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Persistence of ICD indication at the time of replacement in patients with initial implant for primary prevention indication: Effect on subsequent ICD therapies

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ABSTRACT

Background: Indication to implantable cardioverter defibrillator (ICD) for primary prevention of sudden death relies on left ventricular ejection fraction (LVEF). We measured the proportion of patients in whom indication to ICD persisted at the time of generator replacement (GR) and searched for predictors of appropriate therapies after GR.

Methods: We identified all consecutive patients who had received an ICD at our hospital, for LVEF $\leq 35\%$ and no previous arrhythmias or unexplained syncope. Then, we included the 166 patients who outlived their first device and underwent GR.

Results: At the time of GR (mean follow-up 59 ± 20 months), ICD indication (i.e. LVEF $\leq 35\%$ or previously treated ventricular arrhythmias) persisted in 114 (69%) patients. After GR, appropriate ICD therapies were delivered in 30 (26%) patients with persistent ICD indication and in 12 (23%) of the remaining patients ($p = 0.656$). Nonetheless, the annual rate of therapies was higher in the first group (1.08 versus 0.53 events/year; $p < 0.001$), as well as the rate of inappropriate therapies (0.03 versus 0 events/year; $p = 0.031$). The only independent predictor of appropriate ICD therapies after GR was the rate of shocks received before replacement (Hazard Ratio: 1.41; 95% confidence interval: 1.01–1.96; $p = 0.041$).

Conclusion: In heart failure with reduced LVEF, ICD indication persisted at the time of GR in 69% of patients. However, even in the absence of persistent ICD indication at GR, the risk of recurrence of arrhythmic events was not null.

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1. Introduction

Currently, the selection of candidates for implantable cardioverter defibrillator (ICD) implantation for primary prevention of sudden cardiac death relies mainly on left ventricular ejection fraction (LVEF) evaluation at the time of pre-implantation screening [1].

Previous studies have shown that a proportion of patients implanted for primary prevention of sudden death improve their

LVEF after ICD implantation [2–6], especially if treated with cardiac resynchronization therapy ICD (CRT-D).

As a substantial proportion of ICD recipients outlive their first device and must undergo generator replacement, some authors questioned the appropriateness of ICD replacement when primary prevention indication does not persist and no ventricular arrhythmias were documented during follow-up [7]. We hypothesized that patients without persistent ICD indication at device replacement could be at lower risk of ICD therapies after replacement.

We sought to determine the persistence of ICD indication at the time of generator replacement in patients who had received an ICD for primary prevention of sudden cardiac death, and to measure the rate of ICD therapies after replacement. In addition, we investigated the existence of predictors of appropriate therapies after generator

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replacement.

2. Materials and methods

The study was approved by our internal committee for Human Research. At the time of implantation, patients gave informed consent for future use of de-identified data.

2.1. Patient selection, pacemaker implantation and follow-up

We prospectively collected data about all consecutive adult patients who underwent ICD implantation from 2000 to 2015 at our hospital. For the aim of present analysis, we retrospectively evaluated patients who received ICD for primary prevention of sudden cardiac death. All patients were implanted according to the then contemporary international guidelines and underwent a trial of optimized medical therapy and revascularization before receiving an ICD. Thus, we identified patients with LVEF $\leq 35\%$ and no documentation of previous arrhythmias or unexplained syncope at the time of implantation. Of them, we included in analysis all patients who outlived their first device and underwent generator replacement. Data collection included patient characteristics and LVEF value at baseline and at replacement. LVEF was assessed by Simpson's equation using the apical four-chamber view. Data about delivery of appropriate therapies for ventricular arrhythmia were collected from device interrogation records. Spontaneous arrhythmic episodes detected by the device were validated by 2 independent electrophysiologists blinded to the patient outcome. If a consensus could not be reached, a third electrophysiologist was involved in episode review. Device implantation and replacement were performed according to standard clinical practice and optimization of ICD parameters and pharmacological treatments were based on clinical evaluation by the attending physicians. During follow-up, patients underwent standard transthoracic echocardiographic examination every 6 months and before device replacement.

We measured the proportion of patients with persistent ICD indication at the time of generator replacement. In particular, we identified those patients with LVEF $\leq 35\%$ or who received appropriate ICD therapies before replacement. Moreover, we investigated the existence of predictors of appropriate therapies after generator replacement.

