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Predictors and Clinical Impact of Late Ventricular Arrhythmias in Patients With Continuous-Flow Left Ventricular Assist Devices

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ABSTRACT

OBJECTIVES This study aimed to evaluate the incidence, clinical impact, and predictors of late ventricular arrhythmias (VAs) in left ventricular assist device (LVAD) recipients aiming to clarify implantable cardioverter-defibrillator (ICD) indications.

BACKGROUND The arrhythmic risk and need for ICD in patients implanted with an LVAD are not very well known.

METHODS This observational study was conducted in 19 centers between 2006 and 2016. Late VAs were defined as sustained ventricular tachycardia or fibrillation occurring >30 days post-LVAD implantation, without acute reversible cause and requiring appropriate ICD therapy, external electrical shock, or medical therapy.

RESULTS Among 659 LVAD recipients, 494 (median 58.9 years of age; mean left ventricular ejection fraction 20.7 ± 7.4%; 73.1% HeartMate II, 18.6% HeartWare, 8.3% Jarvik 2000) were discharged alive from hospital and included in the final analysis. Late VAs occurred in 133 (26.9%) patients. Multivariable analysis identified 6 independent predictors of late VAs: VAs before LVAD implantation, atrial fibrillation before LVAD implantation, idiopathic etiology of the cardiomyopathy, heart failure duration >12 months, early VAs (<30 days post-LVAD), and no angiotensin-converting enzyme inhibitors during follow-up. The "VT-LVAD score" was created, identifying 4 risk groups: low (score 0 to 1), intermediate (score 2 to 4), high (score 5 to 6), and very high (score 7 to 10). The rates of VAs at 1 year were 0.0%, 8.0%, 31.0% and 55.0%, respectively.

CONCLUSIONS Late VAs are common after LVAD implantation. The VT-LVAD score may help to identify patients at risk of late VAs and guide ICD indications in previously nonimplanted patients. (Determination of Risk Factors of Ventricular Arrhythmias [VAs] after implantation of continuous flow left ventricular assist device with continuous flow left ventricular assist device [CF-LVAD] [ASSIST-ICD]; NCT02873169) (J Am Coll Cardiol EP 2018;4:1166–75) © 2018 by the American College of Cardiology Foundation.

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The prevalence of end-stage heart failure has continued to increase during the last decade. Heart transplantation remains the optimal option for these patients, but access is limited by donor shortage. Continuous-flow left ventricular assist device (LVAD) implantation has been shown to improve survival and is increasingly used as a bridge or alternative to transplantation (the so-called destination therapy) (1-4).

In patients with heart failure and reduced ejection fraction, ventricular arrhythmias (VAs) are common and contribute to increased mortality (5). The role of the implantable cardioverter-defibrillator (ICD) for the primary prevention of sudden cardiac death in this population has been well established in numerous large trials and meta-analyses, especially in ischemic cardiomyopathy (6-8). VAs are common in patients with LVAD, but are often asymptomatic or paucisymptomatique because of the continuous flow of the LVAD, ensuring efficient hemodynamic support (9-17). The residual risk of VAs after LVAD implantation, their clinical impact, and the effectiveness of ICDs in reducing mortality in this population remain controversial (18-20). Data are scarce and are mainly based on small, single-center studies (10-15).

The purpose of this large, multicenter observational study was to characterize the incidence, predictors, and clinical impact of late VAs in patients with LVADs.

METHODS

STUDY DESIGN. The ASSIST-ICD (Determination of Risk Factors of Ventricular Arrhythmias After Implantation of Continuous Flow Left Ventricular Assist Device With Continuous Flow Left Ventricular Assist Device) study is a retrospective, multicenter observational study (NCT02873169) of durable mechanical circulatory support devices implanted in 19 tertiary French centers.

Patients ≥18 years of age who had been implanted with axial HeartMate II (Abbott, Chicago, Illinois), Jarvik 2000 (Jarvik Heart, New York, New York), or centrifugal HeartWare pumps (Medtronic, Columbia Heights, Minnesota) between February 2006 and December 2016 and discharged from the hospital with or without an ICD were included in the final analysis. The type of pump implanted depended on the local heart team's decision in each center. Exclusion criteria were patients who underwent total artificial heart placement or pulsatile-flow LVAD, history of heart transplant, death or heart transplantation before discharge from hospital after LVAD implantation, and VentrAssist (Ventracor, Chatswood, Australia) recipients.

This study was approved by the regional ethic committees, the French Advisory Committee on the Treatment of Research Information in the

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme
AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
IQR = interquartile range
LVAD = left ventricular assist device
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

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Field of Health, and the French National Commission of Informatics and Civil Liberties. A nonopposition letter was sent to the patients, as requested by French authorities for retrospective studies.

