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Comparison of Outcomes and Mortality in Patients Having Left Ventricular Assist Device Implanted Early -vs- Late After Diagnosis of Cardiomyopathy

Running title: LVAD for recently diagnosed cardiomyopathy

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Abstract

LVAD implantation in patients with a recently diagnosed cardiomyopathy has been poorly investigated. This work aims at describing the characteristics and outcomes of patients receiving a LVAD within 30 days following the diagnosis of cardiomyopathy. Patients from the ASSIST-ICD study were divided into recently and remotely diagnosed cardiomyopathy based on the time from initial diagnosis of cardiomyopathy to LVAD implantation using the cut point of 30 days. The primary endpoint of the study was all-cause mortality at 30-days and during follow-up. A total of 652 patients were included and followed during a median time of 9.1 (2.5-22.1) months. Among this population, 117 (17.9%) had a recently diagnosed cardiomyopathy and had LVAD implantation after a median time of 15.0 (9.0-24.0) days following the diagnosis. This group of patients was significantly younger, with more ischemic cardiomyopathy, more sudden cardiac arrest (SCA) events at the time of the diagnosis and were more likely to receive temporary mechanical support prior to LVAD compared to the remotely diagnosed group. Post-operative in-hospital survival was similar among groups, but recently diagnosed patients had a better long-term survival after hospital discharge. SCA prior to LVAD and any cardiac surgery combined with LVAD implantation were identified as two independent predictors of post-operative mortality in recently diagnosed patients. In conclusion, rescue LVAD implantation for recently diagnosed severe cardiomyopathy is common in clinical practice. Such patients experience a relatively low post-operative mortality and have a better long-term survival compared to remotely diagnosed patients.

Key words: Recently diagnosed cardiomyopathy, remotely diagnosed cardiomyopathy, LVAD implantation, survival.

Introduction

Heart failure (HF) remains associated with high morbidity and mortality, especially in patients hospitalized for acute HF. Recent data have shown that patients with acute HF have a 4-fold higher risk of 1-year mortality than those with chronic HF, suggesting that these patients should be carefully managed (1). Left ventricular assistance device (LVAD) therapy improves survival in HF patients and is often implanted in chronic cardiac disease (1-2). Conversely, data about LVAD implantation at the acute stage of new-onset HF in patients with recently diagnosed cardiomyopathy are scarce and limited to small cohorts (3-5). Indeed, a cardiomyopathy may sometimes be diagnosed at the critical stage of severe de novo acute HF with cardiogenic shock and heart transplantation remains the best therapeutic option. However, due to restricted donors, rescue LVAD implantation may represent an interesting alternative. This study aims at investigating the characteristics and outcomes of patients urgently implanted with a LVAD for a recently diagnosed cardiomyopathy.

Methods

This study is based on the ASSIST-ICD study, 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 were included. Exclusion criteria were patients undergoing 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. Details on the ASSIST-ICD database have been previously described (6). This study was approved by the regional ethic committees, the French Advisory Committee on the Treatment of Research Information in the Field of Health, and the French National Commission of Informatics and Civil Liberties.

Baseline data—including demographic characteristics, cardiac disease and heart failure history, supraventricular arrhythmia, other temporary mechanical support before LVAD implantation history, 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. Follow-up was performed according to each center's usual practice. The last day of follow-up was December 31, 2016; the date of heart transplantation; or death, whichever occurred first.

For the purpose of this study, the overall population was divided into recently and remotely diagnosed cardiomyopathy based on the time from initial diagnosis of cardiomyopathy to LVAD implantation using the cut point of 30 days. The primary endpoint of the study was all-cause mortality during follow-up. Deaths were classified as cardiovascular death (cardiac or vascular cause), non-cardiac death, or unknown cause. Secondary endpoints included heart transplantation and LVAD related complications (i.e. thrombosis, stroke, bleeding, and LVAD malfunction) in the 30 days post-operative period and during long-term follow-up.