2.2. Statistical analysis

Continuous data were expressed as means \pm standard deviation. Categorical data were expressed as percentages. Differences between mean data were compared by a *t*-test for Gaussian variables and by the Mann-Whitney-Wilcoxon nonparametric test for non-Gaussian variables. Differences in proportions were compared by a chi-square analysis. Event rates were summarized by constructing Kaplan–Meier curves. The log-rank test was applied to evaluate differences between trends. Cox regression was used to analyze possible predictors of appropriate ICD therapies or shocks after replacement. The rates of events were analyzed by using the Comparison of Incidence Rates (Large Sample) Test. A *P* value < 0.05 was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc.).

3. Results

3.1. Study population and baseline evaluation

From 2000 to 2015, 1130 consecutive patients underwent ICD

implantation at our hospital. Of them, 166 underwent one or more generator replacements during follow-up and had LVEF $\leq 35\%$ and no documentation of previous arrhythmias or unexplained syncope at the time of first implantation (Fig. 1). Table 1 shows baseline clinical variables at the time of first implantation.

3.2. Follow-up (from ICD implantation to first replacement)

The patients in analysis underwent generator replacement for battery depletion after a mean follow-up of 59 ± 20 months. Twenty patients previously implanted with single- or dual-chamber ICD developed CRT indications and received a CRT-D device at replacement. At the time of device removal, ICD interrogations revealed appropriate therapies for ventricular arrhythmia in 48 patients (0.74 events/year in the overall group). In particular, 28 patients had received appropriate shock therapies (0.13 events/year). Moreover, 21 patients had received inappropriate therapies (0.03 events/year) (Fig. 2).

At the time of replacement, the mean LVEF was $33 \pm 11\%$ and 64 patients showed LVEF $> 35\%$ (mean $44 \pm 7\%$ in this subgroup). In particular, 9 patients showed LVEF $> 50\%$, and 20% of patients with ICD alone (no CRT) showed a marked increase in EF (from $27 \pm 5\%$ to $43 \pm 6\%$, $p < 0.001$). We therefore identified a persistent ICD indication for prevention of sudden death in 114 (69%) patients. The clinical parameters of patients with persistent and non-persistent ICD indication are reported in Table 2. More frequently, patients with persistent ICD indication were male, had ischemic disease, and did not receive CRT-D. Persistent ICD indications were reported in 57 (60%) patients initially implanted with CRT-D devices, and in 57 (80%) patients initially implanted with single- or dual-chamber ICDs ($p = 0.005$).

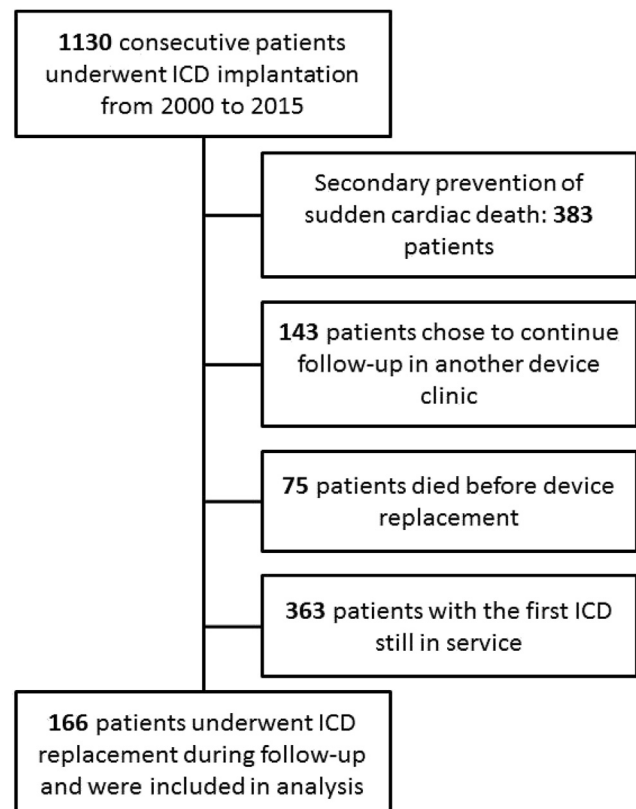


Fig. 1. Study flow diagram.

Table 1
Demographics and clinical parameters at the time of first implantation.

Baseline	N = 166
Male gender, n (%)	135 (81)
Age, years	66 ± 10
Ischemic heart disease, n (%)	90 (54)
NYHA class	
Class I, n (%)	6 (3)
Class II, n (%)	81 (49)
Class III, n (%)	76 (46)
Class IV, n (%)	3 (2)
CRT defibrillator, n (%)	95 (57)
LV ejection fraction, %	25 ± 6
History of atrial fibrillation	
Paroxysmal, n (%)	36 (22)
Persistent, n (%)	26 (16)
Permanent, n (%)	30 (18)
Class III antiarrhythmic use, n (%)	26 (16)

NYHA: New York Heart Association; LV: left ventricular.

