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MAIN TEXT

Real-world data of patients affected by advanced heart failure treated with implantable cardioverter defibrillator and left ventricular assist device: Results of a multicenter observational study

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Abstract

Background: Left ventricular assist device (L-VAD) implantation is increasingly used in patients with heart failure (HF) and most patients also have an implantable cardioverter defibrillator (ICD). Limited data are available on the incidence of ICD therapies and complications in this special setting.

The aim of this study was to analyze the real-world incidence and predictors of ICD therapies, complications and interactions between ICD and L-VAD.

Methods: We conducted a multicenter retrospective observational study in patients with advanced HF implanted with ICD and a continuous-flow L-VAD, followed-up in five advanced HF centers in Northern Italy.

Results: A total of 234 patients (89.7% male, median age 59, 48.3% with ischemic etiology) were enrolled. After a median follow-up of 21 months, 66 patients (28.2%) experienced an appropriate ICD therapy, 22 patients (9.4%) an inappropriate ICD therapy, and 17 patients (7.3%) suffered from an interaction between ICD and L-VAD. The composite outcome of all ICD-related complications was reported in 41 patients (17.5%), and 121 (51.7%) experienced an L-VAD-related complication. At multivariable analysis, an active ventricular tachycardia (VT) zone and a prior ICD generator replacement were

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independent predictors of ICD therapies and of total ICD-related complications, respectively.

Conclusions: Real-world patients with both L-VAD and ICD experience a high rate of ICD therapies and complications. Our findings suggest the importance of tailoring device programming in order to minimize the incidence of unnecessary ICD therapies, thus sparing the need for ICD generator replacement, a procedure associated to a high risk of complications.

KEYWORDS
end-stage heart failure, ICD complications, ICD programming, implantable cardioverter-defibrillator (ICD), left ventricular assist device

1 | INTRODUCTION

In patients with end-stage heart failure (HF), left ventricular assist device (L-VAD) have shown to improve survival and quality of life compared to medical therapy.[1–3] Therefore, their use has increased in recent years.[4]

Ventricular arrhythmias (VAs) are common events in patients with L-VAD and are related to worsening of the underlying pathological substrate or ventricular electrical remodeling after L-VAD implantation.[5,6] The new generation continuous-flow L-VAD guarantees adequate cardiac output even in the presence of sustained VAs; therefore, hemodynamic instability, syncope, and sudden cardiac death are rare events even in the presence of ventricular fibrillation.[7] However, also hemodynamically well tolerated VAs can determine the onset of right ventricular dysfunction or blood stasis resulting in a higher risk of L-VAD thrombosis.[8]

Implantable cardioverter defibrillator (ICD) has demonstrated to reduce mortality in the general population of patients with HF with reduced left ventricle ejection fraction both in primary and secondary prevention. However, even if international guidelines recommend to reactivate the ICD therapies after the implantation of L-VAD (class I, level of evidence A), and to consider the implantation of an ICD following L-VAD implantation in "naïve" patients (class IIa, level of evidence B),[9] the evidence on the prognostic impact of ICD in this population is conflicting.[10–13]

On the other hand, the presence of an ICD in L-VAD patients, is associated with an increased risk of bleeding and infections.[14]

Moreover, a conservative ICD programming, with long detection times and high-rate VA cut-off zones, has demonstrated to significantly improve the outcomes and survival in the general population with ICD,[15–17] but there are few and conflicting data in patients with L-VAD.[18,19]

On this basis, the aims of our study were to evaluate the incidence and predictors of ICD therapies and device-related complications in a real-world population of L-VAD patients with ICD and to identify potential interventions in patients' management or ICD programming in order to maximize the benefits of ICD therapy while reducing the risk of device-related complications.

2 | METHODS

2.1 | Ethical approval

This study received preliminary ethical approval from the local institutional review committee of the coordinating center (P-20200062199/29-07-2020) and, subsequently, from that of each participating hospital.

2.2 | Design

We conducted a multicenter retrospective observational study enrolling all consecutive adult patients implanted with an ICD and a continuous-flow L-VAD followed-up in five advanced HF centers of Lombardy, Italy. L-VADs were implanted between July 2006 and November 2020.

