



HAL
open science

Early Ventricular Arrhythmias After LVAD Implantation Is the Strongest Predictor of 30-Day Post-Operative Mortality

Vincent Galand, Erwan Flécher, Vincent Auffret, Camille Pichard, Stéphane Boulé, André Vincentelli, Anne Rollin, Pierre Mondoly, Laurent Barandon, Mathieu Pernot, et al.

► **To cite this version:**

Vincent Galand, Erwan Flécher, Vincent Auffret, Camille Pichard, Stéphane Boulé, et al.. Early Ventricular Arrhythmias After LVAD Implantation Is the Strongest Predictor of 30-Day Post-Operative Mortality. *JACC: Clinical Electrophysiology*, 2019, 5 (8), pp.944-954. 10.1016/j.jacep.2019.05.025 . hal-02270243

HAL Id: hal-02270243

<https://hal.science/hal-02270243v1>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Early Ventricular Arrhythmias After LVAD Implantation Is The Strongest Predictor Of 30-Day Post-Operative Mortality

Brief title: Early ventricular arrhythmia in LVAD recipients

Vincent Galand, MD,^a Erwan Flécher, MD, PhD,^a Vincent Auffret, MD,^a Camille Pichard, MD,^a Stéphane Boulé, MD,^b André Vincentelli, MD, PhD,^b Anne Rollin, MD,^c Pierre Mondoly, MD,^c Laurent Barandon, MD, PhD,^d Mathieu Pernot, MD,^d Michel Kindo, MD, PhD,^e Thomas Cardi, MD,^e Philippe Gaudard, MD,^f Philippe Rouvière, MD,^f Thomas Sénage, MD,^g Nicolas Jacob, MD,^g Pascal Defaye, MD,^h Olivier Chavanon, MD, PhD,^h Constance Verdonk, MD,ⁱ Walid Ghodbane, MD,ⁱ Edeline Pelcé, MD,^j Vlad Gariboldi, MD, PhD,^j Matteo Pozzi, MD,^k Jean-François Obadia, MD, PhD,^k Arnaud Savouré, MD,^l Frédéric Anselme, MD,^l Gerard Babatasi, MD, PhD,^m Annette Belin, MD,^m Fabien Garnier, MD,ⁿ Marie Bielefeld, MD,ⁿ David Hamon, MD,^o Nicolas Lellouche, MD, PhD,^o Bertrand Pierre, MD,^p Thierry Bourguignon, MD,^p Romain Eschalier, MD, PhD,^q Nicolas D'Ostrevy, MD,^q Marie-Cécile Bories, MD,^r Eloi Marijon, MD, PhD,^r Fabrice Vanhuysse, MD,^s Hugues Blangy, MD,^s Jean-Philippe Verhoye, MD, PhD,^a Christophe Leclercq, MD, PhD,^a, Raphaël P. Martins, MD, PhD,^a

From ^aUniv Rennes, CHU Rennes, INSERM, LTSI - UMR 1099, F-35000 Rennes, France;

^bCHU Lille, Institut Coeur-Poumons, Cardiac Intensive Care Unit, Department of Cardiology, Department of Cardiac Surgery, Lille, France; ^cCentre Hospitalier Universitaire de Toulouse, Toulouse, France; ^dHôpital Cardiologique du Haut-Lévêque, Université Bordeaux II, Bordeaux, France; ^eDépartement de chirurgie cardiovasculaire, hôpitaux universitaires de Strasbourg, Strasbourg, France; ^fDepartment of Cardiac Surgery, Anesthesiology and Critical Care Medicine, Arnaud de Villeneuve Hospital, CHRU Montpellier, Montpellier, France; ^gDepartment of Cardiology and Heart Transplantation Unit, CHU Nantes, France; ^hDepartment of Cardiology and Cardiovascular Surgery, CHU Michallon, Grenoble, France; ⁱDepartment of Cardiology and cardiac surgery, Bichat-Hospital, Paris, France; ^jDepartment of Cardiac Surgery, La Timone Hospital, Marseille, France ^kDepartment of Cardiac Surgery, "Louis Pradel" Cardiologic Hospital, Lyon, France; ^lDepartment of Cardiology and Cardiovascular Surgery, Hospital Charles Nicolle, Rouen, France; ^mDepartment of Cardiology and Cardiac Surgery, University of Caen and University Hospital of Caen, France; ⁿDepartment of Cardiology and cardiac surgery, University Hospital, Dijon, France; ^oDepartment of Cardiology and Cardiac Surgery, AP-HP CHU Henri Mondor, Créteil, France; ^pDepartment of Cardiology and Cardiac Surgery, Tours University Hospital, Tours, France; ^qCHU Clermont-Ferrand, Cardiology Department, Clermont-Ferrand, France; ^rEuropean Georges Pompidou Hospital, Cardiology Department, Paris, France; ^sDepartment of Cardiology and Cardiac Surgery, CHU de Nancy, Hopital de Brabois, Nancy, France.

FUNDING: This research was supported in part by French Federation of Cardiology.

DISCLOSURES: Dr Leclercq and Dr Mondoly have received honoraria from Biotronik, Boston Scientific, Medtronic, Abbott, and LivaNova. Dr Kindo has received honorarium from HeartWare. Dr Defay has received honoraria from Boston Scientific, Medtronic, Abbott, LivaNova. Dr Chavanon has received honorarium from Thoratec. Dr Anselme has received honoraria from Medtronic, Livanova, Boston Scientific, and Abbott. Dr Obadia has received honorarium from Abbott. Dr Garnier has received honoraria from Boston Scientific and Medtronic. Dr Blangy has received honoraria from Boston Scientific, Medtronic, Abbott, and LivaNova. Dr Martins has received honoraria from Medtronic, Abbott, and LivaNova. All other authors have no disclosures.

