International Journal of Cardiology 293 (2019) 119–124

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

ICD replacement in patients with intermediate left ventricular dysfunction under optimal medical treatment☆

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ARTICLE INFO

Article history:
Received 5 May 2019
Received in revised form 21 June 2019
Accepted 27 June 2019
Available online 4 July 2019

Keywords:
Device replacement
Arrhythmias
Intermediate left ventricular dysfunction

ABSTRACT

Background: Implantable cardioverter-defibrillators (ICD) have a pivotal role in preventing major arrhythmic events in patients with severely reduced left ventricular ejection fraction (LVEF). Device replacement strategy is still controversial in patients without severely reduced left ventricular ejection fraction (LVEF) at the end of battery life.
Objective: To evaluate the long-term arrhythmic outcome of patients with ICD or and cardiac resynchronization therapy defibrillators (CRT-D) with normal or intermediate LVEF at the time of device replacement.
Methods: All consecutive patients with reduced ejection fraction heart failure, both from ischemic and non-ischemic origin, implanted with ICD or CRT-D for primary prevention from 2002 to 2009, were considered. The study population included patients without previous ICD interventions and without severe dysfunction (i.e. LVEF ≥ 35%) 60 [53–65] months after implantation (average battery duration). The outcome measure was the occurrence of appropriate ICD interventions in the long-term.
Results: Among the 255 patients (150 ICDs; 105 CRT-D) evaluated, 45 (18%) had LVEF ≥ 35% without ICD interventions 5-year follow-up after implantation (15 ICD [10%]; 30 CRT-D [29%]). In the long term, ICD interventions were 4 (27%) in the ICD group and 5 (17%) in the CRT-D group.
Conclusions: Despite the absence of severe left ventricular dysfunction at the time of battery replacement, a not negligible number of patients with ICD and CRT-D maintained a high risk of appropriate interventions in the long term, suggesting the opportunity of replacing the ICD regardless the amount of LV dysfunction.

1. Introduction

Current guidelines recommend Implantable Cardioverter Defibrillator (ICD) as a cornerstone to reduce sudden cardiac death (SCD) in patients with severely depressed left ventricular ejection fraction (LVEF), NYHA II–III functional classes and at least 1-year life expectancy after at least 3 months of optimal medical treatment [1]. Furthermore, in patients with associated left bundle branch block, Cardiac Resynchronization Therapy (CRT) is recommended to promote left ventricular reverse remodeling (LVRR) with subsequent survival benefit [1].

Noteworthy, approximately 20% to 25% of patients with ischemic cardiomyopathy [2] and 40% [3] of patients with non-ischemic cardiomyopathy (NICM), experience a significant LVEF improvement, as part of the so-called LVRR [4] phenomenon. However, it has been described that LVRR completes within two years since the optimization of medical therapy. Furthermore, around 10 to 26% of patients with CRT, according to the different criteria used to define CRT response [5], normalize LVEF after implantation [6,7]. On the other side, up to 80% of patients implanted for primary prevention do not experience appropriate ICD interventions during the lifetime of their first ICD generator [8]. The benefit of device therapy must be balanced against a non-negligible risk of complications, reoperation and inappropriate shocks [9]. The percentage of patients not fulfilling anymore guidelines criteria for ICD implantation in primary prevention at the time of device replacement (i.e. on average since 5 years after implantation [10]) due to the amelioration of their LVEF remains unknown. Furthermore, the risk of SCD as well as the benefit of ICD in those patients is not well established and device replacement strategy is still controversial. Indeed, at the time of battery replacement, downgrading from CRT-D to CRT-P (to reduce costs and pocket dimensions and increase battery duration) could be a possible strategy.

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

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https://doi.org/10.1016/j.ijcard.2019.06.072
0167-5273/

Therefore, the aim of the present study was to characterize the long-term arrhythmic outcome of patients treated with ICD (single, dual chamber or CRT-D) for primary prevention, normal or intermediate LVEF and no appropriate interventions after a mean of 5 years from device implantation.