Clinical, demographic, and data related to echocardiography, ICD, and L-VAD were collected at baseline (defined as the time-point when the patient met the inclusion criteria of being implanted with both ICD and L-VAD), 1-year follow-up, and at the last available follow-up point for each patient enrolled.

2.3 | Outcomes

The primary outcome of our study was the incidence of appropriate ICD therapies defined as ICD shocks or

anti-tachycardia pacing (ATP) delivered by the device in the event of properly recognized VAs.

Secondary outcomes were the incidence of ICD-related complications, inappropriate ICD therapies, the composite of appropriate and inappropriate ICD therapies, the composite of ICD-related complications and inappropriate therapies, L-VAD-related complications and ICD-LVAD interferences.

Inappropriate ICD therapies were defined as shocks or ATP delivered by the ICD in events other than VAs.

ICD-related complications occurring after L-VAD implantation included pocket hematoma and device-related infections. L-VAD-related complications included L-VAD infections and hemorrhagic events.

2.4 | Statistics

Statistical analyses were performed using MedCalc® Statistical Software version 20.006.

Descriptive variables are presented as number and relative percentage for categorical variables and as mean ± standard deviation or median (interquartile range—IQR) for continuous variables, as appropriate, based on the normality of the distribution verified by Shapiro–Wilk test. Comparisons between means were performed with the *t*-test or the Welch-test, when appropriate based on the result of the *F*-test performed to compare the variances between groups. Comparisons between medians were made with the Mann–Whitney test and categorical variables were compared with the Chi^2 test or Fisher's exact test, as appropriate. Two-sided p values <0.05 were considered statistically significant.

The predictors of the studied outcomes were evaluated by univariate logistic regression analyses and the variables that were significantly associated with the outcome of interest ($p<0.05$) were included in a multivariate model. Moreover, statistical analyses were conducted in order to highlight any heterogeneity in the population across the relatively large enrolling period. Three groups of patients were defined based on the year of enrollment (group 1: from 2006 to 2010; group 2: from 2011 to 2015; group 3: from 2016 to 2020) and the characteristics of these groups were compared for heterogeneity and trends with Chi^2 test or Kruskal–Wallis test and Jonkheere-Terpstra trend test, as appropriate.

3 | RESULTS

3.1 | Population and baseline

A total of 234 patients were included. The median age at ICD implantation was 56.5 (IQR 49–62) years and the median age at L-VAD implantation was 59 (IQR 52–66) years. Detailed baseline clinical and echocardiographic characteristics are summarized in Table 1.

TABLE 1 Baseline clinical and echocardiographic characteristics.

	n	%
Gender		
Male	210	89.7
Diagnosis		
Nonischemic cardiomyopathy	106	45.3
Ischemic cardiopathy	113	48.3
Unknown	3	1.3
Other	12	5.1
Risk factors and comorbidity		
Systemic hypertension	80	34.2
CKD	92	39.3
COPD	36	15.4
Diabetes mellitus	52	22.2
Previous CABG	23	9.8
Other previous cardiac surgery	44	18.8
Previous PTCA	89	38.0
Atrial arrhythmias		
Atrial fibrillation	93	39.7
Paroxysmal	69	74.2
Ventricular arrhythmias		
History of VA	111	47.4
Previous VT ablation	26	11.1
Medical therapy		
Anti-RAAS therapy	158	67.5
ACEi	147	93.0
ARB	7	4.4
ARNI	4	2.5
Beta-blockers	194	82.9
Anti-arrhythmic drugs	95	40.6
Amiodarone	92	96.8
Echocardiographic characteristics	Median (IQR)	
LVEDD (mm)	67 (61–75)	
LVEF (%)	20 (19–25)	
TAPSE (mm)	16 (14–18)	
RVEDA (cm^2)	24 (19–28)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; RAAS, renin angiotensin system; RVEDA, end diastolic right ventricular area; TAPSE, tricuspid annular plan systolic excursion; VA, ventricular arrhythmias; VT, ventricular tachycardia.

