Journal of the American Heart Association

ORIGINAL RESEARCH

Incidence of Ventricular Arrhythmias and 1-Year Predictors of Mortality in Patients Treated With Implantable Cardioverter-Defibrillator Undergoing Generator Replacement

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BACKGROUND: When implantable cardioverter defibrillator (ICD) battery is depleted most patients undergo generator replacement (GR) even in the absence of persistent ICD indication. The aim of this study was to assess the incidence of ventricular arrhythmias and the overall prognosis of patients with and without persistent ICD indication undergoing GR. Predictors of 1-year mortality were also analyzed.

METHODS AND RESULTS: Patients with structural heart disease implanted with primary prevention ICD undergoing GR were included. Patients were stratified based on the presence/absence of persistent ICD indication (left ventricular ejection fraction ≤35% at the time of GR and/or history of appropriate ICD therapies during the first generator's life). The study included 371 patients (82% male, 40% with ischemic heart disease). One third of patients (n=121) no longer met ICD indication at the time of GR. During a median follow-up of 34 months after GR patients without persistent ICD indication showed a significantly lower incidence of appropriate ICD shocks (1.9% versus 16.2%, $P<0.001$) and ICD therapies. 1-year mortality was also significantly lower in patients without persistent ICD indication (1% versus 8.3%, $P=0.009$). At multivariable analysis permanent atrial fibrillation, chronic advanced renal impairment, age >80, and persistent ICD indication were found to be significant predictors of 1-year mortality.

CONCLUSIONS: Patients without persistent ICD indication at the time of GR show a low incidence of appropriate ICD therapies after GR. Persistent ICD indication, atrial fibrillation, advanced chronic renal disease, and age >80 are significant predictors of 1-year mortality. Our findings enlighten the need of performing a comprehensive clinical reevaluation of ICD patients at the time of GR.

Key Words: arrhythmic risk stratification ■ generator replacement ■ implantable cardioverter defibrillator ■ overall prognosis

Progress in heart failure medical therapy has led to a constant decrease in the rate of sudden cardiac death in patients with reduced left ventricular ejection fraction (LVEF).[1] Nonetheless, patients with heart failure and reduced ejection fraction still remain at high risk for malignant ventricular arrhythmias and sudden cardiac death. Implantable cardioverter defibrillator (ICD) with[2,3] or without[4,5] a cardiac

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For Sources of Funding and Disclosures, see page 8.

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CLINICAL PERSPECTIVE

What Is New?

- Most patients undergo implantable cardioverter defibrillator (ICD) generator replacement even in the absence of persistent ICD indication.
- The aim of this study was to assess the incidence of ventricular arrhythmias and the overall prognosis of patients with and without persistent ICD indication undergoing generator replacement.
- During a median follow-up of 34 months patients without persistent ICD indication showed a significantly lower incidence of appropriate ICD therapies.

What Are the Clinical Implications?

- Our findings highlight the necessity of performing a complete clinical reevaluation of patients implanted with ICD at the time of generator replacement.

Nonstandard Abbreviations and Acronyms

CRT-D	cardiac resynchronization therapy defibrillator
GR	generator replacement

resynchronization therapy defibrillator (CRT-D) is an effective treatment in these patients, both for primary and secondary prevention. Current guidelines[6,7] recommend ICD therapy for primary prevention patients with LVEF ≤35%, regardless of heart failure etiology, with an expected life of more than 1 year. Because of years of optimal medical therapy and especially because of the positive effect of CRT-D, many patients show a significant improvement in LVEF after ICD implantation. Moreover, many patients reach the first generator's end of life without receiving appropriate ICD therapies. Patients with LVEF recovery and no ventricular arrhythmias during the first ICD's life may be considered without a persistent ICD indication at the time of battery depletion. Moreover, at the time of generator replacement (GR) patients are older, with a shorter life expectancy and with higher incidence of noncardiological comorbidities that affect the risk/benefit ratio of ICD therapy. However, in current clinical practice the vast majority of the patients undergo GR, despite the lack of current clinical indications. European Society of Cardiology guidelines on heart failure underline the importance of a risk of restratification at the time of GR considering that the patient's needs may have changed as compared with the time of first implantation. Nevertheless, no randomized clinical trials have ever been conducted on patients who are candidates for GR and few data from the literature can help clinicians to drive the decision whether to reimplant an ICD at the time of GR.