Qualitative variables are expressed as number (percentage); continuous data as mean \pm standard deviation 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 post-operative mortality and long-term mortality were analyzed using univariate and multivariable proportional hazard models (cumulative outcomes). The proportional hazard assumption was tested and verified for each covariate. Variables with p-values <0.05 in univariate analysis were included in the multivariable analysis. Statistical analyses were conducted using the Statistical Package for Social Sciences version 22 (SPSS Inc., IBM, Armonk, New York).

Results

Among 652 patients implanted with a LVAD, 117 (17.9%) were implanted during the first 30 days after the diagnosis of the cardiomyopathy and were considered as “recently diagnosed” cardiomyopathy. The median time between diagnosis and implantation was 15.0 (IQR: 9.0-24.0, from 2 to 30 days) days. **Figure 1** shows the underlying etiologies. Notably, the main etiology of de novo acute HF was acute myocardial infarction (74%). Baseline characteristics of the study population are described in **Table 1**. Briefly, the “recently diagnosed” group was significantly younger, with a lower body mass index (BMI), had more ischemic cardiomyopathy, and more sudden cardiac arrest (SCA) events at the time of diagnosis. Notably, they had a less dilated left ventricle but worst left ventricular ejection fraction (LVEF) at the time of LVAD implantation. Importantly, the recently diagnosed group received significantly more temporary mechanical support prior to LVAD but had better renal function at the time of the LVAD surgery. Additionally, they were more likely implanted as bridge to transplantation or bridge to decision/recovery.

During the post-operative period (i.e. <30 days post-operative period), a total of 16 (13.7%) and 101 (18.9%) patients died in the recently and remotely diagnosed

LVAD groups, respectively. As shown in **Table 2**, the causes of death were mostly non-cardiovascular, and similar among groups. **Figure 2** summarizes the causes of death in the recently diagnosed group, predominantly due to mesenteric ischemia, cerebral bleeding, respiratory and multi-organ failure, or right ventricular failure.

The baseline characteristics between survivors (n=101, 86.3%) and deceased (n=16, 13.7%) in the recently diagnosed group are described in **Table 3**. Briefly, patients who died had more impaired LVEF and renal function at baseline, more history of SCA at the time of diagnosis, were more frequently implanted as destination therapy and had more cardiac surgery combined with LVAD implantation. Temporary mechanical support prior to LVAD implantation did not differ among groups. In multivariable analysis, SCA prior to LVAD and any cardiac surgery combined with LVAD implantation were identified as two independent predictors of post-operative mortality (**Table 4**). **Figure 3** illustrates post-operative survival depending on the number of predictors. Interestingly, patients with no predictors were at low risk of post-operative death, those with only 1 predictor were at intermediate risk of death and LVAD recipients with 2 predictors were at high risk of death with only a 40% survival rate at 30-days post-operative.

After 9.1 (2.5-22.1) months of follow-up, a total of 47 (40.2%) and 152 (28.4%) patients were heart transplanted (p=0.017) and 38 (32.5%) and 253 (47.3%) LVAD recipients died (p=0.005) in the recently and remotely diagnosed cardiomyopathy groups, respectively (**Table 2**). Both groups had similar survival rates in the post-operative period (**Figure 4, panel A**). However, among patients discharged alive from hospital, the recently diagnosed group had better mid-term survival (**Figure 4, panel B**). Interestingly, there was no difference regarding LVAD related complications during long-term follow-up. Additionally, 5 (4.3%) patients in the

recently diagnosed group eventually had LVAD removal as a consequence of myocardial recovery (1 patient with ischemic heart disease, 1 with beta-blocker intoxication and 3 with idiopathic dilated cardiomyopathies). Conversely, no patient in the remotely diagnosed group was explanted for myocardial recovery.