Most of the patients underwent ICD implantation for primary prevention (86.8%). A previous history of appropriate ICD therapy was reported in 56 patients (23.9%). With regard to device programming, at baseline at least one VT therapy zone was active in 102 patients (43.6%) with a median detection rate of the lowest VT zone of 167 bpm (IQR 160–171) while two VT zones were active in 13 patients. The median detection rate of ventricular fibrillation (VF) zone was 210 (IQR 200–214) bpm. At the last available follow-up at least one VT zone was active in 63 patients (26.9%) with a median detection rate of 167 (IQR 161–171) bpm, while two VT zones were active in 19 patients. No significant associations have been found between indication for ICD implantation (i.e., primary or secondary prevention) and having a VT therapy zone active at baseline ($p = 0.10$), nor between a history of VAs and having an active VT zone on at follow-up ($p = 0.11$).

Further details about ICD and L-VAD baseline parameters are presented in Table 2.

TABLE 2 ICD and L-VAD baseline parameters.

ICD baseline data	
Age at ICD implantation	56.5 (49–62)
Primary prevention	203 (86.8)
Single chamber ICD	67 (28.6)
Dual chamber ICD	44 (18.8)
CRT-D	109 (46.6)
Previous appropriate therapy	56 (23.9)
Previous inappropriate therapy	14 (6.0)
At least one VT zone on	102 (43.6)
Two VT zones on	13 (5.6)
VT zone threshold[a] (bpm)	167 (160–171)
VF zone threshold (bpm)	210 (200–214)
L-VAD baseline data	
Age at L-VAD implantation	59 (52–66)
Heart Mate II	57 (24.4)
Heart Mate III	27 (11.5)
Heartware	131 (56.0)
Others	19 (8.1)
INTERMACS class I	10 (4.3)
INTERMACS class II	31 (13.2)
INTERMACS class III	112 (47.9)
INTERMACS class IV	67 (28.6)
INTERMACS class V	1 (0.4)
INTERMACS class unknown	13 (5.6)
Pump speed (rpm)	2950 (2580–7100)
L-VAD flow (L/min)	4.35 (3.7–5)
Power (Watts)	3.8 (3.3–4.9)
Pulsatility index	4.6 (3.8–5.6)

Note: Data are presented as number (%) or median (interquartile range).
Abbreviations: bpm, beat per minute; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; L-VAD, left ventricular assist devices; rpm, round per minute; VT zone, ventricular tachycardia zone; VF zone, ventricular fibrillation zone.
[a] If more than one VT zone were active, the median VT zone threshold is calculated for the VT zone programmed with the lowest cut-off.

3.2 | Postoperative course after L-VAD implant

Data regarding the postoperative course after L-VAD implant were available in 165 patients and are reported in Table S1 (supplementary appendix). Only 11 of 234 patients (4.7%) were implanted with ICD after L-VAD implantation.

3.3 | Primary outcome

After a median follow-up of 21 (IQR 8–37) months, 66 patients (28.2%) experienced an appropriate ICD therapy (Table 3). The multivariable logistic regression analysis (Table 4) identified the left ventricle end-diastolic diameter, L-VAD flow and the presence of an active VT zone at follow-up as independent predictors of appropriate ICD therapy.

3.4 | Secondary outcomes

3.4.1 | Inappropriate ICD therapy

During follow-up after L-VAD implantation, 22 patients (9.4%) experienced an inappropriate ICD therapy. Atrial fibrillation (AF) during follow-up was found to be the only significant predictor of inappropriate therapy at univariate analysis while left ventricle end-diastolic diameter and the presence of an active VT zone at follow-up were found to be independent predictors of the composite outcome of appropriate and inappropriate ICD therapy at multivariate logistic regression analysis (Tables S2 and S3, supplementary appendix).

