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To cite this version:

Angeliki Darma, Arash Arya, Nikolaos Dagres, Michael Kuehl, Gerhard Hindricks, et al.. Validation of the VT-LVAD score for prediction of late VAs in LVAD recipients. Journal of Cardiovascular Electrophysiology, 2021, 32 (2), pp.515-522. 10.1111/jce.14827 . hal-03095616

HAL Id: hal-03095616

https://hal.science/hal-03095616

Submitted on 12 Jan 2021

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Validation of the VT-LVAD Score for Prediction of Late VAs in LVAD Recipients

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Short title: VT-LVAD score for prediction of late VAs

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Manuscript type: Original Article

Word count including tables, references and figure legends: 4270

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not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.14827.

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Abstract

INTRODUCTION:

Objectives

This study sought to validate the performance of the VT-LVAD risk model in predicting late ventricular arrhythmias (VAs) in patients after left-ventricular assist device (LVAD) implantation.

Background

The need for ICD-implantation in LVAD-recipients is not well studied. A better selection of the patients with high risk for late VAs could lead to a more targeted ICD-implantation or replacement.

Methods

The study evaluated the performance of the VT-LVAD prognostic score [VAs prior LVAD, no ACE-inhibitor in medication, heart failure duration >12 months, early VAs post LVAD implantation, atrial fibrillation prior LVAD, idiopathic dilated cardiomyopathy] for the endpoint of the occurrence of late VAs in 357 LVAD-patients in Heart Centre of Leipzig.

Results

From the initial 460 patients, 357 (age 58 ± 10 years; left ventricular ejection fraction: 20 ± 6%; HeartWare: 50%; HeartMate III: 42%) were assigned to four risk groups according to their VT-LVAD-score varying from low risk to very high risk. After 25 months, late VAs occurred in 130 patients. The VT-LVAD score was an independent predictor of late VAs (multivariate analysis; p= <0.001; goodness-of-tip p=.347, OR 4.8). While there was no statistically significant difference between the low and intermediate risk group, risk stratification for patients with high risk and very high risk performed more accurately (pairwise comparison p=.005 and p<0.001, respectively).

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Conclusions

The VT-LVAD-score predicted accurately the occurrence of late VAs in high risk LVAD recipients in a large external cohort of LVAD recipients supporting its utility for more targeted ICD implantations.

Key words: LVAD, late ventricular arrhythmia, ICD, mortality, risk stratification

Abbreviations and Acronyms

ACE: angiotensin-converting enzyme, AF: atrial fibrillation, CABG: coronary artery bypass grafting, CI: confidence interval, ECMO: extracorporeal membrane oxygenation, HR: hazard ratio, ICD: implantable cardioverter-defibrillator, LVAD: left ventricular assist device, RVAD: right ventricular assist device, VA: ventricular arrhythmia, VF: ventricular fibrillation, VT: ventricular tachycardia

Introduction

The advances in heart failure treatment over the last decades have prolonged the survival of patients with end-stage heart disease. Because of the ongoing lack of available organs, there is an increasing demand of mechanical circulatory support devices (LVAD) as bridge to heart transplantation (HTX) or destination therapy for these critically ill patients. {2} With the technical advantages of continuous flow LVADs, an 80% 1-year survival has been achieved, approaching that of heart transplantation (86%). {2-3}

With the wide use of LVADs new questions arise in clinical practice. While the use of ICDs has been proved to reduce mortality in heart failure patients, especially in ischemic cardiomyopathy {4-5}, the benefit of ICDs in LVAD recipients remains controversial. The high rate of ICD-related adverse events, such as inappropriate therapies or infections, combined with the fact that many ventricular arrhythmias

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(VAs) remain because of the haemodynamic support asymptomatic in LVAD patients, makes a better selection of the right candidates urgent. {6-10} Furthermore, as ICD-implantation after LVAD implantation has been described as an independent predictor of LVAD infection {11}, these procedures should be limited to the patients who would most benefit. With this study we aim to evaluate the VT-LVAD for its predictive accuracy in identifying high risk LVAD recipients for late VAs.

