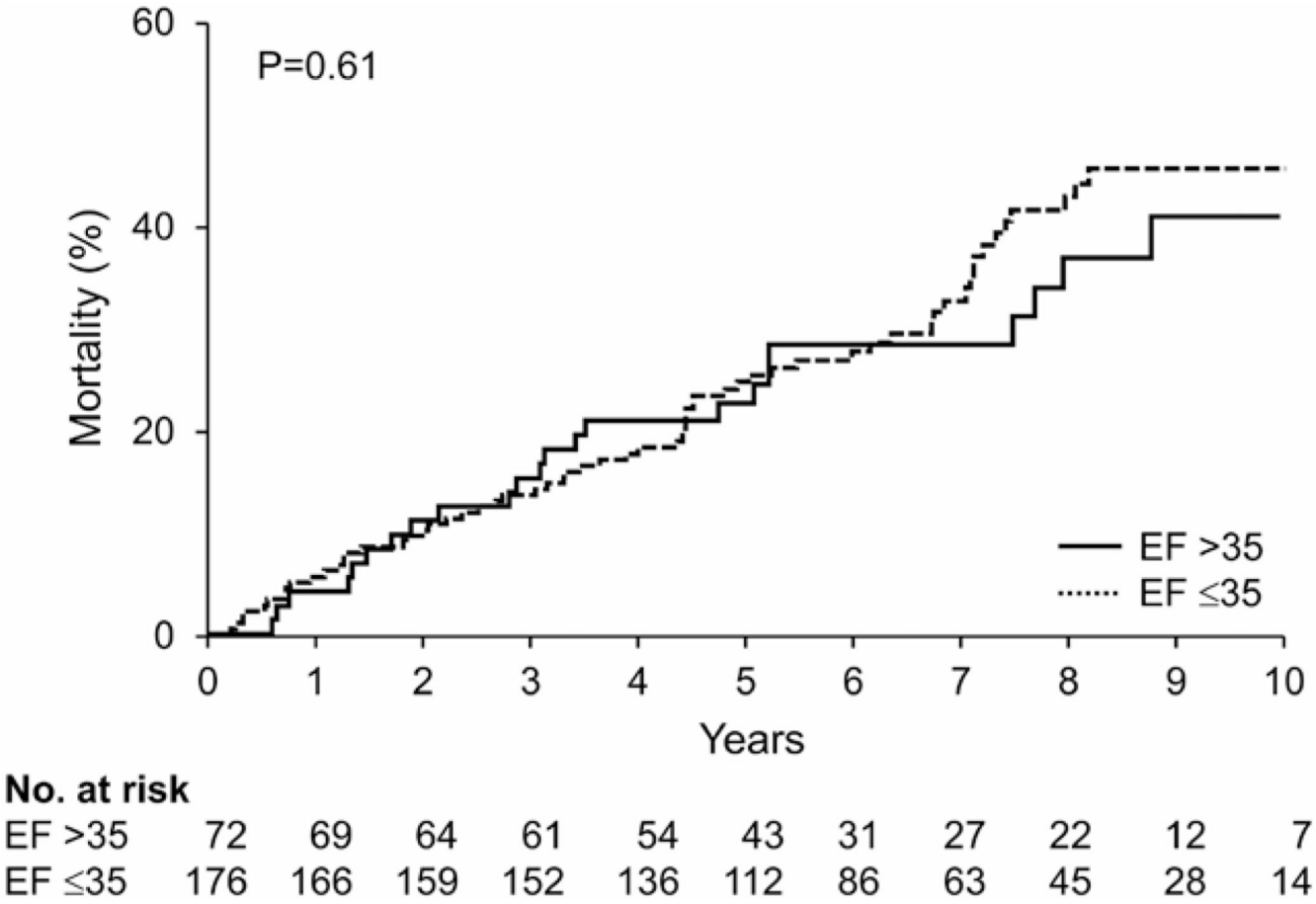

Figure 3.