3.5 | ICD complications after L-VAD implantation

Pocket hematoma was reported in 11 patients (4.7%, all following ICD generator replacement), ICD-related infection in 15 patients (6.4%), and the composite outcome of ICD-related complication and inappropriate therapy in 41

TABLE 3 Outcomes.

	n	%
ICD therapies		
Appropriate ICD therapy	66	28.2
Inappropriate ICD therapy	22	9.4
Total ICD therapy (appropriate and inappropriate)	77	32.9
ICD-related complications		
Pocket hematoma	11	4.7
ICD-related infections	15	6.4
ICD-related complications and inappropriate therapies	41	17.5
L-VAD related complications		
Infections	112	47.9
Hemorrhagic complications	27	11.5
ICD-L-VAD interactions	17	7.3
ICD generator replacement	34	14.5

Abbreviations: ICD, implantable cardioverter defibrillator; L-VAD, left ventricular assist device.

TABLE 4 Predictors of appropriate therapy.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Ventricular arrhythmias at baseline	2.29 (1.21–4.33)	**0.01**	2.00 (0.84–4.76)	0.12
LVEF	1.06 (0.99–1.13)	0.08		
LVEDD	1.05 (1.01–1.08)	**0.009**	**1.07 (1.02–1.12)**	**0.01**
Pump speed at baseline (rpm)	1.002 (1.000–1.0003)	**0.01**		
L-VAD flow at baseline	1.86 (1.26–2.76)	**0.002**	**1.80 (1.14–2.83)**	**0.01**
Diagnosis (ICM vs. NICM)	0.50 (0.26–0.95)	**0.03**	0.64 (0.26–1.57)	0.33
VT on at baseline	0.58 (0.30–1.14)	0.11		
VT on at follow-up	2.28 (1.18–4.40)	**0.01**	**2.39 (1.04–5.53)**	**0.04**
ICD type (dual vs. single chamber)	0.49 (0.20–1.22)	0.13		
ICD type (CRT vs. single chamber)	1.01 (0.50–2.06)	0.97		
INTERMACS class	0.89 (0.61–1.31)	0.56		
Systemic hypertension	1.06 (0.54–2.05)	0.87		
CKD	1.08 (0.58–2.03)	0.80		
COPD	0.33 (0.13–0.85)	**0.02**		
Diabetes	0.48 (0.22–1.07)	0.07		
AF at baseline	0.96 (0.51–1.81)	0.91		
Beta-blockers use	0.92 (0.38–2.18)	0.84		
Anti-arrhythmic drugs use	1.80 (0.96–3.40)	0.07		
Anti-RAAS use	1.33 (0.69–2.57)	0.40		
AF at follow-up	1.20 (0.63–2.30)	0.58		

Note: All variables that were found to be significant predictors of outcome are highlighted in bold.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillators; ICM, ischemic cardiopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; L-VAD, left ventricular assist devices; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; NICM, nonischemic cardiomyopathy; OR, odds ratio; RAAS, renin angiotensin system; rpm, revolutions per minute; VT zone, ventricular tachycardia zone.

patients (17.5%). Of the 15 patients with ICD-related infection the type of infection was specified in 11/15 patients (five pocket infections, four endovascular lead-related infections, and two cases with both pocket and lead infections). Lead extraction was successfully performed in six patients; the remaining were treated medically.

At the time of ICD surgery after L-VAD placement 70.4% of the patients were on uninterrupted warfarin + antiplatelet, 18.5% on warfarin alone, 7.4% on antiplatelet only and 3.7% withheld both warfarin and antiplatelet. Patients in whom oral anticoagulant therapy was temporary interrupted at the time of ICD generator replacement were treated with parenteral anticoagulant in accordance with the protocols of each center. Neither the percentage of use of warfarin and antiplatelet therapy ($p=0.56$) nor the INR ratio (2.31, IQR 2–2.53 vs. 2.1 IQR 1.96–2.38, $p=0.35$) was different in patients with versus without pocket hematoma after surgery.

Table 5 reports the logistic regression analysis revealing L-VAD infection, a prior ICD generator replacement and the presence of an active VT zone at follow-up as independent predictors of the composite outcome of ICD-related complications and inappropriate therapy.