Trying to help in filling the gap in knowledge in this field we conducted a work to evaluate independent predictors of mortality at 1 year after GR and to analyze all-cause mortality and incidence of appropriate ICD therapies in candidates to GR stratified based on the presence/absence of persistent ICD indication.

METHODS

Type of Study and Data Collection

This is a retrospective observational single-center study based on our ICD registry enrolling all patients who underwent a GR in our center from January 1, 2010 to December 31, 2018 (n=414). For the purpose of the present analysis only patients affected by structural heart disease implanted with an ICD with primary prevention indication (N=371) were included. ICD explantations or revisions for other indications than battery depletion (hardware recall, upgrading, infections, leads failure, or any other reasons) were also excluded. This study respected the Declaration of Helsinki, and all patients provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Indication for ICD Implantation/ Replacement and Device Programming

All patients had a class I indication for first implantation according to latest European Society of Cardiology guidelines.[6] Battery status was evaluated by both scheduled in-office visits and remote monitoring. GR was scheduled when the ICD reached the elective replacement indicator in the majority of the cases or when battery longevity's estimate was <6 months. ICDs from all the main manufacturers were implanted.

Devices implanted for primary prevention were programmed with a monitor zone (≥160 bpm) and a ventricular fibrillation zone (≥188 bpm or ≥200 in young patients). Every device was programmed with long detection time for antitachycardia therapies[8] in order to reduce inappropriate or unnecessary ICD therapies. At the time of GR the new device was programmed as previously described in the majority of the cases.

Definitions

Persistent ICD indication at the time of GR was defined as a depression of LVEF (≤35%) and/or history

of appropriate ICD therapies during the first generator's life.

Two different arrhythmic end points were considered: the rate of appropriate shocks and the rate of appropriate ICD therapies, which was defined in case of antitachycardia pacing or shocks delivered for a ventricular tachycardia or ventricular fibrillation. Adjudication of an event as appropriate or inappropriate ICD therapy was made collecting ICD electrograms in our outpatient clinic and from remote monitoring system. Every event was blindly evaluated by 2 experienced electrophysiologists; a third blinded opinion was required in case of controversies.

Statistical Analysis

Categorical variables were presented as numbers and percentage and compared using χ^2 or Fisher exact test when required. Continuous variables were tested for normal distribution with Shapiro-Wilk test and then presented as mean±SD and compared with *t* test in case of normal distribution or presented as median and 25% to 75% interquartile range and compared with Mann–Whitney *U* test in case of nonnormal distribution. Kaplan–Meier curves with their log-rank test were used to investigate 1-year mortality. To investigate predictors of mortality we performed multivariable Cox proportional hazard models as follows. First, univariable hazard ratios were calculated for all the variables known to be predictors of short-term mortality based on previous literature. Second, we performed a multivariable backward stepwise Cox regression model including all the noncorrelated variables with $P \leq 0.1$ in the previous univariate analysis. In the final analysis we kept only covariates that resulted as independent predictors in the previous model. The analysis of the incidence and predictors of mortality was deliberately limited to 1-year follow-up in our study because life expectancy of more than 1 year is usually considered to decide whether to implant an ICD according to current guidelines For all comparisons, $P<0.05$ was considered to be statistically significant. Analysis were performed using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. IBM Corp., Armonk, NY).

RESULTS

General Population

The study cohort includes 371 patients who underwent elective ICD GR from 2010 to 2018. Of those, 39% had a single- or dual-chamber ICD and 61% had a CRT-D device. Across the entire cohort median age at the time of first implantation was 58 (25th–75th percentiles 49–67), whereas median age at the time of GR was 65 (25th–75th percentiles 57–73); ischemic heart disease was present in 40%, basal characteristic of the population are reported in Table 1. As expected, at the time of GR, patients were older than patients undergoing first-time implantation. Median LVEF at the time of first implantation was 28% (25th–75th percentiles 23%–35%)], whereas median LVEF at the time of GR was 34% (25th–75th percentiles 25%–45%). All patients were on optimal medical therapy at the time of GR (93% on beta blockers, 89% on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 54% on mineralcorticoid receptor antagonist). Overall 1-year mortality was 5.7%.