Methods

Study design

We collected the data of consecutive patients who underwent implantation of LVADs at the Heart Centre of Leipzig in the period between January 2011 and March 2020. All patients gave written informed consent for the operation, as is in accordance with the institutional guidelines. The type of LVAD device as well as the decision regarding ICD implantation was left on the attending physicians' discretion. All patients ≥ 18 years of age who had been implanted with axial HeartMate 2 (Abbott, Abbott Park, IL), centrifugal HeartWare (Medtronic, Columbia Heights, Minnesota) or continuous flow HeartMate 3 (Abbott, Abbott Park, IL) regardless of having an implanted ICD, who were discharged alive from the hospital were included in the analysis. Patients with history of congenital heart disease, history of heart transplantation or death before discharge from the hospital were excluded. In order to assess for late arrhythmias, a minimum of 3 month-follow up duration was set.

The classification of the type of heart disease was based on a combination of echocardiography, stress-test, coronary angiography, MRI, genetic testing or heart-biopsy. The apical part of the heart was analysed postoperatively to support the classification. NICM was defined as absence of relevant coronary artery disease and according to the criteria of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. If no specific pathology was identified the patient was classified as 'idiopathic dilated cardiomyopathy'. The baseline

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characteristics, echocardiographic and blood sample data were the last performed before the LVAD implantation.

The patients were then classified in four groups according to their score to develop late VAs {1}; low risk (0-1 point), intermediate risk (2-4 points), high risk (5-6 points) and very high risk (7-10 points) for late VAs. To calculate every patient's score six risk factors were analysed: presence of early VAs (<30 days) post LVAD (2 points) or history of VAs before the implantation (2 points), absence of ACE-inhibitor in the drug medication (2 points), >12 months duration of heart failure (2 points), presence of atrial fibrillation before the LVAD implantation (1 point) and idiopathic dilated cardiomyopathy (1 point).

Ventricular Arrhythmias

The definition of VAs was in accordance with the study of Galand et al {1}, as was their classification on 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). Only episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) lasting > 30 seconds in the monitor-zone or terminated by appropriate ICD therapy were analyzed. We did not distinguish between ventricular fibrillation and polymorphic ventricular tachycardia for analysis.

Follow-Up

All patients were followed up for occurrence of VAs, clinical status, echocardiographic parameters and LVAD control by clinic visits at 4-month intervals. The ICD detection thresholds were analyzed both in patients with and without post-LVAD VAs. The ICD programming was not standardized and reprogramming was performed during follow up when needed.

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Death was classified as cardiovascular death, when resulting from acute heart failure, sudden cardiac death, death due to stroke or death due to cardiovascular hemorrhage. The ICDs were not routinely interrogated post-mortem. The last date of the follow up was June 30, 2020; or the date of heart transplantation; or the date of death; whichever occurred first.

Statistical analysis

Continuous variables were reported as mean ± standard deviation and categorical variables as frequencies. Continuous variables were compared using the Student's *t*-test while categorical variables were compared using the χ^2 test. Univariate and multivariate cox regression analyses were performed in order to determine the predictive factors. Variables with a *P*-value of ≤0.2 in the univariate analysis or important clinical or procedural parameters were then included in the multivariate regression analysis for the determination of hazard ratio (HR) and its 95% confidence interval (CI). A *P*-value of ≤0.05 was considered to be statistically significant. Mortality rates were calculated and graphically depicted with the Kaplan-Meier curves. The Chi-square Goodness of fit test for independence was used to assess the predictive value of the score. All analyses were performed using SPSS v24.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

From the initial 460 LVAD recipients, three had a congenital heart disease, seventy-six died during initial hospitalization, fifteen underwent heart transplantation within the first three months, nine had missing data and were excluded, thereby leaving 357 patients in the final analysis. The clinical characteristics of these patients are listed in Table 1. Eighty-eight percent of the patients in our cohort were men, 47% had an ischemic cardiomyopathy and the median heart failure duration was 36 months

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(range 1-204). Sixty percent of the population had atrial fibrillation (AF) and 39% were under antiarrhythmic therapy. Seventy-five percent of the patients underwent ICD implantation before the LVAD placement; among them 36% acquired a CRT-device. The majority of the patients received a HeartWare device (50%) and the most common indication in our cohort was destination therapy with 40%. The median follow-up was 25 months. When compared to the study of Galand et al {1}, less patients had ICM (47% vs 63%), more had AF (60% vs 46%), much less patients received a HeartMate II device (8% vs 73%) and were candidates for HTX (30% vs 64%).