Discussion

The main results of this study focusing on LVAD implantation in patients recently diagnosed with a cardiomyopathy are as follows : 1) LVAD implantation within 30 days after the diagnosis of a cardiomyopathy is not uncommon, representing 17.9% of the LVAD implantations ; 2) These patients experience a good post-operative survival, with a 30-day mortality incidence of 13.7%, and have a better long-term survival after hospital discharge compared to remotely diagnosed patients ; 3) SCA prior to LVAD and any cardiac surgery combined with LVAD implantation are two independent predictors of post-operative mortality in this subgroup of patients.

The most common etiology remains cardiac ischemia leading to decreased myocardial contractility and potentially life threatening hemodynamic situation (7). Furthermore, non-ischemic myocardial insults (inflammatory, toxic or peri-partum) represent potential other causes of acute HF. De novo acute HF may also be the first expression of an underlying idiopathic dilated cardiomyopathy thus far asymptomatic. Importantly, it has been shown that de novo HF is associated with poor outcomes, especially in patients with HF complicating myocardial infarction who are at high risk of in-hospital death (8). Similarly, in patients experiencing de novo HF with inaugural refractory cardiogenic shock, mortality is high with >50% of in-hospital death (9).

LVAD implantation in the acute period following the diagnosis of de novo cardiomyopathy has been poorly investigated thus far. In a small US cohort including a total of 13 patients with recent myocardial infarction and refractory cardiogenic shock, LVAD as a rescue strategy was implanted between 1 and 23 days following myocardial infarction with a 1-year survival rate of 86%, (3). More recently, Pawale et al. described a more aggressive strategy with an emergency durable LVAD implantation within the 24 hours following the diagnosis of the cardiomyopathy in a cohort of 43 refractory cardiogenic shock patients (5). In this study, authors reported a 74% 1-year mortality. Conversely, we did not enrolled patients scheduled for LVAD in alternative to temporary mechanical support but only refractory HF patients receiving LVAD as a rescue strategy. We confirm the positive results previously described, with a post-operative survival at 30 days of 87%. Our results suggest that this strategy may be an alternative in selected patients not eligible or in the waiting list for heart transplantation, since 40.2% of these patients eventually underwent cardiac transplantation after LVAD implantation. Importantly, patients receiving a rescue LVAD implantation did not experience a higher rate of LVAD-related complications during follow-up. Indeed, 50% of patients in both groups developed LVAD-related complications, slightly more than the 30% complications-free rate at one year described in the literature (10–12), a difference probably explained by different population characteristics among studies.

In our study, we show that the occurrence of SCA prior to LVAD and any combined cardiac surgery during LVAD implantation are 2 independent predictors of post-operative mortality in this population. It has been extensively described that the occurrence of SCA is associated with poor outcomes, with only 1 to 12.4% of survival to hospital discharge in overall population (13). In our study, 38.4% of

patients with a rescue LVAD implantation experienced a SCA in the 30-days prior to the surgery and a large proportion of these patients received a temporary mechanical support prior to LVAD, suggesting a high hemodynamic instability during the pre-operative period. Indeed, SCA leads to inflammatory cascade, coagulopathy phenomena and multiple organ failure (14). This precarious situation potentially impacts the post-operative survival. This result is supported by previous work showing that cardiopulmonary resuscitation at the time of mechanical cardiac support implantation increased by 6-fold the risk of mortality (4). We also showed that any combined surgery during rescue LVAD implantation increased post-operative mortality. Previous works demonstrated that longer cardiopulmonary bypass duration was associated with lower post-operative survival (15–17). Similarly, it was shown that patients scheduled for concomitant cardiac surgery with HeartMate II implantation doubled their post-operative mortality rates at 30 days (18). Lastly, patients requiring a combined surgery to LVAD usually have more complex cardiac disease leading to higher rates of post-operative injuries.