BASELINE ASSESSMENT AND FOLLOW-UP. Baseline data—including demographic characteristics, cardiac disease and heart failure history, VAs and radiofrequency ablation procedures before or after LVAD implantation history, heart failure medical therapy, echocardiography, and blood chemistry values—were collected from hospital files for all enrolled patients. The echocardiographic and blood sample data used for the analysis were the last performed before LVAD implantation. To note, nonischemic cardiomyopathy had an extensive work-up to define the etiology of the cardiomyopathy. Cardiac magnetic resonance or nuclear imaging evaluation were performed on physicians' discretion. In case of young patients or for those with a familial history of dilated cardiomyopathy, genetic analyses were performed. If specific etiology was found, the patient was classified as "other cardiomyopathy" and in cases of no specific etiology, the cardiomyopathy was classified as idiopathic. Regarding pathology, the apical portion of the left ventricle was analyzed after LVAD implantation and patients were reclassified in "other cardiomyopathies" if a specific etiology was found.

Follow-up was performed according to each institution's protocols. ICD interrogation was performed every 3 to 6 months, depending on if the device had remote monitoring capabilities. The LVAD controller monitor was checked during every clinical visit in each center, according to state-of-the-art standard of care for LVAD recipients. The last day of follow-up was December 31, 2016; the date of heart transplantation; or death, whichever occurred first.

VENTRICULAR ARRHYTHMIAS. In this study, VAs were defined as sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) without an acute reversible cause and treated medically, by external electrical shock, or appropriate therapy from an ICD (antitachycardia pacing or shock). The number and type of arrhythmias and specific therapies to restore sinus rhythm were collected. VAs were classified in 3 groups according to their time of occurrence: VAs before LVAD implantation; early VAs post-LVAD implantation (occurring within 30 days after the surgery); and late VAs post-LVAD (VAs occurring after 30 days). Electrical storm was defined as 3 or more VA episodes in <24 h.

In ICD recipients, device interrogation was performed during unplanned hospitalizations or every 3 to 6 months by a local electrophysiologist in each center. ICD programming was left to the physicians' discretion. For patients without ICD before LVAD, the decision to implant an ICD after surgery was left to the discretion of the attending physician. When available, electrocardiogram strips or electrograms of VA episodes were collected. All antiarrhythmic drug therapies introduced or continued after LVAD implantation were recorded. Routine evaluation of patients with VAs included echocardiography (to exclude suction events leading to mechanical VAs) or a coronary angiography (when an ischemic origin of VAs was suspected). Only late VAs were considered for this paper.

STUDY ENDPOINTS. The primary endpoint of the study was the rate of late VAs. Secondary endpoints included all-cause mortality (with or without VA and with or without ICD) and ICD-related complications. Deaths were classified as cardiovascular death (cardiac or vascular cause), noncardiac death, or unknown cause. Postmortem ICD interrogations, when available, were reviewed to exclude an arrhythmic cause of death.

STATISTICAL ANALYSIS. Qualitative variables are expressed as number (percentage) and continuous data as mean ± SD or median (interquartile range [IQR]) depending on their distribution, which was assessed using the Kolmogorov-Smirnov test. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Predictors of late VAs post-LVAD were analyzed using univariate and multivariable proportional hazard models (cumulative outcomes). The proportional hazards assumption was tested and verified for each covariate. Receiver-operating characteristic curves were used to categorize continuous variables with a p value <0.10 in univariable analysis by selecting clinically relevant cutoffs, which were the closest to the optimal cutoff according to the maximum Youden index (sensitivity + specificity) (21). All univariate analyses were performed on complete cases.

Overall, 18.2% of patients had missing values for at least 1 variable, but, of note, only 3 variables were concerned: serum creatinine, left ventricular enddiastolic dimension, and total bilirubin (7.5%, 7.5%, and 13.4% of missing data, respectively). For the purposes of the multivariable analysis, missing data were handled by multiple imputations using the Markov chain Monte Carlo method after Little's test had confirmed that they were missing completely at random. Twenty imputed datasets were created; results were pooled according to Rubin's rule (22) and reported as adjusted hazard ratios (HRs) with their