3.3. Follow-up (after ICD replacement)

After ICD replacement, patients were followed for a mean period of 25 ± 23 months. In this second phase, appropriate therapies for ventricular arrhythmia were delivered in 42 patients (0.86 events/

year in the overall group), and 21 patients received appropriate shock therapies (0.17 events/year). Moreover, 7 patients received inappropriate therapies (0.02 events/year). In particular, appropriate therapies were delivered in 30 (26%) patients with persistent ICD indication and in 12 (23%) of the remaining patients ($p = 0.656$). Nonetheless, the annual rate of therapies was higher in the first group: 1.08 events/year versus 0.53 events/year ($p < 0.001$). Appropriate shock therapies were delivered in 14 (12%) patients with persistent ICD indication and in 7 (13%) of the remaining patients ($p = 0.832$). The annual rate of shock was comparable between groups (0.17 events/year versus 0.17 events/year; $p = 0.971$), while the rate of inappropriate therapies was higher in the first group (0.03 events/year versus 0 events/year; $p = 0.031$). In particular, appropriate ICD therapies were reported in 3 patients with LVEF >50% at replacement.

The Kaplan–Meier analysis of time from generator replacement to first appropriate therapy, stratified by persistence or non-persistence of indication to ICD, showed no differences between groups (Fig. 3).

At Cox regression analysis (Table 3), the only independent predictor of appropriate ICD therapies after replacement was the rate of shocks received before replacement (Hazard Ratio: 1.41; 95% confidence interval: 1.01–1.96; $p = 0.041$).

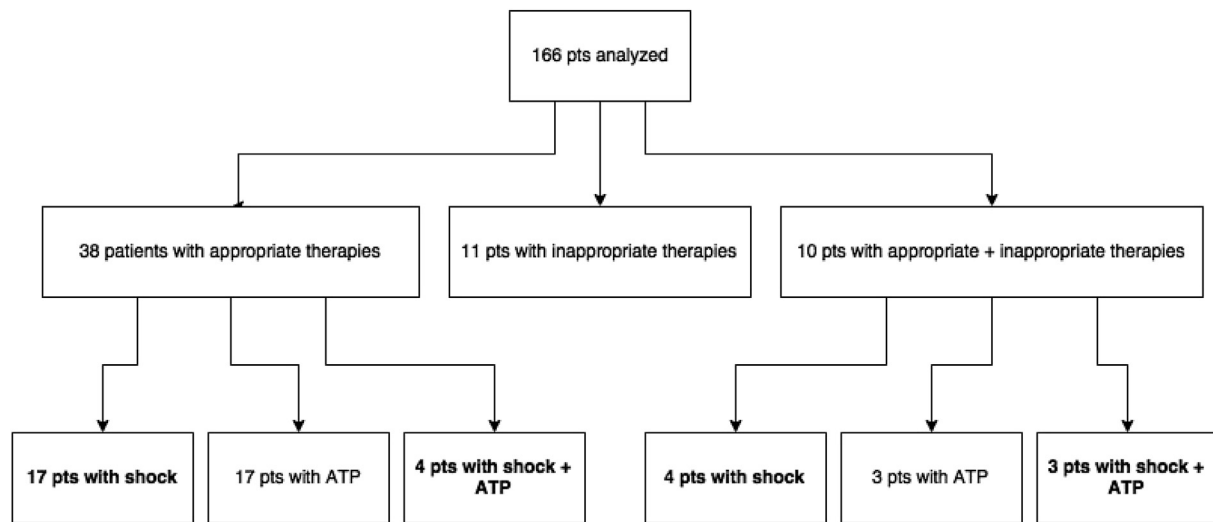


Fig. 2. Number of patients (pts) with therapies before first ICD replacement. Number of patients with at least one appropriate shock is marked in bold in different subgroups (total: 28 patients; see text for details).

Table 2
Clinical parameters and therapy at the time of first implantation and replacement.

	Persistent ICD indication (114)		Non-persistent ICD indication (52)	
	First Implantation	Replacement	First Implantation	Replacement
Male gender, n (%)	98 (86)		37 (71)*	
Age, years	67 ± 9		66 ± 11	
Ischemic heart disease, n (%)	71 (62)		19 (37)*	
NYHA class III-IV, n (%)	51 (45)	25 (22)	27 (52)	7 (13)
CRT defibrillator, n (%)	57 (50)	76 (67)	38 (73)*	39 (75)
LV ejection fraction, %	25 ± 6	28 ± 7	27 ± 5	45 ± 7*
History of atrial fibrillation				
Paroxysmal, n (%)	26 (23)		10 (19)	
Persistent, n (%)	18 (16)		8 (15)	
Permanent, n (%)	19 (17)		11 (21)	
Class III antiarrhythmic use, n (%)	15 (13)	45 (39)	11 (21)	14 (27)

*: $p < 0.05$ versus Persistent.