ADDRESS FOR CORRESPONDENCE:

Raphael P. Martins, MD, PhD

Service de Cardiologie et Maladies Vasculaires

CHU de Rennes, 2 rue Henri Le Guilloux
35000 Rennes, France
Tel: + 33 299 282 507; Fax: +33 299 282 529
Email: raphael.martins@chu-rennes.fr.

ACKNOWLEDGMENTS: Editorial support was provided by Sophie Rushton-Smith, PhD (MedLink Healthcare Communications Limited) and was funded by the French Federation of Cardiology. We acknowledge Céline Chérel for her technical assistance.

ABSTRACT

BACKGROUND Left ventricular assist device (LVAD) implantation is increasingly used in patients with end-stage heart failure. Early ventricular arrhythmias (VAs) may occur during the 30-day post-operative, but many questions remain unanswered regarding their incidence and clinical impact.

OBJECTIVES This study aimed to evaluate incidence, clinical significance, and predictors of early VAs in LVAD recipients.

METHODS This observational study was conducted in 19 centers between 2006 and 2016. Early VAs were defined as sustained ventricular tachycardia/fibrillation occurring <30 days post-LVAD implantation and requiring appropriate implantable cardioverter defibrillator therapy, external electrical shock, or medical therapy.

RESULTS A total of 652 patients (median age 59.8 years; left ventricular ejection fraction $20.7 \pm 7.4\%$; HeartMate 2: 72.8%, HeartWare: 19.5%, Jarvik 2000: 7.7%) were included in the analysis. Early VAs occurred in 162 (24.8%) patients, most frequently during the first week after LVAD implantation. Multivariable analysis identified history of VAs prior to LVAD and any combined surgery with LVAD as 2 predictors of early VAs. The occurrence of early VAs with electrical storm was the strongest predictor of 30-day post-operative mortality, associated with a 7-fold increase of 30-day. However, in patients discharged alive from hospital, occurrence of early VAs did not influence long-term survival.

CONCLUSION Early VAs are common after LVAD implantation and increase 30-day post-operative mortality, without affecting long-term survival. Further studies will be needed to analyze whether pre or pre-operative ablation of VAs may improve post-operative outcomes.

CLINICALTRIALS.GOV IDENTIFIER: NCT02873169

KEY WORDS: Left ventricular assist device, ventricular arrhythmia, post-operative mortality

ABBREVIATIONS

ACE = angiotensin-converting enzyme

AF = atrial fibrillation

CI = confidence interval

ICD = implantable cardioverter-defibrillator

LVAD = left ventricular assist device

LVEDD = left ventricular end-diastolic diameter

LVEF = left ventricular end-ejection fraction

OR = odds ratio

VA = ventricular arrhythmia

VT = ventricular tachycardia

INTRODUCTION

Continuous-flow left ventricular assist device (LVAD) implantation has been shown to improve survival in patients with refractory heart failure and is increasingly used as a bridge or alternative to transplantation (1-3).

Ventricular arrhythmias (VAs) are common in patients with advanced heart failure and contribute to increased mortality (4). After LVAD implantation, late VAs (>30 days after implantation) are frequent with controversial impact on long-term survival (5-7). Little is known about VAs occurring during the first 30 days after LVAD implantation. Recent data regarding their prevalence and clinical impact are scarce or coming from single center studies, and most events are attributed to suction events, inotropic medication or electrolyte disorders (8) (9-11). In the present study, we aimed at describing the prevalence, predictors and clinical impact of early VAs in patient with LVAD included in the ASSIST-ICD observational study.

METHODS

STUDY DESIGN. The ASSIST-ICD is a retrospective, multicenter observational study (NCT02873169) of durable mechanical circulatory support devices implanted in 19 French tertiary centers. The methods of this study have been previously published (5).

Briefly, patients aged ≥ 18 years implanted with axial HeartMate 2 (Abbott, Chicago, Illinois), Jarvik2000 (Jarvik Heart, Inc., New York, New York), or centrifugal HeartWare pumps (Medtronic, Columbia Heights, Minnesota) between February 2006 and December 2016 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; and VentrAssist (Ventricor, Chatswood, NSW, Australia) recipients. Patients deceased during LVAD surgery were excluded from the final analysis.

This study was approved by the regional ethic committees, the French Advisory Committee on the Treatment of Research Information in the Field of Health (CCTIRS), and the French National Commission of Informatics and Civil Liberties (CNIL). A non-opposition 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 prior to or after LVAD implantation history, echocardiography, and blood chemistry values – were collected from hospital files for all patients. Peri-operative data (such as the necessity of a combined surgery or a right extracorporeal life support) was collected.

Follow-up was performed according to each institution's protocols. 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 31st 2016, the date of heart transplantation, or death, whichever occurred first.

VENTRICULAR ARRHYTHMIAS. As previously described (5), VAs were defined as sustained (>30 seconds) ventricular tachycardia (VT) or ventricular fibrillation (VF) without an acute reversible cause and treated medically, by external electrical shock, or appropriate therapy from an implantable cardioverter-defibrillator (ICD) (anti-tachycardia pacing or shock). Of note, the occurrence of early VA associated with acute reversible causes during the post-operative period (i.e. LV suction events or electrolyte abnormalities) was not considered as early VA and was not collected. The number and type of VAs and specific therapies to restore sinus rhythm were collected. VAs were classified according to their time of occurrence: VAs prior to LVAD implantation, early VAs post LVAD implantation (occurring within 30 days after the surgery), or both. Electrical storm was defined as three or

more VA episodes in less than 24 hours.

During the post-operative period, telemetry monitoring, electrocardiogram strips or electrograms of VAs episodes were collected. All antiarrhythmic drug therapies introduced during the post-operative period were collected.