95% confidence intervals (CIs). Variables with p values <0.10 in univariate analysis were included in the multivariable analysis. To account for the multicenter design of the study, the site variable was forced in the model and used as an adjustment variable in all subsequent analyses. A manual backward stepwise process was applied to identify the best parsimonious set of predictors using entry and exit thresholds of 0.05 and 0.10, respectively. The absence of multicollinearity in the final model was verified using tolerance and variance inflation factor measurements. Variables identified in this model were used to derive a risk score stratifying patients regarding their risk of late VA occurrence. A 1,000-fold bootstrap resampling was performed to calculate a shrinkage factor, which was applied as a multiplier to regression coefficients of the final model to avoid overfitting to the development data (23). The corrected coefficients of significant multivariable predictors ($p < 0.05$) were divided by the lowest coefficient value in the model and rounded to the nearest integer to assign a risk score weight to each predictor in the model. Each patient's risk score was calculated by adding these weights. An objective assessment of calibration was obtained by performing the Hosmer-Lemeshow goodness-of-fit test. The predictive performance of the risk score was assessed by the C-statistic, which was 100-fold cross-validated to evaluate the expected decrease in discriminative ability among new patients (23). Kaplan-Meier estimates were used to construct the survival curves based on all available follow-up for the time-to-event analysis and were plotted by risk levels. All tests were 2-sided at the 0.05 significance level. Statistical analyses were conducted using the SPSS version 22 (IBM, Armonk, New York) and Stata Statistical Software release 13 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION. From 2006 to 2016, 659 patients were implanted with a continuous-flow LVAD and included in the study. Among these, 142 patients died and 7 were heart transplanted during initial hospitalization. Three patients were excluded because they received VentrAssist. A total of 507 patients were discharged alive from hospital. Thirteen patients had missing data and 494 were followed up and included in the final analysis.

Baseline characteristics of the 494 patients are presented in Table 1. Overall, 87.0% were men and 63.0% had an ischemic cardiomyopathy, and the median heart failure duration was 55.5 (IQR: 1.9 to 158.9) months. A total of 165 (33.4%) patients had a history of at least 1 sustained VT or VF, whereas 229 (46.4%) patients had a history of atrial fibrillation (AF) before LVAD. The HeartMate II device was the most common LVAD implanted (73.1%) and the leading indication was bridge to transplantation (63.8%). The median duration of follow-up for all patients was 18.84 (IQR: 6.61 to 26.98) months.

After LVAD implantation, the mean VT and VF detection rates programmed in ICDs were 177.5 ± 17.4 beats/min and 226.0 ± 12.5 beats/min, respectively. Monitor zone was activated in 69 patients with a VT detection rate of 152.3 ± 20.9 beats/min.

INCIDENCE, PREDICTORS, AND RISK STRATIFICATION OF LATE VAs. A total of 112 (22.7%) patients had early VAs and 133 (26.9%) had late VAs. Incidence rates of late VAs were 22.30 (IQR: 18.80 to 26.40) patients for 100 person-years. Late VAs occurred a median of 5.30 (IQR: 2.00 to 14.60) months after LVAD implantation. Late VAs were symptomatic in only 15 (11.3%) patients. Three had syncope during episodes of VF, whereas the remaining 12 patients had "minor" symptoms, such as palpitations or dyspnea. No cardiac arrest occurred due to late VAs. Compared with patients without late VAs, those with late VAs were significantly older, were more often men, were more likely to present idiopathic cardiomyopathies, had more dilated left ventricles, and had a longer median heart failure duration (Table 1). They also more often had a history of VAs or AF, and were significantly more likely to have had early VAs. Patients with late VAs were significantly less likely to receive angiotensin-converting enzyme (ACE) inhibitors.

Among patients with late VAs, 31 (23.3%) experienced VF episodes (total number of episodes: 125; median 1.0 (IQR: 1.0 to 3.0) episode per patient) and 118 (88.7%) patients experienced VT episodes (total number of episodes: 1,706; median 3.0 (IQR: 1.0 to 10.0) episodes per patient). The number of late VAs varied widely between patients: 29.3% had 1 late VA episode and 22 (16.5%) patients had >20 episodes. Electrical storms occurred in 21.0% of patients. Catheter ablation of VT was performed in 15 patients, and 3 required redo procedures.

Multivariable analysis identified 6 independent predictors of late VAs: history of VAs before LVAD implantation, history of AF before LVAD implantation, idiopathic etiology of the cardiomyopathy, heart failure duration >12 months, occurrence of early VAs (<30 days) post-LVAD, and no ACE inhibitors post-LVAD (Table 2).