2. Methods

2.1. Study design and population

In the present retrospective study, all consecutive patients who underwent ICD/CRT-D implantation at the University Hospital of Trieste from 2002 to 2009 were analyzed. Among those, the study population met the following criteria:

- Inclusion criteria: (1) ICD/CRT-D implantation for primary prevention of SCD (i.e. LVEF <35% after >6 months of optimal medical therapy); and (2) dilated cardiomyopathy (ischemic or non-ischemic).
- Exclusion criteria: (1) other causes of cardiomyopathy (hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy, ion-channel disease); (2) implantation of ICD/CRT-D for secondary prevention; (3) appropriate ICD intervention in the first 5 years of follow-up; (4) death or heart transplantation or ventricular assist device support in the first 5 years of follow-up; and (5) patients without follow-up data at 5 years from device implantation.

According to the Registry of the Italian Association of Arrhythmology and Cardiac Pacing (AIAC) median life of ICD/CRT-D before replacement is 5.8 years [IQR 4.8–7.2] [10].

According to our standard programming for primary prevention, to protocols used in the literature and current guidelines [11–13], antitachycardia pacing followed by DC-shock was programmed for ventricular arrhythmias at rate 185–188/min lasting >30 beats or >12–15 s. The study was conducted according to the institutional approval of local ethics committee according to the declaration of Helsinki.

2.2. Clinical-echocardiographic assessment and patient management

Demographic characteristics, cardiac and non-cardiac medical comorbidities, electrocardiographic and echocardiographic parameters, laboratory measures, and information recorded during ECG Holter monitoring were obtained from medical records at the time of ICD/CRT-D implantation, at clinical evaluation at 5 years of follow-up and through remote monitoring controls.

Echocardiographic assessment consisted in comprehensive M-mode, 2-dimensional and Doppler studies. Systolic and diastolic ventricular function and valve regurgitation were defined according to international guidelines [9]. In particular, LVEF was calculated from 2-dimensional apical 4 and 2 chambers approach using the biplane method of discs (modified Simpson's rule). LVEF was systematically measured at ICD/CRT-D implantation and at 5-year follow-up evaluation in all patients included in the analysis.

All patients received tailored Heart Failure (HF) medical treatment, as indicated by guidelines at the time of enrollment. Implantation of ICD for primary prevention of sudden death or CRT-D were considered according to international guidelines, at least 6 weeks after an acute ischemic event and at least 3 months after optimal medical therapy in other conditions [1,14].

2.3. Study groups and outcome variables

Patients with LVEF > 35% and without ICD interventions at 5 years since implantation (median 60 months, [interquartile range (IQR) 53–65] were classified as "improved". The end-point of the study was the first appropriate ICD/CRT-D intervention after the 5-year follow-up evaluation in the "improved" patients. Appropriate ICD/CRT-D intervention was defined as shock delivery or anti-tachycardia pacing (ATP) for ventricular tachycardia or ventricular fibrillation. All patients have been followed for 10 years after the device implantation. The administrative end of follow-up was considered as March 31st, 2018 (last check date for alive patients) or the date of end point, death or heart transplant.

2.4. Statistical analysis

Continuous variables are presented as mean (SD) and categorical variables as n (%). Summary statistics of clinical and laboratory variables were expressed as mean and standard deviation, median and interquartile range or counts and percentage, as appropriate (Shapiro-Wilk test was used to test for normal distribution of continuous variables). Comparisons between groups were made by the ANOVA test on continuous variables, using the Brown-Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric Mann-Whitney test when necessary. For categorical data analysis, Fisher's exact or Chi Square-tests were used to explore difference between groups. A non-parametric median test was performed in the subgroup of patients experimenting appropriated intervention comparing ICD/CRT-D. A 2-tailed $p < 0.05$ was considered statistically significant. The IBM-SPSS version 19 was used for statistical analyses.

3. Results

Study population.