3.6 | L-VAD complication

The most frequently reported L-VAD complication was infection (112 patients, 47.9%), followed by L-VAD related hemorrhages reported in 27 patients (11.5%). Among the 112 patients who had a reported L-VAD infection, 14 (12.5%) also experienced an ICD-related infection which was a pocket infection, a lead-related infection, both pocket + lead infection, and unknown in 35.7%, 21.4%, 14.3%, and 28.6% of the cases, respectively. The independent predictors of the composite outcome of L-VAD infections and hemorrhages (Table 6) were age at L-VAD implantation and the occurrence of ICD infection. The results of the logistic regression analysis for the other studied outcomes are available in the supplementary appendix (Tables S4–S7).

3.7 | ICD-L-VAD interaction and the need for ICD generator replacement

In our population an interaction between L-VAD and ICD occurred in 17 cases (7.3%). In five cases the type of interference was not specified, in six cases worsening of electrical parameters of ICD had occurred, in three cases there were episodes of noise interference, in two cases there was

TABLE 5 Predictors of ICD-related complications (i.e., infections, pocket hematoma, and inappropriate therapies).

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Ventricular arrhythmias at baseline	1.43 (0.71–2.91)	0.32		
LVEF	1.03 (0.96–1.10)	0.43		
LVEDD	1.04 (1.005–1.08)	**0.03**		
L-VAD infection at FU	2.50 (1.20–5.21)	**0.01**	**3.77 (1.34–10.61)**	**0.01**
L-VAD-related bleeding	0.50 (0.14–1.78)	0.28		
Pump speed at baseline (rpm)	1.0001 (0.9999–1.0002)	0.49		
L-VAD flow at baseline	1.24 (0.83–1.86)	0.29		
Diagnosis (ICM vs. NICM)	0.54 (0.26–1.13)	0.10		
VT on at baseline	1.19 (0.51–2.77)	0.68		
VT on at FU	2.86 (1.30–6.26)	**0.01**	**3.20 (1.20–8.53)**	**0.02**
ICD type (dual vs. single)	0.48 (0.17–1.31)	0.15		
ICD type (CRT vs. single)	0.65 (0.30–1.44)	0.29		
ICD Generator replacement	3.62 (1.62–8.12)	**0.002**	**3.71 (1.22–11.28)**	**0.02**
INTERMACS class	1.16 (0.74–1.80)	0.52		
Hypertension	0.23 (0.09–0.63)	**0.004**	0.32 (0.09–1.06)	0.06
CKD	0.69 (0.33–1.44)	0.33		
COPD	0.73 (0.28–1.92)	0.52		
Diabetes	0.40 (0.14–1.09)	0.07		
AF at baseline	1.35 (0.67–2.75)	0.40		
Postoperative AF	1.16 (0.39–3.44)	0.79		

Note: All variables that were found to be significant predictors of outcome are highlighted in bold.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; FU, follow-up; ICD, implantable cardioverter defibrillators; ICM, ischemic cardiopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; L-VAD, left ventricular assist devices; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; OR, odds ratio; RPM, revolutions per minute; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 6 Predictors of L-VAD related complications (i.e., infections and hemorrhages).

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age at ICD implant	0.94 (0.91–0.98)	**0.0006**	1.12 (0.99–1.27)	0.08
Age at L-VAD implant	0.94 (0.91–0.97)	**0.0001**	**0.82 (0.71–0.95)**	**0.006**
VT/VF at baseline	0.90 (0.52–1.59)	0.73		
Postoperative VT/VF	3.18 (1.03–9.85)	**0.04**	3.73 (0.68–20.45)	0.13
AF at baseline	1.01 (0.57–1.79)	0.97		
Postoperative AF	1.94 (0.82–4.63)	0.13		
LVEF	1.08 (1.01–1.15)	**0.02**	1.03 (0.94–1.12)	0.57
LVEDD	1.03 (1.01–1.07)	**0.04**	0.99 (0.95–1.05)	0.89
Pump speed at baseline (rpm)	1.00 (0.9999–1.0001)	0.87		
L-VAD flow at baseline	1.49 (1.07–2.09)	**0.02**	**1.73 (1.04–2.90)**	**0.04**
Diagnosis (ICM vs. NICM)	0.68 (0.38–1.24)	0.21		
ICD type (dual vs. single chamber)	0.56 (0.25–1.25)	0.16		
ICD type (CRT vs. single chamber)	1.20 (0.63–2.28)	0.58		
Generator replacement	1.41 (0.60–3.33)	0.42		
ICD infection	10.6 (1.37–82.26)	**0.02**	**12.8 (1.4–118.4)**	**0.03**
ICD pocket hematoma	5.73 (0.70–46.75)	0.10		
INTERMACS class	0.84 (0.61–1.18)	0.32		
Hypertension	0.66 (0.37–1.19)	0.17		
CKD	0.73 (0.41–1.31)	0.30		
COPD	0.67 (0.32–1.39)	0.28		
Diabetes	1.26 (0.64–2.48)	0.50		