To predict the risk of occurrence of late VAs, a score was created using the statistically significant variables independently predictive of the occurrence of late VAs as described in the statistical analysis

TABLE 1 Baseline Demographics

	All Patients (N = 494)	Late VA Post-LVAD (n = 133)	No Late VA Post-LVAD (n = 361)	p Value
Age, yrs	58.9 (50.3–65.8)	60.5 (54.9–66.3)	58.0 (48.9–65.3)	0.006
Male	430 (87.0)	125 (94.0)	305 (84.5)	0.008
Hypertension	172 (34.8)	45 (33.8)	127 (35.2)	0.832
Diabetes mellitus	109 (22.1)	24 (18.0)	85 (23.5)	0.222
Dyslipidemia	209 (42.3)	62 (46.6)	147 (40.7)	0.259
History of smoking	302 (61.1)	84 (63.2)	218 (60.4)	0.604
Family history	81 (16.4)	21 (15.6)	60 (16.6)	0.892
Heart failure etiology				0.007
Ischemic	311 (63.0)	71 (53.4)	240 (66.5)	
Idiopathic	138 (27.9)	51 (38.3)	87 (24.1)	
Other	45 (9.1)	11 (8.3)	34 (9.4)	
Heart failure duration, months	55.5 (1.9–158.9)	113.5 (38.5–215.4)	23.4 (1.1–134.2)	<0.001
History of VAs	165 (33.4)	74 (55.6)	91 (25.2)	<0.001
VT ablation before LVAD	23 (4.7)	15 (11.3)	8 (2.2)	<0.001
History of AF	229 (46.4)	85 (63.9)	144 (39.9)	<0.001
LVEF before LVAD, %	20.7 ± 7.4	20.0 (15.0–25.0)	20.0 (15.0–25.0)	0.996
LVEDD before LVAD, mm	69.7 ± 10.1	73.0 (68.0–78.0)	69.0 (63.0–73.0)	<0.001
Biology				
Serum creatinine, μmol/l	112.0 (87.0–144.2)	124.0 (100.0–147.5)	108.0 (82.0–143.0)	0.005
Total bilirubin, μmol/l	15.0 (10.0–24.0)	15.5 (10.0–27.0)	15.0 (10.0–23.0)	0.409
Serum sodium, mmol/l	136.0 (132.0–139.0)	135.5 (132.0–138.0)	136.0 (132.0–139.0)	0.459
LVAD				0.112
HeartMate II	361 (73.1)	106 (79.7)	255 (70.6)	
HeartWare	92 (18.6)	20 (15.0)	72 (19.9)	
Jarvik 2000	41 (8.3)	7 (5.3)	34 (9.4)	
Indication				0.289
Bridge to transplantation	315 (63.8)	79 (59.4)	236 (65.4)	
Destination therapy	170 (34.4)	50 (37.6)	120 (33.2)	
Bridge to decision/recovery	9 (1.8)	4 (3.0)	5 (1.4)	
Early VAs post-LVAD (<30 days)	112 (22.7)	53 (39.8)	59 (16.3)	<0.001
Drugs post-LVAD implantation				
Beta-blockers	288 (58.9)	76 (57.1)	212 (58.7)	0.579
Angiotensin receptor blockers	8 (1.6)	3 (2.3)	5 (1.4)	1.000
ACE inhibitors	239 (48.4)	47 (35.3)	192 (53.2)	<0.001
MRA	180 (36.4)	58 (43.6)	122 (33.8)	0.049
Amiodarone	195 (39.5)	56 (42.1)	139 (38.5)	0.534
LVAD with ICD	372 (75.3)	125 (94.0)	247 (68.4)	<0.001
LVAD with cardiac resynchronization therapy	148 (30.0)	60 (45.1)	88 (24.4)	<0.001

Values are median (interquartile range), n (%), or mean ± SD.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MRA = Mineralocorticoid receptor antagonist; VA = ventricular arrhythmia; VT =ventricular tachycardia.

parts. The C-statistic of the score was 0.77 (95% CI: 0.73 to 0.82) whereas the p value of the Hosmer-Lemeshow test was 0.59. A 100-fold cross-validation showed only weakly decreased discrimination, with a C-statistic of 0.74 (95% CI: 0.69 to 0.79). This resulted in the VT-LVAD score rule (Figure 1) showing a gradual increase in the risk of late VAs with increasing score. Dividing patients into 4 groups according to their score—low risk: 0 to 1 (n = 69 [14.0%]), intermediate risk: 2 to 4 (n = 213 [43.1%]), high risk: 5 to 6 (n = 121 [24.5%]), and very high risk: 7 to 10 (n = 91 [18.4%])—allowed a good risk assessment of the occurrence of late VAs. Indeed, as shown in Figure 1, the 1-year and 3-year risks of late VAs in patients with scores of 0 to 1, 2 to 4, 5 to 6, and 7 to 10 were 0% and 12%, 8% and 30%, and 31% and 62%, and 55% and 79%, respectively.