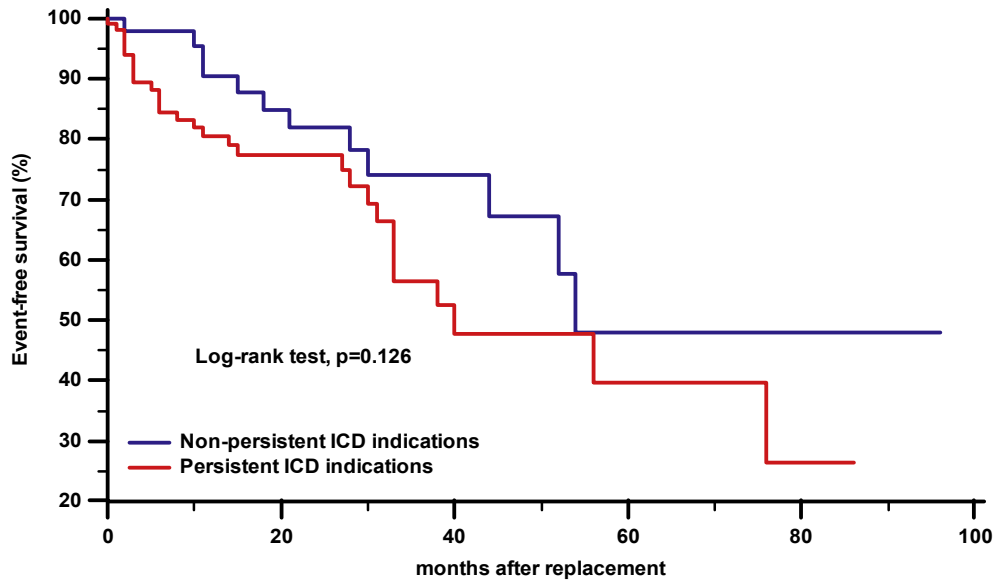


Fig. 3. Kaplan–Meier estimates of time from generator replacement to first appropriate therapy, stratified by persistence or non-persistence of primary prevention indication to ICD.

Table 3
Predictors of appropriate therapies and shocks after generator replacement (p for univariate analysis).

	All therapies			Shocks		
	HR	95% CI	p	HR	95% CI	p
Male gender	1.50	0.63–3.55	0.363	2.60	0.61–11.10	0.199
Age	1.00	0.97–1.04	0.755	0.99	0.95–1.03	0.647
Ischemic etiology	1.22	0.66–2.25	0.533	1.42	0.59–3.41	0.442
CRT defibrillator (first implantation)	1.18	0.63–2.19	0.605	0.86	0.37–2.04	0.740
CRT defibrillator (after replacement)	1.09	0.57–2.10	0.801	1.21	0.47–3.11	0.694
LV ejection fraction (replacement)	0.99	0.97–1.02	0.764	0.99	0.96–1.04	0.940
NYHA class	0.93	0.56–1.55	0.777	1.04	0.50–2.17	0.913
History of paroxysmal atrial fibrillation	2.01	0.98–3.94	0.081	2.09	0.85–5.17	0.111
History of persistent atrial fibrillation	1.07	0.48–2.141	0.868	0.88	0.26–2.97	0.880
History of permanent atrial fibrillation	0.92	0.42–1.98	0.827	1.53	0.60–3.94	0.377
Class III antiarrhythmic use	1.35	0.65–2.81	0.429	1.37	0.50–3.73	0.538
Appropriate therapies before replacement or LVEF \leq 35%	1.68	0.86–3.28	0.133	1.31	0.53–3.25	0.563
Rate of appropriate therapies before replacement	1.03	0.99–1.06	0.057	1.02	0.98–1.07	0.263
Rate of shocks before replacement	1.41	1.01–1.96	0.041	1.31	0.83–2.06	0.256

4. Discussion

In the present study we demonstrated that the ICD indication for prevention of sudden cardiac death persisted at the time of generator replacement in 69% of patients who had received a primary prevention ICD in the setting of heart failure with reduced LVEF. Nonetheless, the persistence of indication was not associated with a higher risk of further appropriate ICD therapies. Indeed, the recurrence of arrhythmic events was only associated with a higher rate of shocks delivered before replacement.