STUDY ENDPOINTS. The primary endpoints of the study were the rates of early VAs. Secondary endpoints included all-cause of mortality during the post-operative period (<30 days after LVAD implantation) and all-cause of mortality in patients discharged from hospital, depending on the occurrence of early VAs or not. Deaths were classified as cardiovascular (cardiac or vascular cause) or non-cardiac deaths.

STATISTICAL ANALYSIS. Qualitative variables are expressed as number (percentage); continuous data as mean \pm standard deviation or median (interquartile range) 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. To account for a potential clustering effect within centers, predictors of early VAs and operative (30 days) mortality post-LVAD were analyzed using univariate and multivariable multilevel logistic regressions with the center of inclusion as a random effect with the use of generalized linear mixed models. Variables with p-values <0.1 in univariate analysis were included in the multivariable analysis. All univariate analyses were performed on complete cases.

Overall, 23% of patients had missing values for at least one variable, but, of note, only 3 variables are concerned: left ventricular end-diastolic diameter (12.0%), left ventricular ejection fraction (3.7%) and serum bilirubin (13.7%). 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. Ten imputed datasets were created; results were pooled according to Rubin's rule (12) and

reported as adjusted odds ratios (ORs) with their 95% confidence intervals (CIs). The absence of multicollinearity in the final model was verified using tolerance and variance inflation factor measurements. 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 according to the occurrence of early VA and the type of early VA. All tests were two-sided at the 0.05 significance level. Statistical analyses were conducted using the Statistical Package for Social Sciences version 22 (SPSS Inc., IBM, Armonk, New York).

RESULTS

STUDY POPULATION. From 2006 to 2016, a total of 659 patients were implanted with a continuous-flow LVAD and included in the study. Among these, 7 patients were excluded (3 patients received a VentrAssist and 4 patients died during the LVAD surgery). A total of 652 patients were included in the final analysis.

Baseline characteristics of the 652 patients are presented in Table 1. Overall, 86.0% were male, 63.2% had an ischemic cardiomyopathy, and the median heart failure duration was 61.4 months (interquartile range: 2.1-168.8). Two hundred and twenty three patients (34.2%) had a history of at least one sustained VT/VF and 36 (16.1%) had a VT ablation procedure performed. The HeartMate 2 was the most common LVAD implanted (72.8%) and the leading indication (59.4%) was bridge to transplantation.

After LVAD implantation, the mean VT and VF detection rates programmed in ICDs were 176.6 ± 16.2 bpm (5.7 ± 3.4 antitachycardia pacing attempts before ICD shock) and 225.9 ± 11.9 bpm (ATP during/after charging then shock).

PREVALENCE AND PREDICTORS OF EARLY VENTRICULAR ARRHYTHMIAS. One hundred and sixty-two (24.8%) patients had at least 1 episode of early VA. Compared to patients without early VAs, those with early VAs had significantly had a longer median heart failure duration and greater LV volumes (Table 1). They also more often had a history of

VAs and more ICDs implanted prior to LVAD implantation. Furthermore, serum creatinine was higher before LVAD surgery in patient with early VAs. No difference was found regarding age, gender and etiology of the underlying cardiomyopathy between the two groups. Regarding the characteristics of the LVAD implantation, there was no difference in the clinical and the type of LVAD but patients with early VAs had more combined surgery at the time of LVAD implantation. In the 30-day post-operative, patient who experienced early VAs presented more AF episodes. Multivariable analysis identified history of VAs prior to LVAD implantation as the strongest significant predictor of early VA (OR 2.36 95% CI: 1.57-3.56, $p < 0.001$). Interestingly, combined surgery with LVAD implantation was also an independent predictor of the occurrence of early VA. Lastly, we observed that temporary right ECLS implantation during LVAD surgery decreases by 2-fold the risk of early VA (Table 2).

Among the 162 patients with early VAs, a total of 1379 early VAs were documented for an average of 2.1 VAs per patient-month. The first episode occurred after a median time of 6.0 days (interquartile range; 2.0-12.0) post-LVAD implantation and 93 (57.4%) patients had the first early VA in the first week post LVAD implantation (Figure 1). Forty patients (24.7%) had VF episodes (total number of episodes: 352; median of 1.0 episode per patient [interquartile range: 1.0-3.0]). VT episodes were documented in 141 patients (87.0%) (total number of episodes: 1,027; median of 3.0 episodes per patient [interquartile range: 1.0-5.25]). Among the 162 patients, 114 (70.4%) experienced between 1 and 5 early VAs episodes (52 had 1 VA episode and 62 between 2 and 5 events) and 21 (13%) had more than 10 early VAs episodes. Electrical storm occurred in 39 patients after a median of 7.0 days (interquartile range 3.0-16.7) after LVAD implantation. A total of 94 patients (58.0%) received at least 1 shock during the 30-day post-operative period (22, 52 and 20 received respectively only external shocks, only ICD shocks or both). Catheter ablation of VT was performed in 7

patients in the post-operative period, 15.5 (1.0-24.0) days after the first early VA episode, without procedural complications (none had catheter ablation prior to LVAD implantation). Of note, radiofrequency ablation was performed for VT and VF episodes in 5 and 2 patients respectively. The left Purkinje area was the targeted ablation sites in both patients with early VF. Among these 7 patients, 2 needed a redo ablation during the index hospitalization. Interestingly, 6 patients were discharged alive from hospital and 2 presented VAs recurrences during follow-up.