Among the whole population of 359 implanted patients, a total of 150 (86 with ICD and 64 with CRT-D) were included in the analysis (Fig. 1). From the original population, 104 patients have been excluded because affected by other causes of cardiomyopathy (15 hypertrophic cardiomyopathy, 12 arrhythmogenic right ventricular cardiomyopathy and 6 channelopaties) or have been implanted for secondary prevention (71 patients). Furthermore, 105 patients have been excluded because died or underwent HTx or VAD implantation during follow-up or because missing information (Fig. 1).

Clinical characteristics at the time of implantation are presented in the Supplementary Table 1. At the time of replacement, only one patient was downgraded from an ICD to a PM, without experiencing adverse events.

3.1. Clinical characterization at 5 years since device implantation

Clinical characteristics of the patients at 5-year follow-up are presented in Table 1. Ischemic cardiomyopathy was the cause of systolic dysfunction in 72 patients (48%). The mean age was 66 ± 11 years. Patients were mostly men (81%), and 23% were in NYHA functional class III or IV. Median LVEF was 30% and median indexed Left Ventricular End-Diastolic Volume was 90 ml/m^2. Patients were under optimal medical therapy for HF (Angiotensin-Converting-Enzyme-Inhibitors Angiotensin II Receptor Blockers in 91%; beta-blockers 81%).

Thirty-percent of patients (n = 45) recovered LVEF (i.e. >35%) and were classified as "improved". Among those, 15 patients were implanted with an ICD and 30 patients were implanted with a CRT-D (17% of the ICD group and 47% of the CRT-D Group, $p < 0.001$; Fig. 1). Compared to the others, patients in the "improved" group had less frequently ischemic cardiomyopathy (24% vs 64% respectively; $p < 0.001$), a greater prevalence of NYHA I functional class (44% vs 13%; $p = 0.003$), smaller left ventricular end diastolic diameter (iLVEDD) (31 vs 36 mm/m^2, $p = 0.001$) and a lower prevalence of right ventricular dysfunction (14% vs 40%; $p = 0.007$) (Table 2).

Compared to "improved" patients with dual or single chamber ICD, at 5 years since implantation, patients with CRT-D classified as "improved" had a higher mean LVEF (51% vs 39%, $p = 0.004$), a lower prevalence of ischemic heart disease (53% vs 10% $p = 0.003$) and of non-sustained ventricular tachycardia at ECG Holter (50% vs 17%; $p = 0.032$. Supplementary Table 2).

3.2. Arrhythmic events during long-term follow-up

During a median follow-up of 59 months [43–78 IQR] after the 5-year re-evaluation, the primary end-point (i.e. appropriate ICD interventions) occurred in 9 of the 45 (20%) "improved" patients (Fig. 1).

Compared to the others, at 5-year follow-up from implantation, patients experiencing the end-point were less frequently in NYHA functional class I (0% vs 55%; $p = 0.006$), whereas LVEF appeared to be similar (48% vs 45%; $p = 0.823$) (Supplementary Table 3). In those patients, the last available LVEF during follow-up was 43 ± 13% over a median follow-up of 4 ± 2 years from the 5-year timepoint. Moreover, the last echocardiogram performed before the ICD intervention, showed a new decline of LVEF (i.e. <35%) in 4 of the 9 improved patients (44%).

Among the 9 patients experiencing the study end-point, 4 (27%) belonged to ICD group (2 shocks and 2 ATP) and 5 (17%) to the CRT-D (no shocks and 5 ATP). The events occurred at median time of 15 [IQR 5.5–29] months after the 5-year re-evaluation in ICD patients vs 42 [IQR 37–52] months in CRT-D patients ($p = 0,048$). Interestingly, CRT-D patients who experienced the end-point, appeared to have an almost-normal LVEF (i.e. 54% [52–63 IQR]) and iLVEDD (i.e. 29 mm/m^2 [26–29 IQR]), at 5-year re-evaluation since the first implantation. (Supplementary Table 4).