Prevalence and predictors of VAs

As far as VAs prior to LVAD are concerned, 153 (43%) patients had experienced previous ventricular arrhythmias and 77 patients (22%) experienced VAs in the first 30 days of the postoperative period. Overall, the occurrence rate of VAs on LVAD support was 36% (n=153) and the median time from LVAD placement to the first VA episode was 16 months (range 1-94). The VAs were terminated through antitachycardic pacing (ATPs) in 8% of the cohort and these patients remained asymptomatic, whereas shock or both therapies occurred in 28%. The main symptom described was the shock itself, while a minority of patients described syncope, palpitations or dyspnoea. Forty-nine patients (14%) without any history of VAs reached the endpoint of late VAs, whereas 81 patients with history of VAs (53%) continue to experience VAs postoperatively. Eight patients died after complications to electrical storm and two were listed as high-urgency because of the incessant arrhythmias and received a heart transplant. Compared to the arrhythmia free patients, the patients with late VAs were older, had more comorbidities, more early VAs, longer heart failure duration, and were more likely to have an ICD and antiarrhythmic medication at baseline (Table 1). Forty-four patients had history of

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catheter ablation of VAs, among them nine patients that underwent ablation after LVAD placement.

The multivariate analysis identified early VAs ($p < 0.001$, HR 2.5; CI 1.7 -3.4), use of antiarrhythmic drugs ($p < 0.001$, HR 2.3; CI 1.6 – 3.4), presence of diabetes mellitus ($p = 0.016$, HR 1.6; CI 1.1 – 2.3), as well as a high VT-LVAD-score with ≥ 5 points ($p < 0.001$, HR 3.1; CI 2.0 – 4.9) to be strong independent predictors of late VAs. (Table 3)

The VT-LVAD score accurately predicted late VAs in patients with high or very high risk were (AUC = 0.7; goodness-of-tip $p = 0.347$, OR 4.8). In pairwise comparison analysis of VT-LVAD score groups, we found low risk and intermediate risk group not having a statistically significant difference in predicting late VAs ($p = 0.627$; Figure 2). Therefore, we combined low and intermediate risk group in one low risk group, so that significant differences among all three groups were present (Group 1-2: $p < 0.001$; Group 1-3: $p < 0.001$; Group 2-3: $p= 0.005$ in pairwise comparison, respectively, Figure 3).

Outcomes

During the follow-up period 66 patients (19%) received heart transplantation, 14 patients (4%) recovered and underwent an occlusion or removal of their LVAD device and 131 patients (37%) died. The majority of the deaths (49%) occurred because of cardiovascular events, with right heart failure being the most common cause (24%), followed by stroke or bleeding (12%). Sepsis with 15% was the most common non-cardiovascular cause of death (Table 4). The occurrence of late VAs was associated with more cardiovascular death, not only due to electrical storm but also due to right heart failure. (Table 4) Regardless, the occurrence of late VAs was not an independent mortality predictor in this analysis (log rank: $p = 0.176$, Figure 4a-b). On the same note, the presence of a high LVAD-VT score also did not predict worse survival in our cohort (log rank, $p = 0.121$). On the contrary, the presence of an ICD

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prior LVAD was associated with worse outcome in the multivariate mortality analysis in our cohort (log rank: p= 0.009, Figure 4a-b). Lastly, 19% of the LVAD recipients in our cohort suffered ICD-related complications, mostly due to inappropriate therapies, electrode dysfunctions and infections.

Discussion

This is the first study to our knowledge to validate the VT-LVAD score for occurrence of late VAs in an independent cohort. According to the VT-LVAD-score, 11% of the patients were low risk (n=39; vs 9% in the study of Galand et al), 34% were intermediate risk (n=122; vs 43%), 30% were high risk (n=107; vs 24%) and 25% were very high risk (n=89; vs 18%). (Table 2, Figure 1)

In our study, we found the score to be accurate in predicting late VAs in high and very-high risk group, whereas we saw no statistically significant difference between the low and intermediate risk population. Moreover, in addition to VT-LVAD score, use of antiarrhythmic drugs ($p < 0.001$, HR 2.3; CI 1.6 – 3.4) and presence of diabetes mellitus ($p = 0.016$, HR 1.6; CI 1.1 – 2.3) were found to be independent predictors of late VAs in our cohort. Late arrhythmias were associated with more cardiovascular death, mainly following right heart failure, but were not an independent mortality predictor (log rank: $p = 0.176$, Figure 4a). The presence of implanted ICD before the LVAD placement was associated with a worse outcome in our study (log rank: p= 0.009, Figure 4b). This could be explained through a longer heart failure duration or history of VAs, which could have worsened the patients' prognosis.