CLINICAL IMPACT OF EARLY VENTRICULAR ARRHYTHMIAS. Patients with early VAs had a significantly longer duration of hospitalization in intensive care unit and a longer total hospital stay than patients without early VAs (Table 1). A total of 138 patients (21.2%) died during the hospitalization period, 50/162 (30.8%) patients with early VAs and 88/490 (18.0%) patients with no early VA ($p < 0.001$, Table 1). As shown in Figure 2, Panel A, occurrence of early VAs was associated with increased mortality during the 30-day post-operative especially in case of early VAs associated with electrical storm (Figure 2, Panel B). In multivariable analysis, the occurrence of early VAs associated with early electrical storm, heart failure duration and any surgery combined with LVAD, were independent predictors of 30-day post-operative mortality (Table 3). Of note, among these predictors, early VAs associated with early electrical storm had the strongest OR, with a 7-fold increase in mortality (OR: 7.36; 95%CI: 2.71-20.00). Conversely, a 2-fold decrease in mortality was observed in patients receiving amiodarone during the intensive care unit (ICU) stay. Of note, amiodarone was initiated after a median time of 2.0 (0.0-5.0) days after LVAD implantation and might have been initiated for the occurrence of VA or AF. Lastly, LVAD recipients with ICD exhibited an important decrease in the risk of post-operative mortality. Importantly, in patients discharged alive from hospital early VAs did not influence long-term mortality (Figure 3).

In the light of the multivariable analysis, we compared patients with early VA with or without electrical storm episode. Results are described in Table 4. Briefly, patients did not differ in terms of baseline characteristics. However, a significantly higher rate of right ECLS implantation during the LVAD surgery was observed in patients with electrical storm.

DISCUSSION

To the best of our knowledge, this is the largest database on early VAs in LVAD recipients aiming to describe their prevalence, predictors and clinical impact after LVAD implantation. The four main findings are as follows: 1) early VAs are common after LVAD implantation, occurring in 24.8% of patients; 2) 57.4% of the patients experience their first early VA during the initial 7 post-operative days; 3) occurrence of VAs prior to LVAD implantation and any surgery combined with LVAD implantation are two independent predictors of early VAs; 4) early VAs associated with electrical storm is the strongest predictor of 30-day post-operative mortality, with a 7-fold increased risk of death.

EARLY VENTRICULAR ARRHYTHMIAS IN LVAD RECIPIENTS. Early VAs frequently occur in LVAD recipients. In recent studies, the incidence of early VAs was estimated between 13.2% and 23.5% in patients with continuous-flow LVAD (1, 10-11). A similar rate was observed in our study with early VAs documented in 24.8% of the patients. In contrast with late VAs, which are often asymptomatic because of the continuous flow of the LVAD ensuring efficient hemodynamic support (13), early VAs, occurring shortly after LVAD implantation, are more likely to be responsible for hemodynamic deterioration (14). In fact, patients with early VAs more often exhibit right ventricular failure, increasing duration of hospitalization (10). We confirm this impact on morbidity with a longer duration in intensive care unit and a longer total hospital length of stay. Data regarding the mortality impact of early VAs in continuous-flow LVAD are scarce. Bedi et al (9) showed that the mortality risk was high when VAs occurred within the first post-operative week, but this study mostly

included patients with pulsatile flow LVAD which is not representative of the current practice. In a recent study, electrical storm has been described as a pejorative feature in the early postoperative period (15). We demonstrate in a large population of LVAD recipients that early VAs associated with electrical storm was the strongest predictor of 30-day post-operative mortality, with a 7-fold increased risk of death. Indeed, despite the continuous flow generated by the LVAD, early VAs can lead to right ventricular failure and hemodynamic deterioration in this high-risk post-operative period.

Interestingly, we also found that heart failure duration and combined surgery with LVAD are independent predictors of post operative mortality. These parameters are probably related to more advanced cardiomyopathy at the time of implantation. Additionally, patients who required combined surgery with LVAD, usually had a multifactorial and more complex cardiomyopathy at baseline. Lastly, those patients experienced a longer cardiopulmonary bypass duration during surgery, possibly leading to higher rate of post-operative myocardial insult.

PREDICTORS OF EARLY VENTRICULAR ARRHYTHMIA. In this study, we identified that history of pre-operative VAs and any surgery combined with LVAD are two independent predictors of early VAs. Indeed, history of pre-operative VAs has been described as a predictor of early VAs (10), undoubtedly explained by the underlying arrhythmic substrate. For a long time, the apical cannula of the LVAD was incriminated as the substrate of early VA (16) but recent data showed that the preexisting scar was the main substrate for early VA. Indeed, Sacher et al found that in 34 patients scheduled for VT ablation after LVAD implantation, only 10/110 (9%) of the targeted VTs were related to the HeartMate II cannula (17). Similarly, Snipelisky et al reported in a cohort of 6 LVAD recipients who had VT ablation, only 2 VTs directly related to the LVAD inflow cannula site (18). Lastly, similar result was found in a large single center experience of 21 LVAD recipients who underwent

catheter ablation and only 5 (24%) patients had cannula-adjacent related VT (19). Finally, the fact that history of VAs prior to LVAD implantation is a predictor of early VAs is a strong argument supporting to the substrate-dependent, macro-reentrant, mechanism of post-LVAD arrhythmias. We also observed that any surgery combined with LVAD is an independent predictor of the occurrence of early VA. Indeed, combined surgery may probably play a role in triggering VA, through ischemia related to an increased procedural time, in patients with an underlying VA substrate. Conversely, we noted that temporary right ECLS implantation at the time of LVAD implantation decreases by 2-fold the risk of early VA events. This finding questions about the impact of the right ventricular function on the occurrence of early VA during the post-operative period.

Some precipitant factors, specific to the post-operative period, may also play a significant role in the onset of early VAs. In fact, fluid and electrolyte shifts or use of inotropic drugs probably intervene in early VAs occurrence (20). An increase in QTc interval after LVAD implantation has been described (21-22) and may trigger VAs through a delayed post-depolarization mechanism. Ventricular unloading, associated with changes in parietal stretch that may alter the electrical properties of the tissue (refractory periods or conduction times), particularly in the scar area, and may favor VAs (17).