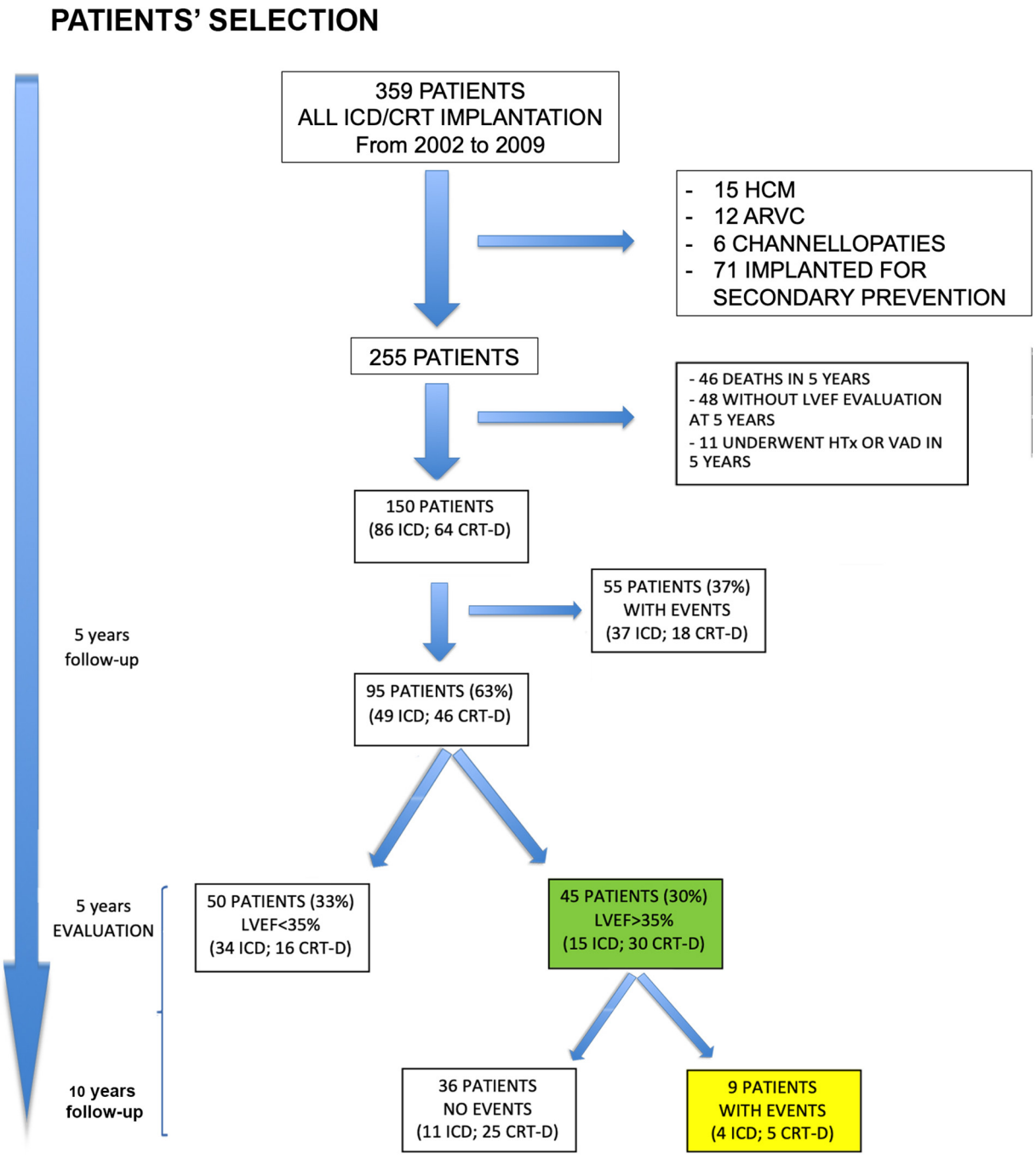

Fig. 1. Study population selection and flow-chart of the study. Legend: ICD: Implantable Cardioverter Defibrillator; CRT-D: Cardiac Resynchronization Therapy-Defibrillator; HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; LVEF: left ventricular ejection fraction; HTx: heart transplantation; VAD: ventricular assist device; F-UP: follow-up. See text for event definition.