Note: All variables that were found to be significant predictors of outcome are highlighted in bold.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; FU, follow-up; ICD, implantable cardioverter defibrillators; ICM, ischemic cardiopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; L-VAD, left ventricular assist devices; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; OR, odds ratio; RPM, revolutions per minute; VF, ventricular fibrillation; VT, ventricular tachycardia.

the inability to interrogate the ICD, and finally in one case there was a displacement of the atrial lead during L-VAD implantation (see Tables S8 and S9). Thirty-eight patients, (about 16% of the total study population), reached the ERI during follow-up, of whom 89% (accounting for 14% of the total study population) actually replaced the generator.

3.8 | Characteristics of the population across different enrolling periods

Twenty-eight patients were enrolled between 2006 and 2010, 112 between 2011 and 2015, and 94 after 2016. Characteristics of the population enrolled in different periods are presented in Tables 7 and S10. Over time, a greater proportion of patients who had an ICD implanted in primary prevention were enrolled (p for trend = 0.0009) and a VT therapy zone was activated more frequently at baseline (p for trend = 0.019) and during follow-up (p for trend = 0.028).

4 | DISCUSSION

In this retrospective multicenter study of patients with advanced HF implanted with both ICD and L-VAD, the occurrence of appropriate and inappropriate ICD therapies was a frequent event. During a median follow-up of 21 months, the incidence of appropriate therapies was 28.2% while inappropriate therapies occurred in 9.4% of the patients. These data are consistent with those of previously published studies where the incidence of appropriate therapies ranged from 26.1% to 43%.[13,20–22] Previous studies identified the history of VAs, old age, elevated body surface area, prolonged QT interval, electrolyte disorders, the absence of beta-blocker therapy, and history of atrial fibrillation as predictors of ventricular arrhythmias.[7,23–26] As a new finding, in our population the presence of an active VT zone at follow-up was found to be an independent predictor of appropriate ICD therapy and of the composite outcome of appropriate and inappropriate therapies.

TABLE 7 Population's characteristics across different enrolling periods.

	2006–2010 (*N* = 28)	2011–2015 (*N* = 112)	2016–2020 (*N* = 94)	*p*	*p* for trend
ICD characteristics					
Age at ICD implantation	52 (43–60)	57 (50–62)	58 (49–64)	0.17	
Primary prevention	20 (71)	99 (88)	84 (89)	0.009	0.009
Single chamber ICD	11 (39)	37 (33)	19 (20)	0.17	
Dual chamber ICD	3 (11)	19 (17)	22 (23)		
CRT-D	13 (46)	51 (46)	45 (48)		
VT zone on at baseline	1 (4)	48 (43)	53 (56)	0.056	0.019
VT zone threshold at baseline	170	169 (161–170)	167 (160–171)	0.92	
VT zone on at follow-up	2 (7)	29 (26)	32 (34)	0.07	0.028
VT zone threshold at follow-up	–	162 (158–168)	170 (162–180)	0.16	

Note: Data are presented as number (%) or median (interquartile range).

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillation capability; ICD, implantable cardioverter defibrillators; VT zone, ventricular tachycardia zone.