CLINICAL IMPLICATIONS. This study strongly suggests that early VAs, and especially the occurrence of early electrical storm, is the strongest predictor of 30-day post-operative mortality, with a 7-fold increased risk of death. In addition, history of VA prior to LVAD is a predictor of 30-day post-operative VAs. The Figure 4 synthesizes the main findings of the paper and their impact in clinical practice. Indeed, a rigorous pre-operative rhythmic evaluation is critically needed to determine those patients at high risk of early arrhythmias and in-hospital death. These findings are a plea to integrate electrophysiologists into the multidisciplinary “LVAD Heart Team” in charge of patients’ selection and management in

order to discuss the following attitudes:

- Patients with a history of VA should be evaluated by electrophysiologists prior to LVAD implantation and a VT ablation could be discussed in selected patients. Of note, catheter ablation could benefit for patients with epicardial substrate (i.e. patients with non-ischemic dilated cardiomyopathy) for whom an epicardial VT ablation is challenging, if not impossible, after LVAD implantation due to pericardial adhesions (23). Alternatively, an open-chest epicardial VT ablation at the time of LVAD implantation, as described in small size studies, (24-27) could be performed in selected patients. Finally, the decision to combine a surgical procedure during LVAD implantation should be carefully discussed to limit myocardial ischemia and decrease the risk of early VA. Prospective studies will be required to compare the effect of beating or stopping heart LVAD implantation on the occurrence of early VA.
- During the post-operative period, especially the first week, ICU physicians should remain vigilant about VAs and rapidly contact electrophysiologists if an arrhythmia occurs. An aggressive management of arrhythmias should be pursued, using anti-arrhythmic drugs and proposing catheter ablation of VAs in selected patients.
- Importantly, we showed that amiodarone (specifically quickly initiated after LVAD implantation as performed in our study) in ICU had a positive impact in post-operative survival, highlighting the potential protective benefit of this therapy on 30-day post-operative outcomes. This finding could question about the empiric use of amiodarone in the immediate post-operative period. Nevertheless, dedicated studies are required to specifically evaluate the impact, optimal delay from LVAD surgery and dose of empiric anti-arrhythmic drugs in the post-operative period. Of

note, amiodarone did not show any beneficial anti-arrhythmic effect during long-term follow-up (5) and we do not encourage continuing this treatment beyond the 30-day post-operative period.

- Lastly, we also observed that ICD positively impacts 30-day post-operative survival. Indeed, ICD may probably quickly terminate VA events using anti-tachycardia pacing therapy compared to patients without ICD and consequently limit the negative impact of prolonged VA episodes or the need for external shock. Furthermore, in the post-operative period, LVAD recipients are often hemodynamically unstable and may probably be more prone to experience deleterious effect of prolonged VA or shocks. However, further studies are warranted to clearly define the optimal device programming and the impact of conservative VT management with longer VA detection delay and aggressive antitachycardia-pacing therapies.

LIMITATIONS. Our observational study has some limitations, including its retrospective design that may have affected the results. Furthermore, in Europe and particularly in France, many patients are in advanced cardiogenic shock at the time of LVAD implantation and probably suggest that the French LVAD recipients are probably sicker than US patients. Thus, our results cannot be necessarily extended to other populations. In addition, early VAs with electrical storm increase the 30-day post-operative mortality, but these patients are often sicker with worst prognosis and this bias cannot be excluded. Additionally, early VAs associated with post-operative specific acute reversible etiology (i.e. LV suction events or electrolyte abnormalities) were excluded from the analysis. However, due to the retrospective inclusion, the real rate of VA without reversible etiology is probably overestimated. Furthermore, duration of inotropic agent administration was not collected and the impact of inotrope drug use on the occurrence of early VAs has not been evaluated. Lastly, the impact

of the pre-operative right ventricular function on the occurrence of early VA has not been accurately investigated and we are not able to specifically explain the protector effect of temporary right ECLS implantation.

CONCLUSION.

Early VAs are common after LVAD implantation and increase post-operative mortality, without affecting long-term survival. Early VAs associated with the occurrence of early electrical storm, is the strongest predictor of the 30-day post-operative mortality, with a 7-fold increased risk of death. Further studies will be needed to analyze whether pre-operative ablation of VAs may improve post-operative outcomes.

PERSPECTIVES:

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Early VAs, and especially the occurrence of early electrical storm, is the strongest predictor of post-operative mortality, with a 7-fold increased risk of death. Occurrence of VAs prior to LVAD implantation and any surgery combined with LVAD are two independent predictors of early VAs. A rigorous pre-operative rhythmic evaluation is critically needed to determine those patients at high risk of early arrhythmias and in-hospital death.

TRANSLATIONAL OUTLOOK: Further studies will be needed to analyze whether pre- or preoperative ablation of VAs improves postoperative outcomes.

REFERENCES

- 1- Pagani FD, Miller LW, Russell SD, et al; HeartMate II Investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol*. 2009;54:312-21.
- 2- Miller LW, Pagani FD, Russell SD, et al; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357 :885-96.
- 3- Slaughter MS, Rogers JG, Milano CA, et al; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009 Dec 3;361(23):2241-51.
- 4- Kreuz J, Horlbeck F, Linhart M, et al. Independent predictors of mortality in patients with advanced heart failure treated by cardiac resynchronization therapy. *Europace* 2012;14:1596-601.
- 5- Galand V, Flécher E, Auffret V, et al. Predictors and Clinical Impact of Late Ventricular Arrhythmias in Patients with Continuous-Flow Left Ventricular Assist Devices. *JACC Clin Electrophysiol*. In revision.
- 6- Efimova E, Fischer J, Bertagnolli L, et al. Predictors of ventricular arrhythmia after left ventricular assist device implantation: A large single-center observational study. *Heart Rhythm*. 2017; 17: 1547-5271
- 7- Yoruk A, Sherazi S, Massey HT et al. Predictors and clinical relevance of ventricular tachyarrhythmias in ambulatory patients with a continuous flow left ventricular assist device. *Heart Rhythm* 2016;13:1052-6.
- 8- Nakahara S, Chien C, Gelow J, et al. Ventricular arrhythmias after left ventricular assist device. *Circ Arrhythm Electrophysiol* 2013; 6: 648-54.
- 9- Bedi M, Kormos R, Winowich S, McNamara DM, Mathier MA, Murali S. Ventricular