This study brings important information about LVAD candidates' selection in patients with newly diagnosed severe cardiomyopathy requiring a rescue LVAD implantation. Indeed, these patients remain challenging to manage since they are frequently implanted with temporary mechanical support and under mechanical ventilation with deep sedation, making difficult any pre-operative discussion about other advanced therapeutic options. For patients not eligible to heart transplantation, the hemodynamic compromise despite the use of temporary mechanical support calls for consideration of a rescue LVAD implantation which represents a major challenging decision. We show that these LVAD candidates experience a relatively low post-operative mortality, no higher risk of device related complications during

follow-up and high proportion to be heart transplanted. However, patients requiring a rescue LVAD for a recently diagnosed cardiomyopathy should be carefully selected and the decision to combine a surgical procedure during pump implantation should be discussed.

Our observational study has some limitations, including its retrospective design, which may have affected the results. Furthermore, many French patients are in advanced cardiogenic shock at the time of LVAD implantation, suggesting that our population is probably sicker than U.S. patients at time of implantation. Thus, our results cannot necessarily be extended to other populations. Moreover, we did not collect hemodynamic data that limit an accurate description. Furthermore, patients with recently diagnosed cardiomyopathy had probably less physical deconditioning than remotely cardiomyopathy, potentially explaining better outcomes after LVAD implantation but we cannot provide these information. Lastly, the use of old LVAD generation may not reflect our current practice with the implantation of the HeartMate III pump.

Our study demonstrated that rescue LVAD implantation for recently diagnosed cardiomyopathy is common. These LVAD candidates experience a relatively low post-operative mortality and many of them are eventually heart transplanted during follow-up. Patients with a history of SCA and those requiring a combined cardiac surgery during LVAD implantation are at higher risk of mortality.

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Figure legends

Figure 1: Cardiomyopathy etiology among the patients receiving a LVAD for a recently diagnosed cardiomyopathy

Figure 2: Causes of death in the post-operative period among patients with recently diagnosed cardiomyopathies

Figure 3: Survival rates by number of predictors of post-operative mortality among patients with recently diagnosed cardiomyopathies

Figure 4: Comparison of survival rates after LVAD implantation in patients with a recently or a remotely diagnosed cardiomyopathy, over the 30 days post-operative days (A) and after hospital discharge (B).