Table 1. Baseline Characteristics of the Study Population

Descriptive Statistics at GR	% (n), or Median (25th–75th Percentiles)
Male sex	82% (304)
Ischemic heart disease	41.8% (148)
Non-IHD	68.2% (223)
Diabetes mellitus	14.3% (53)
Permanent atrial fibrillation at GR	4.7% (17)
Atrial fibrillation (all types)	15.6% (57)
EF ≤35% at GR	62% (230)
Left ventricle EF	
At GR	34% (25–45)
At first implantation	28% (23–35)
Device type (single-/dual-chamber)	39% (144)
CRT defibrillator	61% (226)
Age ≥80 at GR	7% (25)
Active smokers	17% (63)
Glomerular filtration rate ≤30 at GR	5.2% (19)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	89% (330)
Beta blocker	93% (345)
Digoxin	8% (30)
Loop diuretics	70% (260)
Mineralcorticoid receptors antagonist	54% (200)
Sacubritil-valsartan	4% (15)
Antiaarhythmic drugs at GR	27% (100)
Age at first implant, y	58 (49–67)
Age at GR. y	65 (57–73)
Median longevity (CRT), y	5.9 (4.8–7.8)
Median longevity (no CRT), y	7.3 (6.5–9.2)
Median follow-up	34 months (18–55)
New York Heart Association class >2 at GR	76.6% 285

EF indicates ejection fraction; GR, generator replacement; and IHD, ischemic heart disease.

Persistent Versus Nonpersistent Indication to ICD

Approximately one third (32.5%) of our population no longer presented ICD indication at the time of GR, after

a long follow-up that lasted for all of the first generator's life (mean first generator's life 7±1 years); these patients had higher median LVEF and a better renal function compared with patients with persistent ICD indication at the time of GR. Table 2 summarizes the main clinical differences of patients with and without persistent ICD indication at the time of GR.

Incidence of Ventricular Arrhythmias

During a median follow-up of 34 months (25th–75th percentile 18 months–55 months) patients without persistent ICD indication after GR showed a significantly lower long-term incidence of both appropriate shock (1.9% versus 16.2%, *P*<0.001) and appropriate ICD therapies (3.8% versus 22.7%, *P*<0.001). Inappropriate ICD therapies before and after GR did not significantly differ between patients with or without persistent indication at the time of GR.

Considering only the subgroup of patients with single-chamber and dual-chamber devices, despite the small number of this group, the absence of persistent indication was associated also in this population with a significantly lower rate of both appropriate shocks (0% versus 15%, *P*=0.019) and appropriate ICD therapies (5.6% versus 25.2%, *P*=0.001) after GR.

Survival Analysis

Patients without persistent indication at the time of GR showed reduced 1-year all-cause mortality compared with patients with persistent indication (1% versus 8.3%, *P*=0.008, see Figure 1). Moreover, they also showed a markedly lower rate of hospitalization for heart failure (0% versus 20%, *P*<0.001). At multivariable analysis, age >80 years at the time of GR, permanent atrial fibrillation (AF), advanced abnormal renal impairment (defined as glomerular filtration rate <30 mL/min) and persistent indication to ICD at the time of GR were significant independent predictors of 1-year mortality at multivariable analysis (Table 3). Permanent AF maintained its independent role after forcing the variable "atrioventricular node ablation" into the multivariable model. Patients with at least 1 risk factor between age >80, advanced renal impairment,

Table 2. Differences in Baseline Characteristics and Clinical Outcome Between Patients With and Without Persistent ICD Indication at the Time of Generator Replacement