- arrhythmias during left ventricular assist device support. *Am J Cardiol.* 2007; 99:1151–3.
- 10-Garan AR, Levin AP, Topkara V, Thomas SS, Yuzefpolskaya M, Colombo PC, Takeda K, Takayama H, Naka Y, Whang W, Jorde UP, Uriel N. Early post-operative ventricular arrhythmias in patients with continuous-flow left ventricular assist devices. *J Heart Lung Transplant.* 2015; 3 :1611-6.
- 11- Greet BD, Pujara D, Burkland D, Pollet M, Sudhakar D, Rojas F, Costello B, Postalian A, Hale Z, Jenny B, Lai C, Igbalode K, Wadhera D, Nair A, Ono M, Morgan J, Simpson L, Civitello A, Cheng J, Mathuria N. Incidence, Predictors, and Significance of Ventricular Arrhythmias in Patients With Continuous-Flow Left Ventricular Assist Devices. *JACC Clin Electrophysiol.* 2017
- 12-Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* New York, NY: John Wiley & Sons, Inc., 1987.
- 13-Sims DB, Rosner G, Uriel N, Gonzalez-Costello J, Ehlert FA, Jorde UP. Twelve hours of sustained ventricular fibrillation supported by a continuous-flow left ventricular assist device. *Pacing Clin Electrophysiol* 2012; 35: 144-8.
- 14-Yaksh A, Kik C, Knops P, et al. Hemodynamic deterioration precedes onset of ventricular tachyarrhythmia after Heartmate II implantation. *Journal of Cardiothoracic Surgery* 2016 Jul 8;11(1):97.
- 15-Corre J, Picard F, Garcia R, et al. Electrical storm in the early phase of HeartMate® II device implantation: Incidence, risk factors and prognosis. *Arch Cardiovasc Dis.* 2017 Dec 4. pii: S1875-2136(17)30220-6
- 16-Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. *J Am Coll Cardiol* 2005; 45:1428-34.

- 17-Sacher F, Reichlin T, Zado ES, et al. Characteristics of ventricular tachycardia ablation in patients with continuous flow left ventricular assist devices. *Circ Arrhythm Electrophysiol* 2015; 8: 592-597
- 18-Snipelisky D, Reddy YN, Manocha K, et al. Effect of Ventricular Arrhythmia Ablation in Patients With Heart Mate II Left Ventricular Assist Devices: An Evaluation of Ablation Therapy. *J Cardiovasc Electrophysiol*. 2017 Jan;28(1):68-77
- 19-Moss JD, Flatley EE, Beaser AD, et al. Characterization of Ventricular Tachycardia After Left Ventricular Assist Device Implantation as Destination Therapy: A Single-Center Ablation Experience. *JACC Clin Electrophysiol*. 2017 Dec 11;3(12):1412-1424.
- 20-Shirazi JT, Lopshire JC, Gradus-Pizlo I, Hadi MA, Wozniak TC, Malik AS. Ventricular arrhythmias in patients with implanted ventricular assist devices: a contemporary review. *Europace*. 2013;15:11-7.
- 21-Harding JD, Piacentino V, Gaughan JP, Houser SR, Margulies KB. Electrophysiological alterations after mechanical circulatory support in patients with advanced cardiac failure. *Circulation*. 2001;104:1241-7.
- 22-Harding JD, Piacentino V, Rothman S, Chambers S, Jessup M, Margulies KB. Prolonged repolarization after ventricular assist device support is associated with arrhythmias in humans with congestive heart failure. *J Card Fail*. 2005;11: 227-32.
- 23-Briceño DF, Romero J, Villablanca PA, et al. Long-term outcomes of different ablation strategies for ventricular tachycardia in patients with structural heart disease: systematic review and meta-analysis. *Europace*. 2018; 20 :104-115
- 24-Mulloy DP, Bhamidipati CM, Stone ML, et al. Cryoablation during left ventricular assist device implantation reduces postoperative ventricular tachyarrhythmias. *J Thorac Cardiovasc Surg*. 2013;145:1207–1213.

- 25-Patel M, Rojas F, Shabari FR, et al. Safety and Feasibility of Open Chest Epicardial Mapping and Ablation of Ventricular Tachycardia During the Period of Left Ventricular Assist Device Implantation. *J Cardiovasc Electrophysiol.* 2016; 27: 95-101
- 26-Moss JD, Oesterle A, Raiman M, et al. Feasibility and utility of intraoperative epicardial scar characterization during left ventricular assist device implantation. *J Cardiovasc Electrophysiol.* 2019 Feb;30(2):183-192.
- 27-Cantillon DJ, Bianco C, Wazni OM, et al. Electrophysiologic characteristics and catheter ablation of ventricular tachyarrhythmias among patients with heart failure on ventricular assist device support. *Heart Rhythm.* 2012; 9: 859–864.

FIGURE TITLES AND LEGENDS

FIGURE 1: Type and number of early vas per patient and timing of the occurrence of the first early VA. LVAD = Left ventricular assist device; VA = ventricular arrhythmia.