4. Discussion

While data regarding ICD and CRT-D implantation in patients with LVEF < 35% are well known [15,16], a general consensus regarding the ICD replacement in patients who recover LVEF is lacking. The arrhythmic risk stratification in patients with improved left ventricular function is indeed a current major concern. So far, the specific issue regarding the arrhythmic risk in patients who do not currently meet ICD indications during follow-up, has been scarcely addressed [17].

At the time of battery depletion, patients are older and in some cases with more and new comorbidities compared to the time of implantation. Furthermore, in patients with a relatively lower risk of SCD, the risk of inappropriate ICD interventions and the procedural complications can be overwhelming. Recently, Madhavan and colleague identified that approximately one third of patients with ICD no longer meet implantation criteria at the time of generator replacement, maintaining a non-negligible risk of appropriate intervention in the subsequent follow-up [18]. However, the decision whether to deactivate, avoid to replace or downgrade the device (form CRT-D to CRT without ICD backup) in patients who no longer meet criteria for ICD implantation is still an unresolved issue, due to the lack of definite, multicenter, data. Indeed, a recent analysis [18] did not address the role of CRT and was poorly focused to investigate the occurrence of LVRR.

In our analysis, 30% of patients implanted with an ICD or CRT-D in primary prevention showed a significant improvement of LVEF without device interventions at the moment of battery depletion. As expected,

Table 1
5-year follow-up characteristics of the study population stratified by ICD or CRT-D implantation.

Data at 5-years follow-up	All patients (n = 150)	ICD patients (n = 86, 57%)	CRT-D patients (n = 64, 43%)	*p*-Value
Age (years)	66 ± 11	65 ± 11	66 ± 9	0.490
Male sex, n (%)	122 (81%)	72 (84%)	50 (78%)	0.384
ICM, n (%)	72 (48%)	51 (59%)	21 (33%)	**0.001**
History of syncope, n (%)	25 (17%)	13 (15%)	12 (19%)	0.555
Disease duration (months)	150 [92–222]	142 [76–224]	162 [114–209]	0.617
NYHA Class I, n (%)	28 (22%)	17 (21%)	11 (24%)	0.729
NYHA Classes III–IV, n (%)	29 (23%)	20 (25%)	9 (20%)	0.485
SBP (mmHg)	118 ± 17	119 ± 17	117 ± 17	0.459
Atrial fibrillation, n (%)	15 (10%)	12 (14%)	3 (5%)	0.070
QRS duration (ms)	162 [130–183]	145 [124–175]	172 [161–193]	<**0.001**
PVC > 1000/24 h*, n (%)	57 (46%)	36 (53%)	21 (38%)	0.103
NSVT/24 h*, n (%)	44 (30%)	30 (35%)	14 (22%)	0.085
iLV-EDD (mm/m^2)	34 [31–38]	35 [31–38]	33 [30–40]	0.517
LVEF (%)	30 [24–41]	30 [25–38]	36[26–52]	0.022
RV dysfunction, n (%)	40 (30%)	29 (36%)	11 (22%)	0.083
Moderate-severe MR, n (%)	43 (32%)	29 (35%)	14 (27%)	0.331
RFP, n (%)	39 (29%)	26 (33%)	13 (24%)	0.264
ACEi/ARB, n (%)	134 (91%)	76 (91%)	58 (92%)	0.779
Amiodarone, n (%)	58 (40%)	42 (49%)	16 (26%)	**0.004**
Beta-blockers, n (%)	119 (81%)	67 (80%)	52 (83%)	0.671
MRAs, n (%)	59 (40%)	38 (44%)	21 (33%)	0.158

Legend: ICD: Implantable Cardioverter Defibrillator; CRT-D: Cardiac Resynchronization Therapy-Defibrillator; ICM: ischemic cardiomyopathy; NYHA: New York Heart Association; SBP: systolic blood pressure; LV: left ventricle; EF: ejection fraction; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contractions; i: indexed; EDD: end diastolic diameter; EDV: end diastolic volume; RV: right ventricle; MR: mitral regurgitation; RPF: restrictive diastolic filling pattern; ACEi: Angiotensin-Converting-Enzyme-Inhibitors; ARB: Angiotensin II Receptor Blockers; MRAs: mineralcorticoid receptor antagonist.
Data are expressed as median [1st–3rd interquartile] for continuous variables.
* At Holter-ECG monitoring.