Figure 1

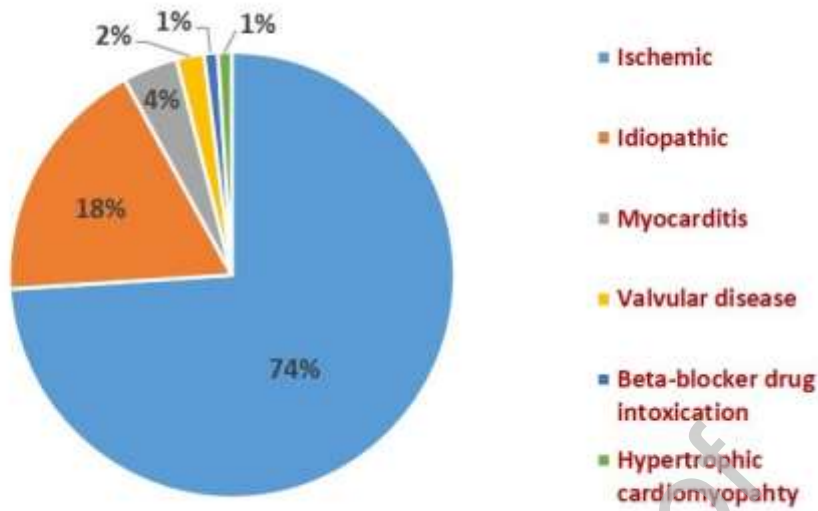


Figure 2

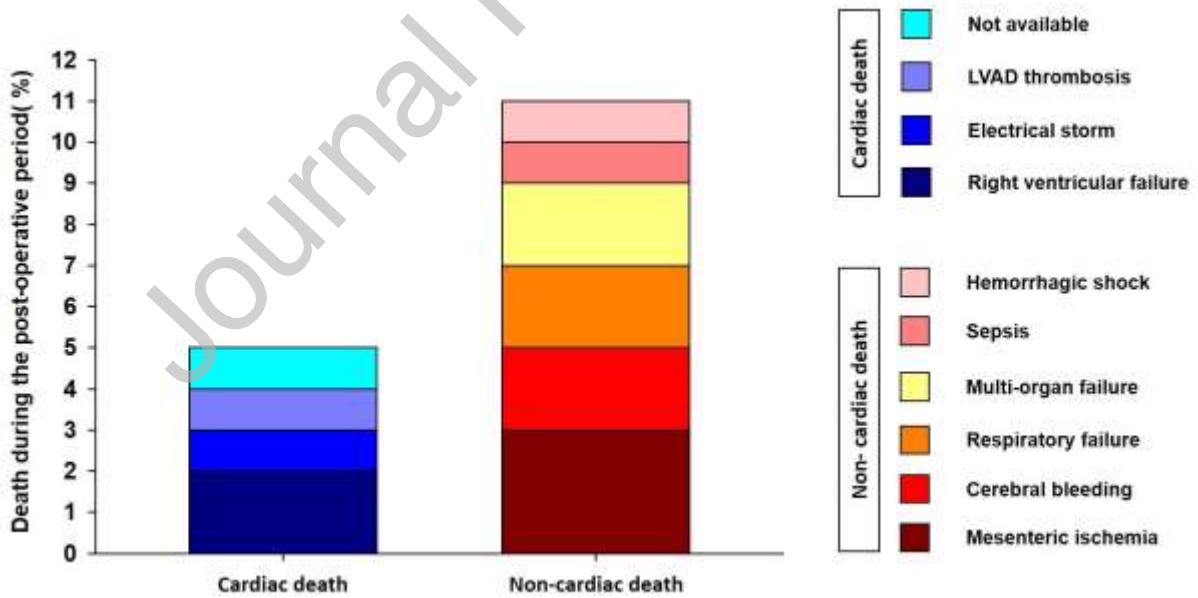


Figure 3

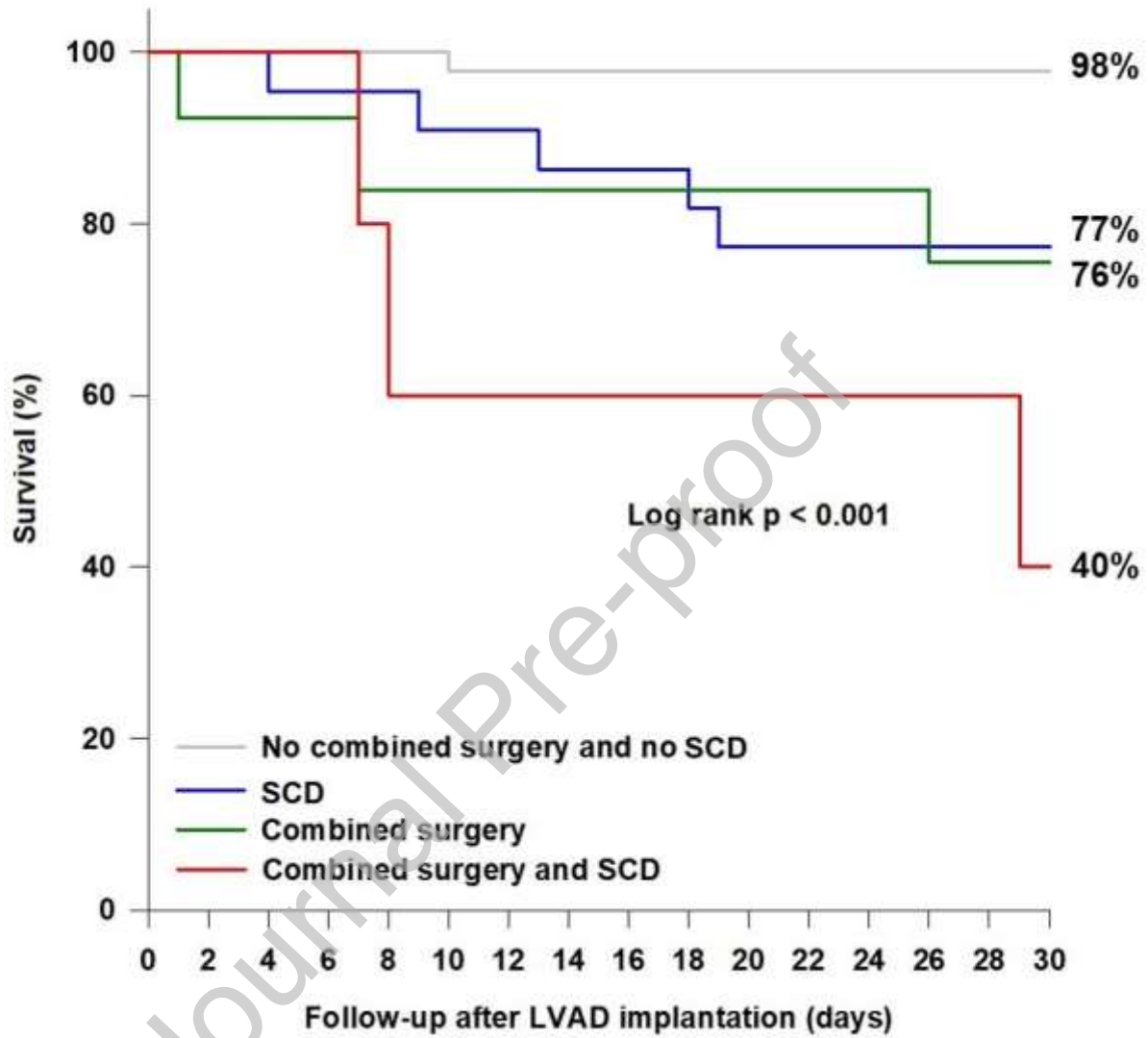