FIGURE 2: 30-day survival after LVAD implantation depending on (A) the occurrence of early VAs, (B) the occurrence of early electrical storm. VA = ventricular arrhythmia

FIGURE 3: Survival after hospital discharge according to the occurrence of early VAs during in-hospital stay. VA = ventricular arrhythmia

CENTRAL ILLUSTRATION: Suggested management for early VA in LVAD recipients. ICU = intensive care unit; LVAD= Left ventricular assist device; VA = ventricular arrhythmia

TABLE 1 Baseline Demographics.

	All patients (n=652)	Patients with early VAs (n=162)	Patients without early VAs (n=490)	p Value
Age. Yrs	59.8 (51.4-66.4)	59.5 (53.3-65.4)	59.9 (50.9-66.6)	0.820
Men	561 (86.0)	143 (88.3)	418 (85.3)	0.416
Body mass index. kg/m ²	25.3 (22.6-27.8)	26.5 (23.7-29.3)	25.0 (22.2-27.5)	<0.001
Heart failure etiology				
Ischemic	412 (63.2)	102 (63.0)	310 (63.3)	0.983
Idiopathic	178 (27.3)	45 (27.7)	133 (27.1)	
Other	62 (12.9)	15 (9.3)	47 (9.6)	
Heart failure duration. months	61.4 (2.1-168.8)	87.6 (12.2-184.4)	45.0 (1.6-160.6)	0.012
LVEDD prior to LVAD. mm	70.0 (64.0-75.0)	72.0 (65.0-77.0)	69.0 (62.0-74.5)	<0.001
LVEF prior to LVAD. %	20.0 (15.0-25.0)	20.0 (15.0-25.0)	20.0 (15.0-25.0)	0.076
History of VAs	223 (34.2)	87 (53.7)	136 (27.8)	<0.001
VT ablation prior to LVAD	36 (5.5)	13 (8.0)	23 (4.7)	0.158
ICD prior to LVAD	403 (61.8)	117 (72.2)	286 (58.4)	0.002
CRT prior to LVAD	198 (30.4)	51 (31.7)	147 (28.7)	0.797
Biology Serum				
-Creatinine. μmol/L (n=598)	115.0 (87.0-148.0)	125.0 (95.0-154.0)	110.0 (85.0-145)	0.012
-Serum sodium. mmol/L (n=599)	136.0 (132.0-139.0)	135.0 (132.0-138.0)	136.0 (132.0-139.0)	0.457
-Total bilirubin. μmol/L (n=563)	16.0 (10.0-27.0)	16.5 (11.0-31.0)	16.0 (10.0-25.0)	0.079
Temporary mechanical circulatory support				
-Extracorporeal life support	136 (20.9)	33 (20.4)	103 (21.0)	0.816
-Intra-aortic pump balloon	58 (8.9)	8 (4.9)	50 (10.2)	0.06
-Impella	64 (9.8)	13 (8.0)	51 (10.4)	0.439
Type of LVAD				
-HeartMate 2	475 (72.8)	118 (72.8)	357 (72.8)	0.231
-HeartWare	127 (19.5)	36 (22.2)	91 (18.6)	
-Jarvik2000	50 (7.7)	8 (4.9)	42 (8.6)	
LVAD indication				
-Bridge to transplantation	387 (59.4)	97 (59.9)	290 (59.2)	0.961
-Destination therapy	247 (37.9)	61 (37.6)	186 (38.0)	
-Bridge to decision / recovery	18 (2.8)	4 (2.5)	14 (2.8)	
Surgery combined with LVAD	95 (14.6)	32 (19.8)	63 (12.9)	0.043
Temporary right ECLS during surgery	81 (12.4)	13 (8.0)	68 (13.9)	0.069
Drugs post LVAD implantation in ICU				
-Beta-blockers	88 (13.5)	33 (20.4)	55 (11.2)	0.005
-Amiodarone	321 (49.2)	121 (74.7)	200 (40.8)	<0.001
AF post LVAD in ICU	267 (41.0)	81 (50.0)	186 (38.0)	0.006
Total days in ICU	14.0 (9.0-27.0)	21.0 (13.5-28.0)	13.0 (8.0-25.7)	0.001
Total days in hospital	41.0 (30.0-59.0)	47.0 (34.0-66.0)	39.0 (29.0-57.0)	0.007
Death during hospitalization	138 (21.2)	50 (30.8)	88 (18.0)	<0.001
Cause of death				
-Cardiovascular death	62 (44.9)	27 (54.0)	35 (37.9)	0.151

-Non-cardiovascular death	76 (55.1)	23 (46.0)	53 (60.2)	
Heart transplant during hospitalization	7 (1.1)	1 (0.6)	6 (1.2)	0.833

Values are median (interquartile range), n (%), or mean \pm standard deviation. AF = atrial fibrillation; CRT = cardiac resynchronization therapy; ECLS = extracorporeal life support; ICD = implantable cardioverter-defibrillator; ICU = intensive care unit; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; VAs = ventricular arrhythmias; VT = ventricular tachycardia

TABLE 2 Multivariable Analysis for Risk Prediction of Early VAs.

	β coefficient	OR (95% CI)	p Value
Body mass index,kg/m ²	0.028	1.03 (0.99-1.07)	0.186
Heart failure duration, months	0.001	1.00 (0.99-1.00)	0.831
LVEDD prior to LVAD, mm	0.012	1.01 (0.99-1.03)	0.103
VAs prior to LVAD	0.859	2.36 (1.57-3.56)	<0.001
ICD prior to LVAD	0.115	1.12 (0.69-1.82)	0.639
Total bilirubin prior to LVAD, mmol/L*	0.006	1.01 (1.00-1.01)	0.064
Intra-aortic pump balloon prior to LVAD	-0.275	0.76 (0.33-1.77)	0.524
Surgery combined with LVAD	0.561	1.75 (1.05-2.93)	0.033
Temporary right ECLS during LVAD surgery	-0.739	0.48 (0.24-0.95)	0.035
AF post LVAD in ICU	0.293	1.34 (0.91-1.97)	0.137

AF: atrial fibrillation; CI = confidence interval; ECLS = extracorporeal life support; ICD = implantable cardioverter-defibrillator; ICU = intensive care unit; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; OR = odds ratio; VA = ventricular arrhythmia, VT = ventricular tachycardia.