this was more common in patients implanted with CRT-D (around 50%), but still, a significant percentage of patients implanted with ICD completed LVRR in the long term. Furthermore, despite LVRR, 20% of improved patients experienced appropriate ICD interventions relatively soon after the 5-year re-evaluation timepoint (i.e. median time of 15 months and 42 months in the ICD and CRT-D groups respectively), indicating the need of ICD despite functional improvement. These findings, even requiring further confirmation, importantly expand the body of knowledge in this field. Furthermore, this study introduces a novelty adding a subgroup of CRT-D patients and assessing the occurrence of LVRR during long-term follow-up.

4.1. Improvement of left ventricular function

4.1.1. ICD patients

In our study, 17% of patients with an ICD resulted "improved" at 5-year follow-up. Despite the timeframe in which LVRR occurs has been described ranging from 6 months to 5 years [3], most of the authors agreed that LVRR is mostly complete after 12 to 24 months of optimal medical therapy [3,19]. Current guidelines recommend up-titrating medical treatment for a wait-and-see period of 40 days for ischemic and 3 to 6 months for non-ischemic, mainly to overcome the acute phase and to select the best candidates [20]. The present study confirms that LVRR can be completed even after that timeframe. Indeed, almost one fifth of patients with ICD patients did not meet anymore guidelines' indication to ICD 5 years after implantation (roughly at time or close to device replacement), confirming that early identification of patients more prone to develop LVRR in the long term is difficult, both in ischemic and non-ischemic cardiomyopathies in the long-term follow-up is missing. Multiparametric, comprehensive scores are advocated in order to overcome this important gap of knowledge in the management of HF patients.

4.1.2. CRT-D patients

Compared to patients with ICD, a much higher percentage of CRT-D patients (47% for CRT-D vs 17% for ICD $p \leq 0.001$) experienced improvement of LVEF at 5 years, confirming the role of CRT to promote LVRR, at least in non-ischemic patients. In fact, only 10% of ischemic patients in the CRT-D group resulted "improved" at 5 years (Supplementary Table 2). The presence of myocardial scar following a myocardial infarction could be associated to a higher rate of non-response to CRT and, at the same time, makes major ventricular arrhythmias more likely [21,22]. Nowadays, patients with implantable devices are mainly excluded from Cardiac Magnetic Resonance (CMR) studies. However, in the future, with technical advancements, novel CMR-compatible devices might overcome this issue and CMR might be useful for proper characterization of CRT responders in ischemic patients to assess this hypothesis.

4.2. ICD interventions: the need for dynamic models for arrhythmic risk assessment

4.2.1. ICD patients

The most important result of this study suggests that the risk of major ventricular arrhythmias, even in the subgroup of patients with LVEF > 35% after the expected time for generator replacement, is still elevated. Therefore, at the time of battery depletion, ICD replacement seems to be unavoidable to reduce the risk of SCD [23].

In our analysis, among the analyzed variables, there were no reliable indicators to identifying patients at increased arrhythmic risk during the follow-up (Supplementary Table 4). Even if this was out of the aims of the study, this issue highlights the need of a future development of more accurate predictive models for arrhythmic risk stratification, adjusted for disease duration and using multiple variables other than LVEF.

4.2.2. CRT-D patients

In the subgroup of CRT-D patients with LVEF > 35% at the time of battery depletion, a downgrading of the device or a deactivation of the shock function to avoid non-appropriate ICD interventions could be conceivable [24]. However, 17% of these patients had appropriate device interventions in the following 5 years, despite an almost normalized LVEF (median LVEF 54%), mostly in NICM patients. Among those, a new drop in LVEF below 35% appears to be related to the subsequent arrhythmic event. The so-called apparent healing phenomenon [25,26] may lead to an underestimation of the arrhythmic risk mainly dictated by the recovered LVEF, confirming the dynamicity of this condition and suggesting that a real healing in these patients is not accomplished [27].