Late VAs appears to be a common problem in LVAD-recipients (19-59% {1, 9, 12}) and have been associated with worse survival, especially for patients with continuous flow VAD devices {6-7}. These arrhythmias are mainly reentry tachycardias caused by fibrosis, either pre-existing or caused from the apical wedge around the inflow

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cannula {8}. The ongoing reverse remodelling, the mechanical trauma caused by the LVAD, as well as the physiological adaption to the device can increase the electrical vulnerability, not only at the first postoperative period but also as a late phenomenon {13}. While sudden cardiac death or syncope is not as common as with the first generation VAD devices {6}, recurrent VAs can have severe consequences, such as progressive right ventricular and renal failure, low output condition with consecutive suction and increased thrombogenicity {14, 15, 16, 17}. As a result, recurrent VAs tend to increase unscheduled hospitalisations and morbidity in these patients. {18}

Previous studies regarding ICD implantation in LVAD patients as a primary prevention have been inconclusive and clear recommendations are lacking {8}. On one hand, ICDs come with a risk as high as 6.1% complications per year needing hospitalisation or operation {18}. On the other hand, in a recent meta-analysis of six observational studies {10}, ICD implantation was associated with a significant reduction in mortality in LVAD patients, but not for the patients with continuous flow LVADs. This highlights the need for a risk stratification strategy and a patient-tailored approach to address this increasing problem. In our study, the VT-LVAD score was predictive of late VAs for the high and very high-risk population. Furthermore, given that 41% of the patients in our cohort received a HeartMate III device, which was not included in the study of Galand, the VT-LVAD score can also be applied to patients with state-of-the-art devices. Although the predictive value of the score was more moderate when compared to the study of Galand et al, the score appears to be a useful tool for risk stratification in LVAD recipients and can be helpful in guiding the implantation or replacement of ICDs.

Limitations

There were several limitations in our study. Our study is a retrospective, observational, single centre analysis. 25% of the patients did not have an implanted

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ICD and asymptomatic VAs may have been missed. Nevertheless, recurrent or sustained VAs tend to become clinically apparent through right heart decompensation or syncope and would have been eventually recognised. Moreover, the ICD-programming was adjusted to each patient's needs, which could have influenced the detection of asymptomatic VAs. Nevertheless, this only underlies the fact that not all VAs are clinically relevant for this population. Lastly, a post-mortem ICD interrogation did not take place routinely and cardiac deaths due to VAs may have been underestimated.

Conclusions

The VT-LVAD score predicted accurately the occurrence of VAs in high risk population in an independent cohort and could be used as a guide for ICD implantation in LVAD recipients. Late VAs did not influence the survival in our cohort.

Conflict of interest

Dr. Leclercq has served as a speaker for Biotronic, BSI, Medtronic, Abbott, and LivaNova. Dr. Martins has received honoraria from Medtronic, Abbott, and LivaNova. All other authors have reported they have no relationships relevant to the contents of this paper to disclosure.

Funding: None.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

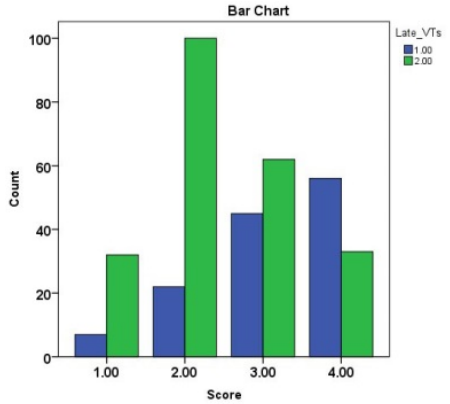

Figure 1. Bar chart of the classification of the LVAD recipients and the distribution of late VAs in the four risk groups (blue bar: patients without late VAs, green bar: patients with late VAs).