	Without Persistent ICD Indication (n=121)	Persistent ICD Indication (n=250)	*P* Value
Descriptive characteristics			
LVEF at first implant, % (IQR)	28 (25–35)	26 (20–32)	0.7
LVEF at GR, % (IQR)	48 (40–55)	30 (25–34)	<0.001
Age at first implant, y (IQR)	58 (47–66)	58 (50–67)	0.5
Age at GR, y (IQR)	64 (54–71)	65 (57–73)	0.2
Body mass index at GR, kg/m^2 (IQR)	26.2 (24–28)	26.6 (24–29)	0.9
GFR at GR, mL/min (IQR)	87.5 (63–104.5)	68.9 (48.3–92.7)	<0.001
IHD, %	25.7	46.5	<0.001
Non-IHD, %	74.3	53.5	<0.001
New York Heart Association class >2 at GR, %	33	66.7	0.068
Diabetes mellitus, %	16.5	22.4	0.3
Permanent atrial fibrillation, %	5.7	4.7	0.7
Neoplastic history, %	10.8	13.9	0.5
Appropriate shock first generator %	0	19	<0.001
Appropriate antitachycardia pacing first generator %	0	18	<0.001
Cardiac resynchronization therapy %	59.2	64	0.3
Age ≥80 at GR %	6.4	7.6	0.8
Active smokers at GR%	16.5	16.2	0.9
Glomerular filtration rate ≤30 at GR %	1	6.4	0.04
Antiarrhythmic drugs at GR, %	11.4	34.7	<0.001
Clinical outcome after GR			
Appropriate shock after GR, %	1.9	16.2	<0.001
Appropriate therapies after GR, %	3.8	22.7	<0.001
Inappropriate shocks after GR, %	1.7	1.4	0.8
Heart failure hospitalization after GR, %	0	20	<0.001
1 y all-cause mortality, %	1	8.3	0.009

GR indicates generator replacement; IHD, ischemic heart disease; IQR, interquartile range; and LVEF, left ventricle ejection fraction.

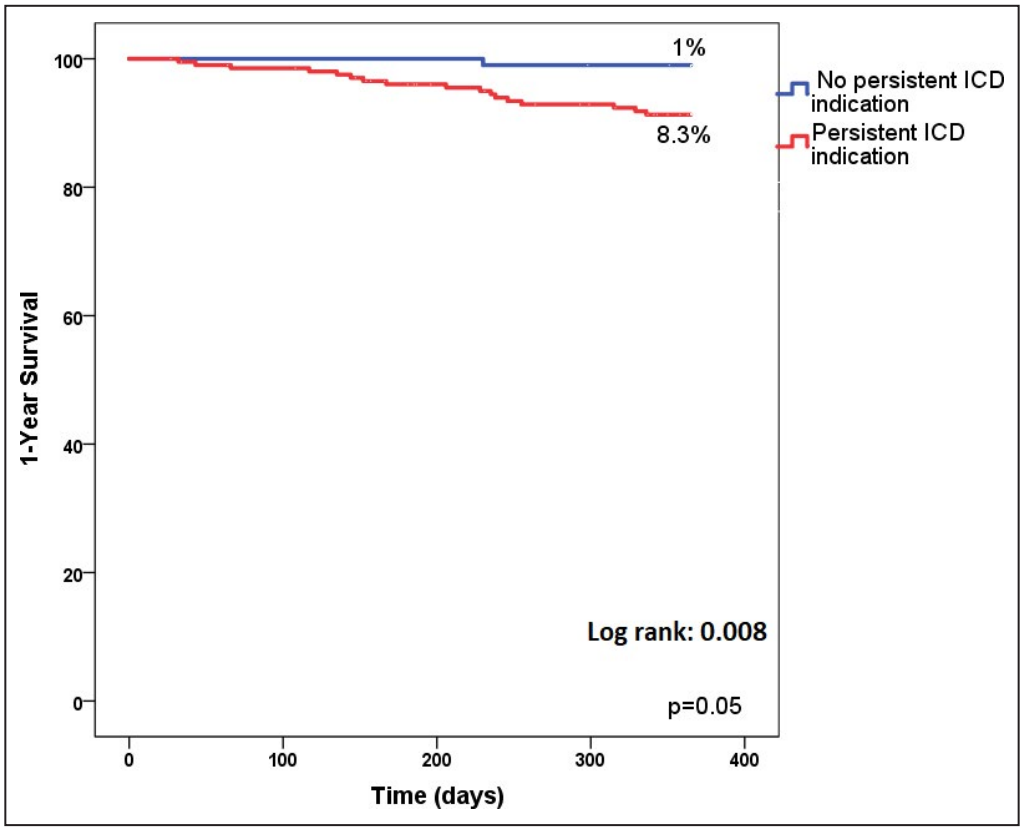

Figure 1. Kaplan–Meier's curves showing overall 1-year survival in patients with vs without persistent ICD indication at the time of generator replacement.
ICD indicates implantable cardioverter defibrillator.

and permanent AF showed a significantly higher all-cause mortality compared with patients without any of these risk factors at the time of GR (see Figure 2). Notably, patients with 1 out of 3 risk factors showed a more than 10-fold higher 1-year mortality (19.6% versus 1.4%, $P<0.001$), and patients with 2 out of 3 risk factors showed an almost 50-fold higher risk of 1-year mortality compared with patients without risk factors (50% versus 1.4%, $P<0.001$).