This finding could have a strong clinical importance. Indeed, in our multicenter real-world observational study a VT zone was found to be active in around 40% of the patients with a median detection rate of 167 bpm at the time of L-VAD implantation; this percentage significantly decreased during follow-up but still almost one quarter of the patients had an active VT zone with a median detection rate of 164 bpm at last available visit. This result is particularly striking if we consider that no correlation was found between the presence of an active VT zone and neither the indication for ICD implantation (primary vs. secondary) nor the history of ventricular arrhythmias. This suggest that ICD programming with an active VT zone was mostly driven by a physicians' perceived risk of VA, potentially causing hemodynamically deterioration in this high risk patients, rather than by a real clinical need. Moreover, when we analyzed ICD programming across different study periods we observed a similar- or even higher- percentage of patients with an active VT zone when comparing patients implanted in the last 5 years of the study versus previous periods.

In patients with continuous-flow LVADs, ventricular arrhythmias are often hemodynamically well tolerated and the risk of sudden arrhythmic death is low.[7] Considering the excellent hemodynamically tolerance, most patients remain conscious at the time of an ICD shock with significant negative consequences, both physical and psychological. In addition, most ventricular arrhythmias terminate spontaneously within 24 h.[22,27]

A more conservative programming with longer ICD detection times and higher VA rate cut-off zone has been demonstrated to improve outcomes and survival in general ICD population,[15–17] but few and conflicting data are available in patients with L-VAD.[18,19]

Richardson and colleagues, in a prospective randomized single-center study, compared long detection time programming versus standard ICD programming in patients implanted with L-VAD and found no significant differences in the incidence of total ICD shocks, mortality and hospitalizations between the two groups.[18] On the contrary, Robinson and co-workers, in a single-center retrospective cohort study, observed a reduction of unnecessary ICD treatments with the use of an ultraconservative ICD programming.[19]

Our data suggest that in this population it could be reasonable to choose a conservative programming with only a high-rate active zone in order to reduce the occurrence of both appropriate and inappropriate therapies, also considering that most of the appropriate therapy could be unnecessary.[22,27]

In summary our and previous report can help to drive some practical consideration on ICD programming in patients implanted with L-VAD and to make some considerations for this specific patients' population. First, a single VF zone should be programmed in the vast majority of the patients with the use of the longest as possible detection time. The activation of a VT zone should be reserved to a minority of cases and tailored based on patient's clinical history. When the activation of a VT zone is deemed necessary, ICD programming with an extremely long detection time and ATP only therapy should be considered. Unfortunately, currently available ICDs are not designed for patients implanted with a L-VAD that prevent hemodynamic deterioration even in the case of a fast ventricular arrhythmias. Detection time both for fast and relative slow arrhythmias cannot be prolonged beyond a certain cut-off (i.e., max 25–30 s in VF zone and max 1 min in VT zone for all manufacturers). Moreover ICD are not embedded with

indicators of cardiac output that could trigger therapy delivery only in case of hemodynamic deterioration.

Conversely, prolonged and undetected VAs could cause deterioration of right ventricular function or device thrombosis. In this setting, the use of remote monitoring with active alert in case of sustained monitored VAs could play a central role.

Another important finding of our study was that the rate of both ICD and L-VAD complications was not trivial. Regarding ICD complications, the incidence of pocket hematoma was 4.7% while the incidence of infections was 6.4%.

In a previous study, the incidence of device-related infections at 1 year was 2.8%.[28] The higher incidence of infective complications observed in our population may be partly explained by the longer follow-up and the higher prevalence of CRT-D than in other studies.

Moreover, we observed an independent increase in the risk of the composite outcome of ICD-related complications (defined as infection, hematoma, and inappropriate therapies) in patients who underwent ICD generator replacement during the study. This finding is globally consistent with the observation that the reported rate of infections and pocket hematomas across previously published studies varies according to the proportion of patients included that underwent ICD generator replacement.