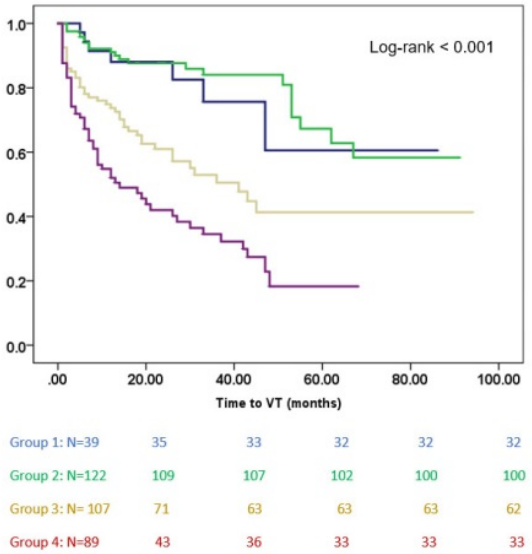

Figure 2. Kaplan Meier analysis of the four risk groups (blue line: low risk group, green line: intermediate risk, yellow line: high risk, red line: very high risk, n = number at risk).

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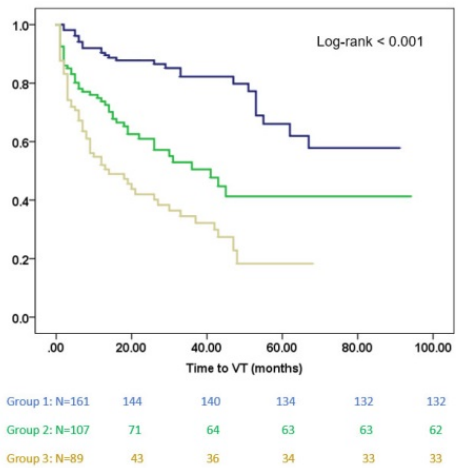

Figure 3. Kaplan Meier curves after combining low risk and intermediate risk group in one low risk group (low risk: blue line, high risk: green line, very high risk: yellow line, n = number at risk).

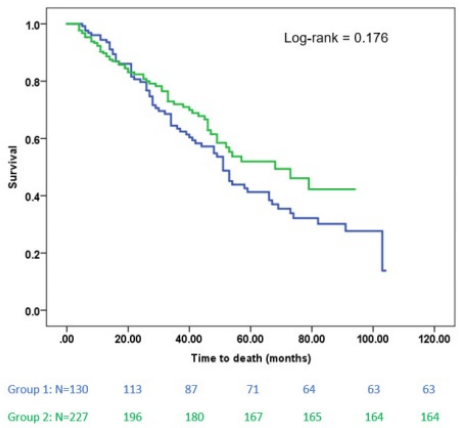

Figure 4a-b. Influence of late VAs (a) (blue line: control group, green line: patients with late VAs) and pre-existing ICD (b) (blue line: patients without ICDs, green line: ICD-recipients) on survival.

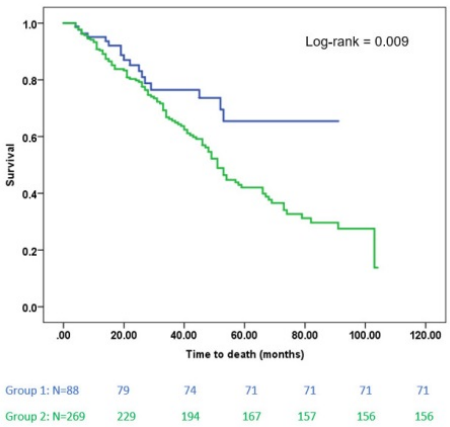

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Table 1. Baseline Characteristics.

Variable	Total	Control Group	Late VA Group	p-Value univariate analysis
Baseline characteristics				
Male Female	314 43	193 (85%) 34 (15%)	121 (93%) 9 (7%)	0.024
Age (years)	58 ± 10	56 ± 11	59 ± 9	0.003
Art. hypertension	312	193 (85%)	112 (92%)	0.074
Diabetes mellitus 2	149	83 (37%)	66 (51%)	0.009
Hyperlipidaemia	269	169 (74%)	100 (77%)	0.602
Atrial fibrillation prior to LVAD	214	120 (53%)	94 (72%)	<0.001
ICM DCM Other cardiomyopathy	169 124 64	110 (48%) 72 (32%) 45 (20%)	59 (45%) 52 (40%) 19 (15%)	0.187
Heart failure duration, months	49 ± 45	45 ± 48	55 ± 39	0.036
VA-history	153	72 (32%)	81 (62%)	<0.001
LV-EF before LVAD, %	20 ± 6	20 ± 7	20 ± 6	0.354
LV-EDV before LVAD, mm	256 ± 88	249 ± 91	267 ± 81	0.077
Renal function, GFR	64 ± 33	66 ± 29	59 ± 39	0.060
Bilirubin, µmol/L	14 ± 16	14 ± 17	14 ± 13	0.995
Sodium, µmol/L	138 ± 4	138 ± 4	137 ± 4	0.812
Heart Mate II	29	14 (6%)	15 (12%)	0.074
Heart Ware	180	100 (44%)	80 (62%)	0.001
Heart Mate III	148	113 (50%)	35 (27%)	<0.001
Bridge to transplantation	107	72 (32%)	35 (27%)	0.341
Bridge to decision/ recovery	108	81 (36%)	27 (21%)	0.003
Destination therapy	142	74 (33%)	68 (52%)	<0.001