Furthermore, patients with at least 1 risk factor between age >80, advanced renal impairment, and permanent AF did not show a higher incidence of appropriate shock (9.8% versus 14.3%, $P=0.69$) or appropriate ICD therapies after GR compared with those without risk factors (15.7% versus 11.1%, $P=0.64$).

DISCUSSION

The main findings of the present study are the following: (1) patients without persistent ICD indication at the time of battery depletion show a very low incidence of arrhythmias and a good overall prognosis; (2) persistent ICD indication, AF, advanced renal impairment, and age >80 years are significant predictors of 1-year mortality; And (3) patients with 2 out of 3 risk factors (AF, chronic renal failure, and age >80 years) show a risk of mortality as high as 50% at 1 year.

Current guidelines on the management of patients with heart failure suggest a careful evaluation of patients at the time of GR to assess whether ICD therapy is still needed. Nevertheless, there is a paucity of studies regarding patients undergoing GR and no randomized studies on this issue. In 2012, of the more than 100 000 ICDs implanted in the United States annually, at least 25% were GRs required for depleted batteries suggesting the dimension of the problem, which will even increase in the near future.[9] In current practice most patients undergo GR even when ICD indication no longer persists. Data from registries[10,11] and meta-analysis[12,13] suggest that patients without history of appropriate ICD therapies during the first generator's life, or without persistent ICD indication at the time of GR, are at lower risk of subsequent arrhythmic events.

In agreement with previous data, our study shows that one third of patients undergoing GR no longer presents formal criteria for ICD implantation. This subgroup of patients shows an extremely low incidence of appropriate ICD therapies and a significant reduced incidence of all-cause mortality and heart failure hospitalization when compared with patients with persistent

Table 3. Univariate and Multivariate Analysis for 1-Year All-Cause Mortality Predictors

	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	*P* Value	HR (CI 95%)	*P* Value
Ischemic heart disease	1.5 (0.6–3.8)	0.3		
Nonischemic heart disease	0.5 (0.1–1.3)	0.2		
Diabetes mellitus at GR	0.8 (0.1–3.8)	0.8		
Permanent atrial fibrillation at GR	7.8 (2.1–28.6)	0.002	5.4 (1.2–24.3)	0.02
Inappropriate shock before GR	0.04 (0–181)	0.4		
Appropriate therapy before GR	2.9 (1.1–67.4)	0.02		
Persistent implantable cardioverter defibrillator indication	9.2 (1.2–69.7)	0.03	8.8 (1.1–71.4)	0.04
Age at GR >80 y	9.5 (1.6–14)	0.003	5.1 (1.3–19.3)	0.01
Active smoker at GR	0.03 (0–9)	0.2		
Glomerular filtration rate <30 at GR	6.8 (2.5–18.7)	<0.001	5.5 (1.1–26.4)	0.03
Antiarrhythmics drug at GR	2.6 (1.1–6.4)	0.03		

GR indicates generator replacement; and HR, hazard ratio.

ICD indication. The difference in the arrhythmic risk is even more remarkable in patients implanted with CRT-D devices.

These findings may be explained by the protective effect of a LVEF recovery during the first generator's life because of years of optimal medical therapy and the positive reverse remodeling effect of CRT-D. The degree of LVEF improvement is expected to be more important in recipients of CRT-D devices[14]; the paradigm "recovery of LVEF-reduced arrhythmic risk" was already proposed in a subanalysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) trial[15]: CRT responders, identified by a left ventricular end-diastolic volume reduction >25%, had a significantly lower risk of developing ventricular arrhythmias and a lower cumulative incidence of appropriate ICD therapies when compared with nonresponders. Patients without CRT-D, however, could present a LVEF improvement during the first life of the ICD as a result of a positive effect of years of optimized medical therapy. Similar findings were highlighted by the results of a DEFINITE[16] (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) Trial subanalysis: patients were divided according to LVEF changes during follow-up, and those who experienced a recovery of more than 5% of LVEF had a significantly better overall survival than those with stable or decreased left ventricular function. Therefore, beyond being the strongest predictor of arrhythmic risk in patients who are ICD naïve, LVEF seems to be still one of the main predictors of arrhythmic risk even in patients undergoing GR. According to our results and results of previous studies the need for ICD replacement in patients without ventricular arrhythmias in first ICD's life and with normal or near normal LVEF at the time of GR could be questioned.[17] This could also be the case for patients treated with cardiac resynchronization therapy (around 60% of our population) in whom a downgrade to a simpler and less expensive CRT pacemaker device could be taken into consideration.