OUTCOMES. A total of 151 (30.6%) patients died during the follow-up period, among whom 47 had a history of late VAs and 104 did not (Table 3). Neither the occurrence of late VAs nor the presence of an ICD significantly had an impact on overall survival (Figure 2). However, patients with late VAs

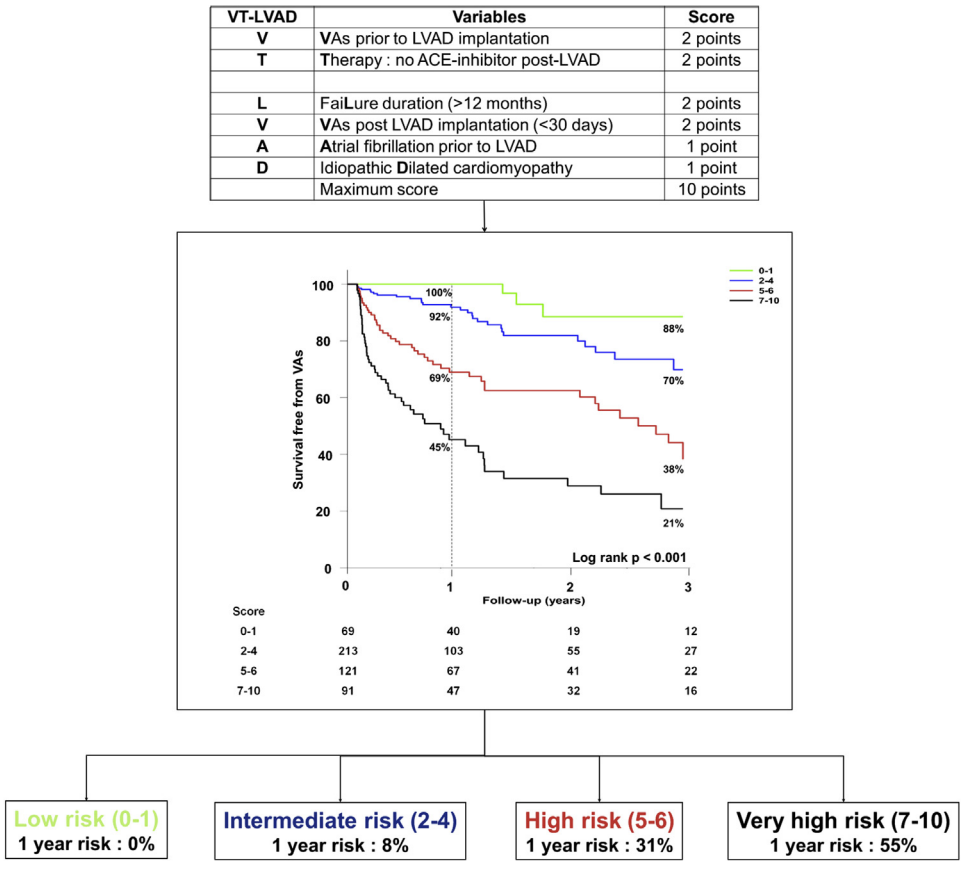
TABLE 2 Multivariable Analysis for Risk Prediction of Late VAs

	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value	β	Shrinkage Factor-Corrected β	Risk Score-Assigned Weight
Age >50 yrs	1.020 (1.003–1.038)	0.019	–	–	–	–	
Male	2.280 (1.120–4.660)	0.024	–	–	–	–	
LVEDD >70 mm	1.030 (1.020–1.050)	<0.001	–	–	–	–	
VAs before LVAD	3.090 (2.19–4.350)	<0.001	2.320 (1.560–3.430)	<0.001	0.840	0.746	2
VT ablation before LVAD	3.410 (1.990–5.850)	<0.001	–	–	–	–	
AF before LVAD	2.310 (1.620–3.300)	<0.001	1.720 (1.150–2.580)	0.009	0.543	0.482	1
Idiopathic DCM (vs. ischemic)	2.000 (1.390–2.870)	<0.001	1.500 (1.010–2.220)	0.045	0.404	0.359	1
Creatinine >100 μmol/l*	1.002 (1.000–1.004)	0.058	–	–	–	–	
Bilirubin >20 mmol/l*	1.008 (0.999–1.020)	0.078	–	–	–	–	
Heart failure duration >12 months*	1.002 (1.002–1.003)	<0.001	2.580 (1.470–4.530)	0.001	0.946	0.840	2
Early VA post-LVAD	2.700 (1.910–3.830)	<0.001	2.050 (1.390–3.020)	<0.001	0.717	0.637	2
No ACE inhibitors post-LVAD	2.020 (1.420–2.890)	<0.001	2.140 (1.420–3.240)	<0.001	0.762	0.677	2
No MRA post-LVAD	0.720 (0.510–1.020)	0.061	–	–	–	–	
LVAD with CRT	2.210 (1.570–3.120)	<0.001	–	–	–	–	

*Creatinine, bilirubin, and heart failure duration optimal cutoff were defined using receiver-operating characteristic curves.