Currently, the selection of ICD candidates relies mainly on LVEF evaluation at the time of pre-implantation screening [1], as reduced LVEF was the principal inclusion criterion in trials for primary prevention of sudden cardiac death. Nonetheless, although no other strong and reliable tools are available at the moment, in the last ten years growing evidence is accumulating that LVEF is not an optimal risk discriminator [8]. Indeed, LVEF has a limited specificity for the underlying risk, meaning that a reduced LVEF is a risk factor not only for sudden but also for non-sudden death [9,10]. Moreover, only relatively few patients with reduced LVEF benefit from an ICD, and indeed the number of ICDs needed to prevent a death over 45

months of observation was estimated to be approximately 14 [11]. In addition, strong evidences are missing about patients with EF recovery after optimal therapy; in this setting ICD implantation is not usually recommended (a waiting time of 1–3 months is usually warranted before SCD prophylaxis [1]), because early ICD implantation showed no benefit on overall mortality. However, some Authors proposed early implantation or bridge therapy with wearable defibrillator in patients at “high risk” (a poorly defined category) because SCD is not null and, after EF recovery or when a borderline EF is observed, a residual risk may persist in selected patients (e.g. the ones with anatomical substrate for ventricular arrhythmias) [12].

Our analysis confirmed that LVEF alone is a poor risk stratifier and that, even in the absence of documented ventricular arrhythmias, a subsequent life threatening arrhythmic event cannot be excluded in patients with improved LVEF at follow-up (and, maybe, even before primary prevention implant). We identified a large proportion of patients implanted for primary prevention of sudden cardiac death who had no ICD interventions and who improved their LVEF to more than 35% at the time of generator replacement. Although we noticed a lower rate of appropriate ICD therapies in

this group after replacement, the proportion of patients with events was comparable in the two groups, and we also reported arrhythmic events among patients who showed full recovery of LVEF (i.e. >50%). Therefore, although the discontinuation of ICD therapy in these patients may be tempting from an economic point of view, as well as the possibility of downgrading a CRT-D to a CRT pacemaker in patients requiring biventricular pacing, the risk of sudden cardiac death remains not null. Nonetheless, although the potential complications associated with the replacement procedure are not negligible [13], we showed a lower rate of inappropriate therapies in patients with no persistent ICD indication, and thus a potentially lower negative impact on the outcome and the quality of life.

In the perspective of discontinuing ICD therapy, one additional open question concerns the management of the depleted device: leaving it in place, removing the generator or the complete system, using the ICD lead for right ventricular pacing in case of concomitant CRT or pacing indications. Every option is associated with different potential risks and should be carefully evaluated. Of course, the adoption of modern technologies, such as the totally subcutaneous ICD, would allow an easier management of possible system removal.

Looking at the question from a different perspective, the problem of changes in indication at the time of ICD replacement can be solved by decreasing the proportion of ICD recipients who outlive their first device. In our study, the mean longevity of ICDs implanted over the last 15 years was approximately 5 years. As Hauser suggested in 2005 [14], a 10-years battery would allow to provide an ICD that lasts a lifetime in the majority of patients, and recent data seem to show that modern battery technology (e.g. high capacity cells, highly efficient chemistry) has finally reached this goal [15].

4.1. Limitations

The first limitation of the present study is the retrospective design of the analysis. However, all the patients included were consecutive. Secondly, the number of patients in analysis was relatively small. Thirdly, several clinical variables or comorbid conditions at baseline and at replacement were not considered in our analysis of potential predictors. Fourthly, the long duration of the enrollment period may have impacted the results, as the implantation criteria and the ICD programming may have changed over time. However, the study was carried out in a single center, the operators in charge of patient selection, device implantation and clinical management did not change during the study period. Lastly, the therapies delivered by the ICD are only a surrogate endpoint and may not be necessarily considered as prevented sudden cardiac death, as episodes of nonsustained ventricular tachycardia frequently terminate spontaneously [16]. However, this approach was previously adopted by other Authors [5,6] and, in our opinion, is the only feasible in a retrospective setting.

5. Conclusions

In our study we did not find sensitive predictors of recurrent arrhythmias after generator replacement, in patients who had received an ICD for primary prevention of sudden death in the setting of heart failure with reduced LVEF. Therefore, although current criteria for ICD indication did not persist at the time of

replacement in about 30% of patients, in our opinion ICD therapy discontinuation seems not perfectly safe. Larger prospective trials are needed to identify reliable risk factors at the time of first ICD implantation and replacement.

Conflict of interest

Sergio Valsecchi is employee of Boston Scientific, Inc. No other conflicts of interest exist.

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