For instances, a recently published study showed an incidence of pocket hematoma of 2.9% in a population with only around 25% of patients in the need of generator replacement[29]; on the contrary, in other studies including only patients who underwent ICD de novo implantation, device revision or generator replacement (about 60%) after L-VAD implantation, the incidence of pocket hematoma was significantly higher (ranged from 13.1% to 18%).[14,30] In our study the incidence of pocket hematoma was 4.7% and about 16% of patients reached the ERI during follow-up, the vast majority of whom (88% accounting for 14% of the total study population) actually replaced the ICD generator.

With this in mind, at the time of battery depletion it may be reasonable to carefully evaluate the risk/benefit ratio of device replacement, since generator replacement significantly increases the risk of infections and all ICD-related complications, while survival benefit of ICD therapy is not fully proven in this population.

As mentioned earlier, a first strategy to reduce battery consumption is to optimize the device programming in order to avoid early intervention on arrhythmias that are well hemodynamically tolerated and potentially self-limiting.

At the time of generator replacement, it is essential to pay the utmost attention to surgical asepsis and the use of an antibacterial envelope might be considered. Moreover, especially in patients implanted with new generation L-VAD, which are associated with a lower thrombotic risk, it is possible to keep a relatively low peri-procedural INR ratio (between 1.5 and 2) in order to reduce the risk of pocket hematoma, which is a well-known risk factor of infections.[31,32]

4.1 | Limitation

Our study has several limitations. First, its observational and retrospective nature determines intrinsic limitations in term of selection bias and unmeasured confounding factors. However we included all consecutive L-VAD patients implanted with an ICD from five different tertiary centers, while focusing on modifiable data related to baseline characteristics, and ICD and L-VAD features. Second, data regarding mortality and hospitalizations were not available so we cannot rule out whether a conservative ICD programming might affect hard clinical endpoints. Future studies are needed to clarify this issue.

Third, the clinical reasons why a VT zone with low ventricular rate was activated were not known. Nevertheless, the fact that an active VT zone was an independent predictor of total ICD therapies even when corrected for the indication to ICD implantation (primary vs. secondary prevention) significantly strengthen our findings.

Moreover, data about VT/VF detection time, incidence of atrial arrhythmias and whether SVT discriminators were active and optimized was not consistently reported in our study. It is well acknowledged that well-programmed SVT discriminators can reach a good diagnostic accuracy thus limiting the risk of inappropriate therapies.[33]

Finally, all device interventions were considered in the outcome. Therefore, it was not possible to separately analyze ICD shock from anti-tachycardia pacing (ATP).

Although the sample size is relevant in view of the type of patients under study, further data on a larger sample of patients are needed to confirm our results.

5 | CONCLUSIONS

Patients with L-VAD implanted with an ICD experience a high rate of appropriate and inappropriate ICD therapies. An active VT zone at low heart rate was found to be an independent predictor of ICD therapies. Moreover, ICD generator replacement was found to be an independent predictor of total complications related to the ICD. Considering that a clear survival benefit of ICD therapy is not fully proven in this population, our findings underline the importance of tailoring the device programming

in order to minimize the incidence of unnecessary ICD therapies, thus improving patients' quality of life and also reducing the need for generator replacement, a procedure associated to a higher risk of complications.

AUTHOR CONTRIBUTIONS

Roberto Rordorf, Leonardo Pignalosa, Matteo Casula, Simone Gulletta: Concept/design; Data analysis/interpretation; Data collection; Drafting article; Critical revision of article. **Enrico Perna, Matteo Baroni, Andrea Garascia, Stefania Guida, Fabrizio Gazzoli, Daniela Pini, Francesco Cannata, Marta Pellegrino, Claudia Vittori, Paolo De Filippo, Giovanni Malanchini, Pasquale Vergara, Paolo Della Bella**: Data collection; Critical revision of article; Approval of article.

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CONFLICT OF INTEREST STATEMENT

Roberto Rordorf received modest speaker fees from Abbot and Boston Scientific, Enrico Perna and Andrea Garascia received fees for lectures by Abbott, Matteo Baroni received fees for lectures and proctorship by Abbott and Biotronik, Paolo De Filippo received speaker fees and educational grants from Abbot, Boston Scientific, Biotronik and Medtronic. The other authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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