Recent large registries[18,19] have highlighted that residual arrhythmic risk might be not trivial even in patients without persistent ICD indication at the time of GR. Indeed previous studies found an incidence of appropriate ICD therapies after GR replacement of 3% to 5%/year, which is significantly higher as compared with our experience. Nevertheless, it should be taken into account that, at variance from previous studies, ours enrolled an homogeneous population of primary prevention only patients. In addition, LVEF assessment at the time of GR was available in all included cases.

Our study adds some important new insights in the management of patients in the need for ICD replacement. In the current analysis we identified significant 1-year predictors of mortality other than persistent ICD indication at the time of GR. Indeed permanent AF, advanced chronic kidney disease, and age >80 years at the time of GR were found to be strong predictors of short-term mortality. Remarkably, 1 out of 2 patients with at least 2 of the risk predictors died at 1 year, raising the question of whether GR itself could be futile in this subgroup. The statistical associations of these predictors with subsequent mortality may find several explanations: a history of permanent AF is associated with a reduced percentage of biventricular pacing, which may lead to a reduced positive remodeling in CRT carriers but may also cause a deterioration of the already imbalanced hemodynamic status of these patients because of the loss of atrioventricular synchronism and atrial contribution to diastolic filling. Moreover, AF may also lead to inappropriate ICD shocks, which, in other studies, have been related to an increased mortality.[20] Advanced renal impairment has