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Additional operation* Support-system**	151 35	91 (40%) 26 (12%)	60 (46%) 9 (7%)	0.288
Early VAs	77	31 (14%)	46 (35%)	<0.001
Beta-blocker	327	206 (91%)	121 (95%)	0.446
ACE-Inhibitor	165	110 (49%)	55 (42%)	0.262
AT1-Antagonist	53	33 (15%)	20 (15%)	0.828
Sacubitril/Valsartan	52	34 (15%)	18 (14%)	0.771
Aldosterone-Antagonist	286	185 (82%)	101 (78%)	0.386
Antiarrhythmic	138	67 (30%)	71 (55%)	<0.001
Amiodarone	122	61 (27%)	61 (47%)	<0.001
ICD	269	145 (64%)	124 (95%)	<0.001
CRT	127	62 (27%)	65 (50%)	<0.001
ICD-complications	67	28 (12%)	39 (30%)	<0.001

- Additional pre-existing operation, for example CABG, heart valve operations etc.
- Need for RVAD, Impella, ECMO- implantation (mostly temporarily).

Table 2. Classification of the patients in four risk groups according to the VT-LVAD score (1: low risk, 2: intermediate risk, 3: high risk, 4: very high risk).

Variable	Total	Control Group	Late VA Group	p-Value
VT-LVAD group 1	39	32 (14%)	7 (5%)	<0.001
VT-LVAD group 2	122	100 (44%)	22 (17%)	
VT-LVAD group 3	107	62 (27%)	45 (35%)	
VT-LVAD group 4	89	33 (15%)	56 (43%)	

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Table 3. Multivariable analysis for prediction of late VAs.

Variable	Univariable analysis p-Value	Multivariable HR (95% CI)	Multivariable analysis p-Value
Gender	0.024		0.902
Age	0.003		0.118
Art. hypertension	0.074		0.657
Diabetes mellitus	0.009	1.6 (1.1 - 2.3)	0.016
Atrial fibrillation	<0.001		0.685
Cardiomyopathy	0.187		0.855
Heart failure duration	0.036		0.587
VAs-history	<0.001		0.219
LV-EDV before LVAD	0.077		0.935
GFR	0.060		0.646
HeartMate II	0.074		0.592
HeartWare	0.001		0.212
HeartMate III	<0.001		0.104
Bridge to decision/recovery	0.003		0.063
Destination therapy	<0.001		0.132
Early VAs	<0.001	2.5 (1.7 – 3.4)	<0.001
Antiarrhythmics	<0.001	2.3 (1.6 – 3.4)	<0.001
Amiodarone	<0.001		0.541
High VT-LVAD score (≥ 5)	<0.001	3.1 (2.0 – 4.9)	<0.001

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Table 4. Outcomes after LVAD placement.

Variable	Total	Control Group	Late VA Group	P-Value
Heart transplantation	66	42 (19%)	24 (19%)	0.992
Total death	131	63 (28%)	68 (52%)	< 0.001
- Cardiovascular	64	29 (13%)	35 (27%)	0.001
- Non-cardiovascular	3	1 (0.4%)	2 (2%)	0.274
- Sepsis	20	9 (4%)	11 (9%)	0.075
- Unknown cause	42	24 (11%)	18 (14%)	0.356
Cardiovascular death				
- LVAD thrombosis	6	4 (2%)	2 (2%)	0.874
- RH-failure	32	14 (6%)	18 (14%)	0.015
- Electrical storm	8	0 (0%)	8 (6%)	<0.001
- LVAD dysfunction	2	0 (0%)	2 (2%)	0.061
- Stroke/bleeding	16	10 (4%)	6 (4%)	0.926

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