Figure 4

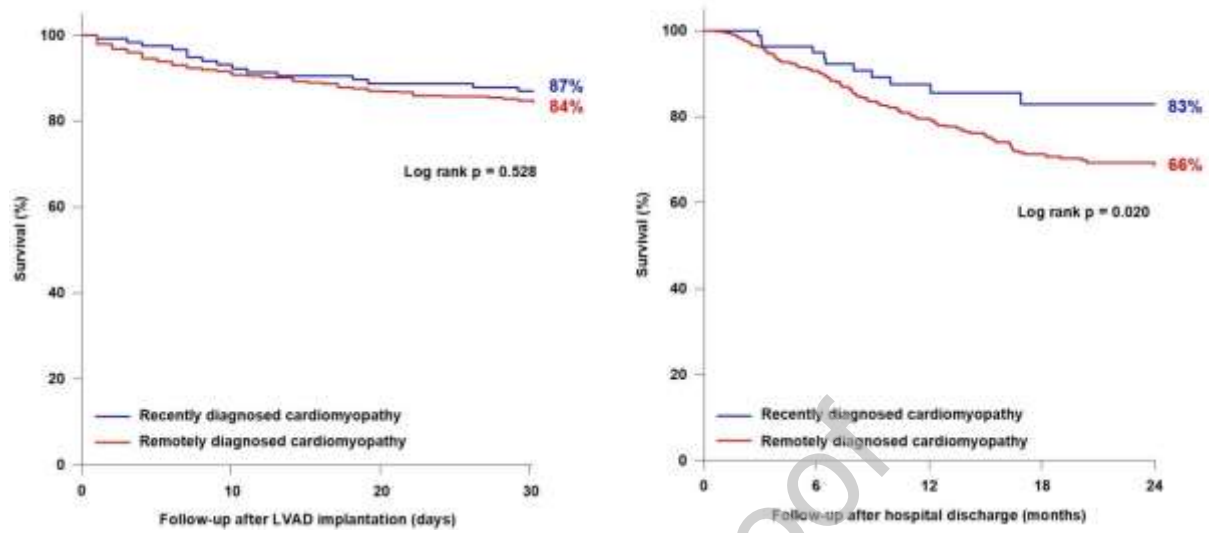


Table 1: Baseline characteristics among patients with recently or remotely diagnosed cardiomyopathies.