CI = confidence interval; CRT = cardiac resynchronization therapy; DCM = dilated cardiomyopathy; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 1 VT-LVAD Risk Score



Risk stratification by the VT-LVAD score and the proposed strategy in patients without an implantable cardioverter-defibrillator (ICD) before left ventricular assist device (LVAD) implantation. ACE = angiotensin-converting enzyme; VA = ventricular arrhythmia.

TABLE 3 Outcomes During Follow-Up Period

	All Patients (N = 494)	Late VA Post-LVAD (n = 133)	No Late VA Post-LVAD (n = 361)	p Value
Heart transplantation	187 (37.8)	43 (32.2)	144 (39.9)	0.152
Total death	151 (30.6)	47 (35.3)	104 (28.8)	0.198
Cause of death				0.005
Cardiovascular death*	64 (42.4)	29 (61.7)	35 (33.7)	
Noncardiaovascular death*	82 (54.3)	17 (36.2)	65 (62.5)	
Unknown cause*	5 (3.3)	1 (2.1)	4 (3.8)	
Cardiovascular death				0.616
LVAD thrombosis	25 (5.1)	9 (6.8)	16 (4.4)	
Right ventricular failure	23 (4.7)	10 (7.5)	13 (3.6)	
Electrical storm	7 (1.4)	7 (5.3)	0 (0)	
LVAD dysfunction	2 (0.4)	1 (0.8)	1 (0.3)	
No precision	5 (1.0)	2 (1.5)	3 (0.8)	

Values are n (%). *Percentage of total deaths.
Abbreviations as in Table 1.

were significantly more likely to die from a cardiovascular cause than were patients with no late VAs (Table 3).

Among the 372 patients with an ICD (71%), 57 (15.3%) patients had complications related to their device after LVAD implantation. The main complications were inappropriate therapies, including shocks (n = 23 [6.2%]) or antitachycardia pacing (n = 7 [1.9%]), and device infections (n = 7 [1.9%]). Among patients with ICD related infections, 4 did not undergo reimplantation of an ICD. Interference between the ICD and the LVAD were documented in 18 (4.8%) patients. They were temporary for 10 patients but necessitated an ICD replacement in the other 8.