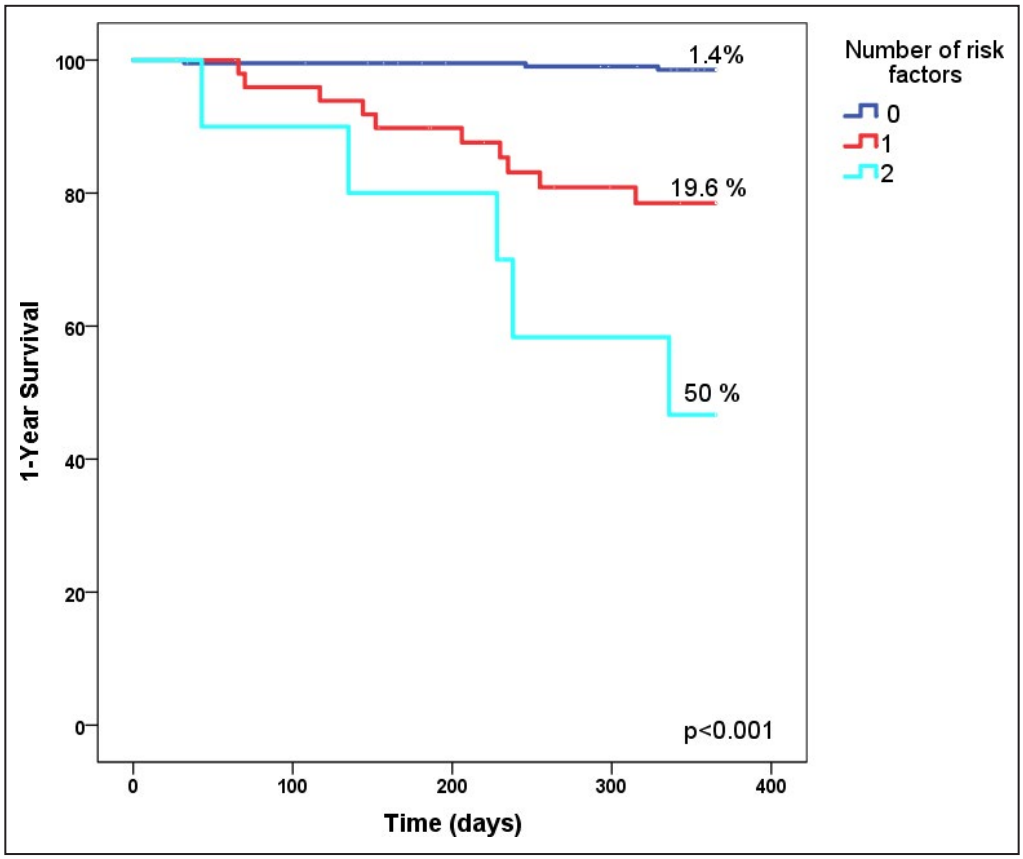

Figure 2. Kaplan–Meier's curves showing overall 1-year survival in patients with 1, 2 or without independent predictors of 1-year mortality (age >80 year, advanced chronic renal disease and AF).

already been associated in studies on ICD carriers with higher mid-long-term mortality and higher incidence of periprocedural complications during implantation.[21] The importance of considering age when assessing the risk/benefit ratio of a GR has been highlighted by studies reporting high incidence of ICD shocks during the last days of life in patients who subsequently died of nonarrhythmic death[22] Age, AF, and advanced renal impairment are also part of the well-known MADIT Risk Score,[23] an important risk score designed for patients undergoing first ICD implantation. Notably, in our cohort, patients in the highest risk group did not experience higher incidence of appropriate ICD therapies after GR indicating that in a certain subgroup of patients the competing risk of death may be unbalanced toward nonarrhythmic death.[18] Furthermore, GR, often viewed as a straightforward procedure, is associated with potential important complications; in the multicenter REPLACE registry[24] (Implantable Cardiac Pulse Generator Replacement) GR led to a 4.9% major complication rate, with an even higher event rate noted among those with CRT-D. Major complications occurring during GR are associated with an important negative prognostic impact, being linked with a more than 10-fold higher risk of short-term all-cause mortality.[25]

Summarizing our study we suggest that there are two kinds of patients who might be worth discussing whether to implant a new ICD at the time of battery depletion. Those "too healthy," without persistent ICD indication, and those "too sick" with a high risk of short-term nonarrhythmic risk of death in whom ICD might be futile. In the absence of clinical evidences, most of the patients reaching the end of first generator's life are implanted with a new generator without further investigations; we believe that our findings could help cardiologists to better identify patients who would benefit the most from a new generator.

Limitations

The major limitations of this study is that it is observational and retrospective and with a relatively small number of enrolled patients. Our data need to be validated in large prospective registries and/or randomized clinical trials. Nevertheless, a randomized clinical trial on patients undergoing ICD GR is complex and unlikely to be ever performed.[26]

A second limitation is the duration of follow-up; although we showed that patients without persistent ICD indication have a low incidence of arrhythmias at

a median follow-up of almost 3 years, we cannot rule out a potential residual more significant arrhythmic risk over a longer time period. Nonetheless, as previously suggested,[17] in all cases when ICD replacement is denied arrhythmic risk should be periodically reevaluated by means of LVEF assessment.

Considering that our analysis was retrospective, it was not possible to adjudicate the cause of death in all cases. Therefore, we could not analyze the incidence of cardiovascular mortality and estimate the competitive risk between arrhythmic death versus noncardiac death in our population. However, because the aim of our study was to assess the benefit of replacing an ICD overall mortality is more informative.

Of more, because not all patients were followed at our outpatient clinic, it was not possible to systematically record data regarding complications rates (infective complications, leads fractures, necessity for extraction) related to the first implantation and GR, thus limiting the discussion on the possible drawback of replacing an ICD.

Finally, the relative small sample size of our population prevented us to perform analysis in specific subgroups of interest such as patients who are nonischemic, non-White, and have diabetes mellitus.

CONCLUSIONS

Our study suggests that patients without a formal persistent ICD indication at the time of GR have a very low likelihood of major arrhythmic events after GR. Moreover, patients >80 years of age, with permanent AF and/or with advanced chronic kidney disease, show an extremely higher 1-year mortality, calling into question the need of replacing the ICD in this subgroup.

Our findings highlight the necessity of performing a complete clinical reevaluation of patients implanted with ICD at the time of GR.

ARTICLE INFORMATION

Received June 18, 2020; accepted November 17, 2020.

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Acknowledgments

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Sources of Funding

None.

Disclosures

Dr R. Rordorf received modest speaking fees from Abbott and Boston Scientific. The remaining authors have no disclosures to report.

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