Variable	LVAD implantation after diagnosis of cardiomyopathy		p-Value
	<30 days (n=117)	>30 days (n=535)	
Ages, (years)	55.2 (46.9-61.4)	60.7 (53.3-66.9)	<0.001
Men	96 (82%)	465 (86%)	0.219
Body mass index, (kg/m²)	24.5 (21.6-26.4)	25.5 (22.8-28.4)	<0.001
Hypertension	33 (28%)	200 (37%)	0.077
Diabetes mellitus	23 (20%)	131 (24%)	0.320
Heart failure etiology			
- Ischemic	87 (74%)	325 (61%)	
- Idiopathic	21 (18%)	157 (29%)	
- Other	9 (8%)	53 (10%)	
Heart failure duration, (months)	0.5 (0.3-0.8)	91.9 (17.4-193.3)	<0.001
LVEDD prior to LVAD, (mm)	66.0 (60.0-71.0)	70.0 (64.0-76.0)	<0.001
LVEF prior to LVAD, (%)	18.8 ± 8.9	20.9 ± 7.2	0.003
Sudden cardiac arrest prior to LVAD	45(38%)	61 (11%)	<0.001
Prior supra-ventricular arrhythmia	18 (15%)	284 (53%)	<0.001
ICD prior to LVAD insertion	2 (2%)	401 (75%)	<0.001
CRT prior to LVAD insertion	2 (2%)	196 (37%)	<0.001
Temporary mechanical circulatory support prior to LVAD			
- Impella	26 (22%)	38 (7%)	<0.001

- Intra-aortic balloon pump	42 (36%)	16 (3%)	<0.001
- Extra-corporeal life support	66 (56%)	70 (13%)	<0.001
- Creatinine, (µmol/L)	105.0 (72.0-142.0)	116.0 (89.0-148.2)	0.020
- Serum sodium, (mmol/L)	138.0 (135.0-142.0)	135.0 (132.0-138.0)	<0.001
- Total bilirubin, (µmol/L)	16.7 (10.0-28.0)	16.0 (10.0-26.0)	0.556
Type of LVAD			0.070
- HeartMate 2	89 (76%)	386 (72%)	
- HeartWare	25 (21%)	102 (19%)	
- Jarvik2000	3 (3%)	47 (8%)	
LVAD indication			<0.001
- Bridge to transplantation	83 (71%)	304 (57%)	
- Destination therapy	25 (21%)	222 (41%)	
- Bridge to decision / recovery	9 (8%)	9 (2%)	
Surgery combined with LVAD*	18 (15%)	77 (14%)	0.986
Temporary right ECLS during surgery	15 (13%)	66 (12%)	0.991
Total days in ICU	21.0 (12.0-34.2)	13.0 (8.0-25.0)	0.003
Total days in hospital	48.0 (32.0-69.0)	40.0 (29.0-56.7)	0.005

* Surgery combined with LVAD included any additional cardiac intervention increasing the total surgical duration time (i.e. coronary artery bypass grafting, valve replacement/repair, ventricular arrhythmia ablation, foramen oval closure, septal defect closure)

Table 2: Mid-term outcomes for patients with recently diagnosed cardiomyopathies.