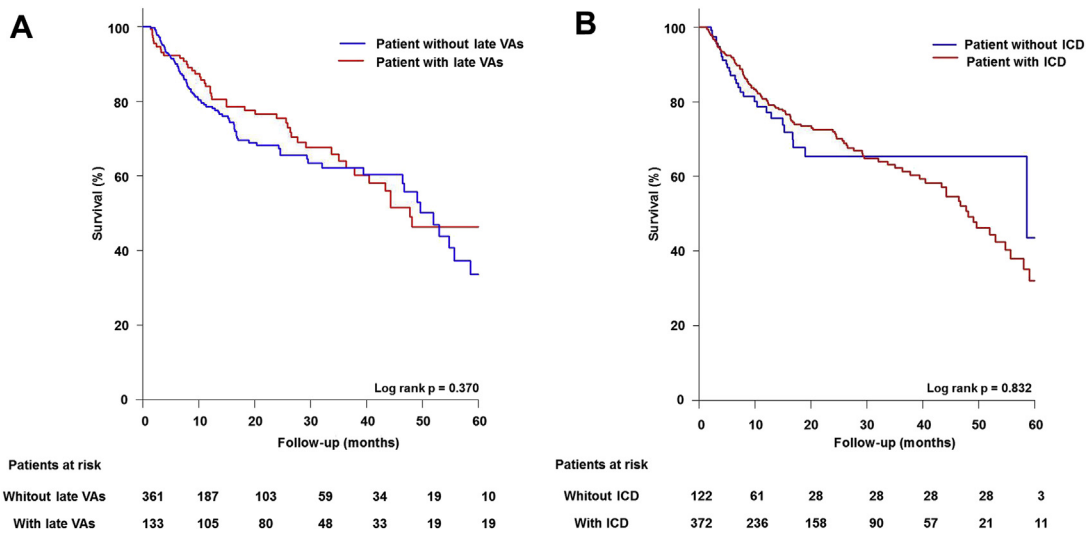
DISCUSSION

To our knowledge, this is the largest database on VAs in patients with LVADs that aimed to describe the predictors and clinical significance of late VAs after LVAD implantation. There are 4 main findings. First, late VAs are common in patients with LVADs, affecting 26.9% of patients during a median follow-up of 18.84 (IQR: 6.61 to 26.98) months. Second, we identified 6 predictors of late VAs: history of VAs before LVAD implantation, history of AF before LVAD implantation, idiopathic etiology of the cardiomyopathy, heart failure duration >12 months, occurrence of early VAs (<30 days) post-LVAD, and no ACE inhibitors post-LVAD. Third, we created a risk-stratification scale to estimate the probability of late VAs in LVAD patients—the "VT-LVAD score"—enabling the differentiation of 4 groups of patients with varying risks of late VAs (0 to 1 = low, 2 to 4 = intermediate, 5 to 6 = high, and 7 to 10 = very high). Fourth, there were no significant differences in total mortality between patients with or without late VAs and patients with or without an ICD.

VAs IN LVAD RECIPIENTS. VAs occur frequently in LVAD recipients. In patients with continuous-flow LVADs, the rate of late VAs has been estimated to range between 19% and 34% after a mean follow-up of 8 to 12 months (9-15). A similar rate was observed in our study, with late VAs documented in 26.9% of patients after a median follow-up of 18.84 months. Usually, VAs in patients with LVADs are well tolerated (17,24). Indeed, an efficient cardiac output is ensured by the LVAD, which explains why some patients may remain asymptomatic in VT or VF during hours or days before presenting with dyspnea or right ventricular dysfunction. To avoid such complications, which have been shown to increase mortality (25,26), patients are often implanted with an ICD, although clear recommendations are lacking. To clarify this point, some authors have analyzed whether concomitant ICD implantation was necessary in LVAD recipients. In a cohort of 94 patients, Garan et al. (10) found no difference in survival between patients with and without an ICD, and suggested recommending ICD implantation only in patients with VAs before LVAD. Similarly, Younes et al. (19) showed that the presence of an ICD in bridge-to-transplantation LVAD patients was not associated with lower waitlist mortality. Two recent meta-analyses showed that ICD use was associated with a significant reduction in mortality in LVAD patients, although this effect was not significant in patients with continuous-flow LVADs (20,27). Thus, a careful evaluation of LVAD recipients must be performed to select patients at risk of VAs requiring ICD implantation, particularly because the ICD itself may be responsible for complications (15.3% of our population).

PREDICTORS OF VAs. In our study, 6 independent predictors of late VAs were identified. The occurrence of pre-LVAD arrhythmias, regardless of their atrial or ventricular origin, has been described as a strong predictor of late VAs. Indeed, a history of VAs increases the risk of recurrence (12,14), as is the case for all cardiomyopathies. Positive and negative predictive values of preoperative VAs to predict the occurrence of late VAs have been reported to reach 45.5% and 96.0%, respectively (10), undoubtedly explained by the persistence of the underlying substrate despite LVAD implantation. Regarding the history of AF, the occurrence of atrial arrhythmias in patients with cardiomyopathies is a well-known turning point in the disease process, reflecting the impact of advanced heart failure on myocardial

FIGURE 2 Survival Curves



Survival depending **(A)** the occurrence of late ventricular arrhythmias (VAs) and **(B)** the presence of an implantable cardioverter-defibrillator (ICD).

substrate. Similarly to what was observed in the present study, Yoruk et al. (12) found that AF was a significant predictor of late VAs in a cohort of 145 patients implanted with the HeartMate II. Recently, Efimova et al. (28) found that AF predict the occurrence of late VAs after LVAD implantation. Thus, the arrhythmic history—including atrial and ventricular arrhythmia—of LVAD recipients should be carefully assessed to evaluate their future risk of VAs.

The etiology of the cardiomyopathy is a controversial predictive factor of late VAs. A study published in 2005 suggested that patients with ischemic cardiomyopathies were at higher risk for late VAs (29), but this result should be interpreted with caution, as patients were implanted with pulsatile- and continuous-flow LVADs, which is not representative of current practice. Conversely, in 2015, Garan et al. (30) showed that patients with nonischemic cardiomyopathies were at risk for early VAs. In our cohort, as demonstrated by others (13,15), we found that idiopathic dilated cardiomyopathy was an independent predictor of late VAs. In addition to the type of underlying cardiomyopathy, the delay between heart failure diagnosis and LVAD implantation was found to be a strong predictor of late VAs. One may hypothesize that patients with a shorter history of heart failure have less adverse electrophysiological and structural remodeling predisposing to VAs (31).