Unadjusted Kaplan–Meier analysis of death after generator replacement stratified by the presence or the absence of continuing indication for implantable cardioverter-defibrillator therapy. EF indicates ejection fraction.

Table 1

Baseline Characteristics of Patients Who Underwent ICD Generator Change Stratified by EF

Clinical Characteristics*	Overall Cohort (n=253)	EF≤35% (n=181)	EF>35% (n=72)	*P* Value
Age, y	68.3 (12.7)	68.2 (12.8)	68.4 (12.6)	0.77
Male sex, n (%)	207 (81.8)	154 (85.1)	53 (73.6)	0.033
White race	231 (91.3)	166 (91.7)	65 (90.3)	0.08
Body mass index, kg/m^2	28.7 (5.7)	28.3 (5.5)	29.5 (6.2)	0.23
Underlying cardiomyopathy, n (%)				
Ischemic cardiomyopathy	194 (81.9)	141 (83.4)	55 (80.9)	0.61
Nonischemic cardiomyopathy	41 (17.3)	28 (16.6)	13 (19.1)	
Reason for ICD generator change, n (%)				
Elective replacement indicator	177 (70.0)	124 (68.5)	53 (73.6)	0.67
Device advisory or malfunction	59 (23.3)	43 (23.8)	16 (22.2)	
Device upgrade	10 (4.0)	9 (5.0)	1 (1.4)	
Infection	6 (2.4)	4 (2.2)	2 (2.8)	
Lead revision at the time of ICD generator replacement, n (%)	41 (16.2)	33 (18.2)	8 (11.1)	0.17
Left ventricular ejection fraction, n (%)	32.3 (12.4)	26.0 (6.4)	47.7 (9.6)	<0.001
NYHA class, n (%)				
Class I	100 (50.3)	65 (45.1)	35 (63.6)	0.043
Class II	70 (35.2)	54 (37.5)	16 (29.1)	
Class III	29 (14.6)	25 (17.4)	4 (7.3)	
Rhythm, n (%)				
Sinus rhythm with intrinsic conduction	134 (60.9)	95 (62.1)	39 (58.2)	0.94
Atrial fibrillation with intrinsic conduction	12 (5.5)	8 (5.2)	4 (6.0)	
Ventricular paced rhythm	60 (27.3)	40 (26.1)	20 (29.9)	
QRS duration, ms (median, interquartile range)	118 (100–158)	122 (104–156)	113 (94–162)	0.29
Medications, n (%)				
ACE inhibitor/angiotensin receptor blocker	197 (84.5)	148 (89.2)	49 (73.1)	0.002
β-Blocker	217 (93.1)	158 (95.2)	59 (88.1)	0.05
Cardiovascular history, n (%)				
Myocardial infarction	179 (70.8)	128 (70.7)	51 (70.8)	0.99
Coronary artery disease	203 (80.2)	150 (82.9)	53 (73.6)	0.10
Atrial fibrillation	115 (45.5)	81 (44.8)	34 (47.2)	0.72
Peripheral vascular disease	40 (15.8)	35 (19.3)	5 (6.9)	0.015
Stroke/transient ischemic attack	40 (15.8)	32 (17.7)	8 (11.1)	0.20
Medical comorbidities, n (%)				
Hypertension	192 (75.9)	134 (74.0)	58 (80.6)	0.27
Diabetes mellitus	88 (34.8)	65 (35.9)	23 (31.9)	0.55
Chronic lung disease	33 (13.0)	17 (9.4)	16 (22.2)	0.006
Laboratory parameters				

Clinical Characteristics*	Overall Cohort (n=253)	EF≤35% (n=181)	EF>35% (n=72)	*P* Value
Hemoglobin, g/dL	12.9 (1.9)	12.8 (2.0)	13.1 (1.8)	0.35
Serum sodium, mEq/L	139.4 (3.1)	139.3 (3.2)	139.6 (3.1)	0.57
Creatinine, mg/dL	1.4 (1.0)	1.5 (1.1)	1.3 (0.7)	0.040
Blood urea nitrogen, mg/dL	27.9 (18.1)	29.2 (19.7)	25.0 (13.8)	0.17
Estimated glomerular filtration rate, mL/min per 1.73 m^2	65.3 (27.4)	63.8 (27.1)	69.2 (28.0)	0.18
Programmed zone (median and minimum–maximum), beats per min				
VF zone	188 (170–316)	188 (170–316)	200 (185–220)	…
VTzone	164 (150–194) (n=72)	160 (150–194) (n=54)	170 (140–182) (n=18)	…

ACE indicates angiotensin-converting enzyme; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; VF, ventricular fibrillation; and VT, ventricular tachycardia.