4.3. Limitations

Due to the rarity of events in this setting of patients, the relatively small size of this retrospective study may represent a limiting issue despite the long-term follow-up. Furthermore, due to the exiguous number of events in the ICD and CRT-D groups, statistical significances may be misleading. However, this is, so far, one of the largest available populations with follow-up data that could improve the knowledge on this specific topic.

Time of LVRR is disputable, but most of the studies convey between 12 and 24 months since diagnosis.

Unfortunately, an echocardiogram was not always available just at the time of battery replacement. However, all patients were evaluated every year, and, in most of them, an echocardiogram was performed

Table 2
5-year follow-up characteristics of improved vs. non-improved patients.

Data at 5-years follow-up	"Non-improved" patients (n = 50, 53%)	"Improved" patients (n = 45, 47%)	*p*-Value
Age (years)	67 ± 12	64 ± 9	0.522
Male sex, n (%)	39 (78%)	37 (82%)	0.607
ICM, n (%)	32 (64%)	11 (24%)	**<0.001**
History of syncope, n (%)	5 (10%)	11 (24%)	0.098
NYHA Class I, n (%)	5 (13%)	17 (44%)	**0.003**
NYHA Classes III–IV, n (%)	9 (23%)	4 (10%)	0.225
NSVT at Holter-monitoring, n (%)	9 (18%)	12 (27%)	0.305
PVC > 1000 at Holter-monitoring, n (%)	14 (29%)	13 (34%)	0.810
iLV-EDD (mm/m^2)	36 [33–39]	31 [28–33]	**0.001**
LVEF (%)	27 [23−31]	46 [38–55]	**<0.001**
RV dysfunction, n (%)	16 (40%)	6 (14%)	**0.007**
Moderate-severe MR, n (%)	14 (36%)	8 (18%)	0.068
ACEi/ARB, n (%)	42 (86%)	44 (98%)	0.061
Beta-blockers, n (%)	39 (80%)	40 (89%)	0.267
MRAs, n (%)	22 (44%)	9 (20%)	**0.013**

Legend: ICM: ischemic cardiomyopathy; NYHA: New York Heart Association; LV: left ventricle; EF: ejection fraction; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contractions; i: indexed; EDD: end diastolic diameter; RV: right ventricle; MR: mitral regurgitation; ACEi: Angiotensin-Converting-Enzyme-Inhibitors; ARB: Angiotensin II Receptor Blockers; MRAs: mineralcorticoid receptor antagonist.
Data are expressed as median [1st-3rd interquartile] for continuous variables.

5 years after the implantation was available. Despite the high variability of battery duration [28], we chose a theoretical replacement time of 5 years after the implant since it is the average longevity of the batteries [10], and it makes data reliable and more clinically relevant. Finally, this study has been designed to characterize predictors of adverse arrhythmic outcomes in patients who might undergo generator replacement at a 5-years follow-up. Future studies investigating predictors of events in a population of patients who replaced their generator are warranted.

There is not a standard protocol for programming ICD interventions [11–13]. Therefore, we follow the internal protocol, as previously reported [29].

Information from CMR, advanced echocardiographic features, biomarker and genetic testing were not systematically available because these tests were performed only in a minority of selected cases.

5. Conclusions

Patients with apparently recovered or ameliorated LVEF represent a specific subgroup in which generator replacement may be futile. However, from our results, patients who implanted an ICD or a CRT-D and experience an improvement of left ventricular function during follow-up, appear still to be at risk of major ventricular arrhythmias, suggesting the opportunity of replacing the device. Larger, multicenter studies are required to identify multi-parametric models for the detection of patients in which ICD inactivation or the choice to avoid generator replacement could be safe, especially in NICM and CRT-D carriers.

Declaration of Competing Interest

None.

Acknowledgements

We would like to thank Fondazione CRTrieste, Fondazione CariGO and Fincantieri for the continuous support to the clinical management of patients affected by cardiomyopathies, followed in Heart Failure Outpatient Clinic of Trieste, and their families.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.072.

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