Last, regarding the postoperative period, early VAs and medical therapy were found to be strong predictors of late VAs. Early VAs are frequently related to postoperative instable hemodynamics, proarrhythmic effects of inotropic agent, electrolyte imbalance, or a suction effect of the pump, but also reflect per se the severity of myocardial remodeling and its susceptibility to VAs, as recently demonstrated by Garan et al. (30). Regarding medical treatment after LVAD implantation, the lack of ACE inhibitor therapy was found to be predictive of late VAs. In fact, no ACE inhibitor in LVAD-supported patients is associated with a significant reversal in adverse cardiac remodeling compared with LVAD support alone (32). Reverse myocardial remodeling could explain such an effect, although a prescription bias (potential nonprescription of the drug to sicker patients) or a different blood potassium level cannot be excluded. Furthermore, right ventricular function after LVAD implantation was not systematically collected. Patients with poor right ventricular function often cannot tolerate an ACE inhibitor, and an influence of right ventricular function on the occurrence of VA cannot be excluded. Of note, post-LVAD amiodarone and beta-blocker prescription did not decrease the risk of late VAs.

CLINICAL IMPLICATIONS. To evaluate the long-term arrhythmic risk in LVAD recipients, a score using 6 variables was developed, with a total score ranging

from 0 to 10. Using this so-called VT-LVAD score, a risk stratification can be proposed as follows: low risk (score 0 to 1), intermediate risk (score 2 to 4), high risk (score 5 to 6), and very high risk (7 to 10), corresponding to 1- and 3-year VA risks of 0% and 12%, 8% and 30%, 31% and 62%, and 55% and 79%, respectively. As ICD implantation carries its own risk, we propose the VT-LVAD score as a patient-tailored approach to predict arrhythmias and help physicians deciding whether an ICD should be implanted or replaced. In fact, ICD implantation should be considered for patients at high and very high risk of VAs, whereas those with no predictor could be considered at low risk of VAs and ICD implantation questioned due to the potential lower benefit of ICDs with the same risks. In the same way, the decision for patients at intermediate risk should be made on an individual basis, balancing the likely benefit of ICD against the risk of complications. This stratification system and attitude should be externally validated in future studies.

One may question the importance of predicting VT or VF in LVAD recipients, knowing that the occurrence of late VAs and the presence of an ICD did not influence overall survival. However, although often initially asymptomatic, sustained VAs may be responsible for heart failure symptoms and right ventricular dysfunction, if not treated. Such sustained arrhythmias may lead to unplanned hospitalizations and significant morbidity. The potentially deleterious effects of untreated VT or VF on outcome in LVAD patients will need to be more carefully studied. Last, VT ablation could be proposed after LVAD implantation in patients with recurrent late VT episodes. Data are compelling, showing that radiofrequency ablation is feasible and safe in such patients (33,34).

STUDY LIMITATIONS. Our observational study has some limitations, including its retrospective design, which might have affected the results. Some patients did not have an ICD during follow-up and might have presented nondetected self-terminated VT. However, this represents the "real life" of LVAD recipients. Indeed, some patients have a long history of heart failure and are already implanted with an ICD before receiving mechanical support, whereas some have a rapidly evolving cardiomyopathy that requires LVAD implantation before an ICD could be implanted.

As previously stated, VAs are often asymptomatic in LVAD recipients, and consequently, the real rate of VAs in patients without ICDs is probably underestimated. However, as stated previously, although often initially asymptomatic, sustained VAs, if not treated, will eventually lead to HF symptoms and arrhythmia recognition. Thus, we believe that a limited number of self-terminated sustained events might have been missed during the follow-up of patients with no ICDs.

Conversely, for ICD recipients, device programming was left to the physicians' discretion, which largely influences the number of detected and treated VAs. Indeed, some VT or VF episodes could have been nonsustained and self-terminated if not treated by the ICD, possibly overestimating the rate of VAs. However, the 26.9% rate of VAs after a median of 18.84 months of follow-up is consistent with published data (9–15). Furthermore, postmortem ICD interrogation was not routinely performed, possibly underestimating the rate of VAs and cardiac deaths.

Last, the lack of an adequate external validation for the VT-LVAD score is a major limitation of the present study that should be addressed in future studies.

CONCLUSIONS

Late VAs are common after LVAD implantation. The VT-LVAD score, based on 6 parameters, might help to identify patients at risk of late VAs and guide ICD indications in previously nonimplanted patients or for ICD replacement in LVAD recipients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The proposed VT-LVAD score combines 6 factors of late VAs in patients with LVADs. This can be used to guide the need for an ICD.

TRANSLATIONAL OUTLOOK: This score risk requires prospective external validation in other LVAD populations.

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