* Data are presented as mean (SD) or n (%) except when indicated otherwise.

Table 2

Univariate Predictors of the First Appropriate Implantable Cardioverter-Defibrillator Therapy After Generator Replacement

Risk Factor	HR	95% CI	*P* Value
Left ventricular ejection fraction (per 10% decrement)	1.48	1.16–1.89	0.002
NYHA functional class (per increase in NYHA class of 1)	1.72	1.18–2.45	0.005
QRS duration (per increment of 10 ms)	1.06	0.99–1.12	0.08
Stroke or transient ischemic attack	1.78	0.99–3.21	0.055
Hemoglobin (per decrement of 1 g/dL)	1.18	1.04–1.35	0.011
Estimated glomerular filtration rate (per decrement of 10 mL/min 1.73 m^2)	1.12	1.02–1.23	0.02
Blood urea nitrogen (per increment of 10 mg/dL)	1.14	1.03–1.26	0.010
Serum sodium (per decrement of 10 mEq/L)	2.18	0.97–4.90	0.060

CI indicates confidence interval; HR, hazard ratio; and NYHA, New York Heart Association.

Table 3

Predictors of First Appropriate Implantable Cardioverter-Defibrillator Therapy After Generator Replacement in Multivariable Analysis

Risk Factor	HR	95% CI	*P* Value
Left ventricular ejection fraction (per decrement of 10%)	1.96	1.35–2.87	0.001
Serum sodium (per decrement of 10 mEq/L)	4.31	1.41–13.16	0.010
Hemoglobin (per decrement of 1 g/dL)	1.21	1.03–1.42	0.021

CI indicates confidence interval; and HR, hazard ratio.

Table 4
Univariate Predictors of Mortality After Generator Replacement

Risk Factor	HR	95% CI	*P* Value
Age (per increment of 1 y)	1.05	1.03–1.07	<0.001
Hypertension	2.58	1.37–4.84	0.003
Atrial fibrillation	2.90	1.86–4.51	<0.001
Peripheral vascular disease	1.73	1.06–2.82	0.029
Stroke or transient ischemic attack	2.26	1.39–3.65	0.001
NYHA functional class (per increase in NYHA class of 1)	1.66	1.21–2.28	0.002
QRS duration (per increment of 10 ms)	1.08	1.03–1.13	0.003
Hemoglobin (per decrement of 1 g/dL)	1.32	1.17–1.49	<0.001
Estimated glomerular filtration rate (per decrement of 10 mL/min 1.73 m^2)	1.18	1.08–1.29	<0.001
Blood urea nitrogen (per increment of 10 mg/dL)	1.23	1.13–1.34	<0.001
Serum sodium (per decrement of 10 mEq/L)	1.79	0.94–3.38	0.07
ACE inhibitor/ARB therapy	0.61	0.35–1.07	0.08

ACE/ARB indicates angiotensin-converting enzyme inhibitor/aldosterone receptor blocker; CI, confidence interval; HR, hazard ratio; and NYHA, New York Heart Association.

Table 5

Predictors of Mortality After Implantable Cardioverter-Defibrillator Generator Replacement in Multivariable Analysis

Risk Factor	HR	95% CI	*P* Value
Atrial fibrillation	3.24	1.63–6.43	<0.001
Blood urea nitrogen (per increment of 10 mg/dL)	1.28	1.14–1.45	<0.001

CI indicates confidence interval; and HR, hazard ratio.