Variable	LVAD implantation after diagnosis of cardiomyopathy		p-Value
	<30 days (n=117)	>30 days (n=535)	
Heart transplantation	47 (40%)	152 (28%)	0.017
Total death	38 (32%)	253 (47%)	0.005
Cause of death			0.269
- Cardiovascular	12 (32%)	113 (44%)	
- Non cardiovascular	25 (66%)	137 (54%)	
- Unknown	1 (3%)	3 (1%)	
Any LVAD-related complications	61 (52%)	293 (55%)	0.678
LVAD thrombosis	12 (10%)	72 (13%)	0.433
Stroke	15 (13%)	73 (14%)	0.931
Bleeding	18 (15%)	91 (17%)	0.772
Percutaneous driveline infection	34 (29%)	137 (26%)	0.514
LVAD exchange	3 (3%)	30 (6%)	0.260

Table 3: Baseline characteristics between survivors and deceased in the recently diagnosed group

Variable	Recently LVAD implantation after diagnosis of cardiomyopathy		p-Value
	30-days post-operative mortality (n=16)	Alive at 30-days post-operative (n=101)	
Ages, (years)	57.0 (51.4-66.3)	54.0 (45.2-61.1)	0.095
Men	14 (87%)	82 (82%)	0.794
Body mass index, (kg/m²)	24.0±3.2	25.5±2.8	0.071
Hypertension	7 (44%)	26 (26%)	0.235
Diabetes mellitus	1 (6%)	22 (22%)	0.265
Heart failure etiology			0.362
- Ischemic	13 (81%)	74 (73%)	
- Idiopathic	1 (6%)	20 (20%)	
- Other	2 (12%)	7 (7%)	
Heart failure duration, (days)	19.5 (13.0-23.5)	15.0 (10.0-23.2)	0.482
LVEDD prior to LVAD, (mm)	62.0 (59.5-65.0)	66.0 (60.2-71.0)	0.231
LVEF prior to LVAD, (%)	15.0 (10.0-20.0)	20.0 (15.0-25.0)	0.045
Sudden cardiac arrest prior to LVAD	11 (69%)	34 (34%)	0.016
Prior supra-ventricular arrhythmia	1 (6%)	17 (17%)	0.482
Temporary mechanical circulatory support prior to LVAD	15 (94%)	72 (83%)	0.109
- Impella	6 (37%)	20 (20%)	0.208
- Intra-aortic balloon pump	5 (31%)	37 (37%)	0.891
- Extra-corporeal life support	11 (69%)	55 (54%)	0.424
- Creatinine, µmol/L	137.5 (118.5-246.0)	98.0 (70.5-131.0)	0.006
- Serum sodium, mmol/L	139.0±6.1	138.0±6.2	0.529
- Total bilirubin, µmol/L	21.0 (9.2-37.0)	16.4 (10.0-27.7)	0.723
Type of LVAD			0.484
- HeartMate 2	11 (69%)	78 (77%)	

- HeartWare	5 (31%)	20 (20%)	
- Jarvik2000	0 (0%)	3 (3%)	
LVAD indication			<0.001
- Bridge to transplant	5 (31%)	78 (77%)	
- Destination therapy	6 (37%)	19 (19%)	
- Other	5 (31%)	4 (4%)	
Surgery combined with LVAD	6 (37%)	12 (12%)	0.023
Temporary right ECLS during surgery	3 (19%)	12 (12%)	0.718
Early ventricular arrhythmia (<30 days)	5 (31%)	20 (20%)	0.478

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Table 4: Multivariate analysis

Variable	B coefficient	Multivariable HR (95%CI)	p-value
LVEF >20%	-0.930	0.39 (0.073-2.14)	0.281
Sudden cardiac arrest prior to LVAD	2.470	11.82 (1.95-71.69)	0.007
Creatinine, ($\mu\text{mol/L}$)	0.011	1.01 (0.99-1.02)	0.101
Destination therapy	0.983	2.67 (0.42-16.79)	0.295
Cardiac surgery combined with LVAD	1.839	6.29 (1.06-37.41)	0.043