TABLE 3 Multivariable Analysis for Risk Prediction of 30-day post-operative mortality

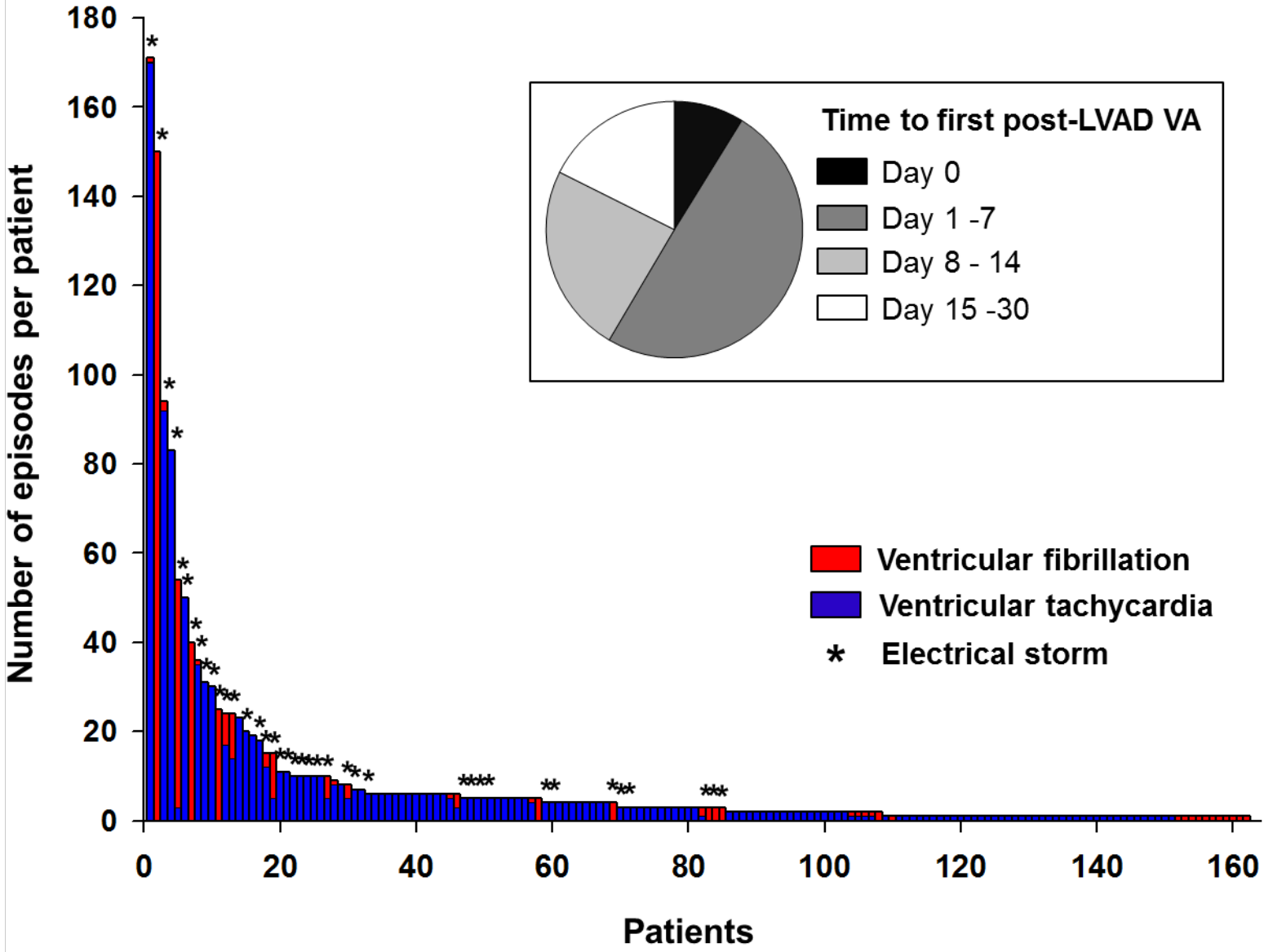
	β coefficient	OR (95% CI)	p Value
Age	0.015	1.01 (0.98-1.05)	0.328
Hypertension	0.404	1.50 (0.83-2.71)	0.180
Heart failure duration	0.003	1.003 (1.001-1.005)	0.003
LVAD recipients with ICD	-3.161	0.04 (0.02-0.09)	0.001
VT ablation prior to LVAD	0.532	1.70 (0.57-5.08)	0.341
Total bilirubin prior to LVAD	0.006	1.01 (0.99-1.01)	0.150
Impella prior to LVAD	0.580	1.79 (0.78-4.08)	0.718
Surgery combined with LVAD	1.106	3.02 (1.49-6.11)	0.002
Temporary right ECLS during surgery	0.218	1.24 (0.57-2.73)	0.586
Early VAs without electrical storm	0.707	2.03 (0.96-4.29)	0.065
Early VAs with electrical storm	1.996	7.36 (2.71-20.00)	0.001
AF post LVAD in ICU	-0.734	0.48 (0.25-0.93)	0.028
Beta blockers in ICU	-0.859	0.42 (0.15-1.20)	0.105
Amiodarone in ICU	-0.765	0.46 (0.23-0.92)	0.028

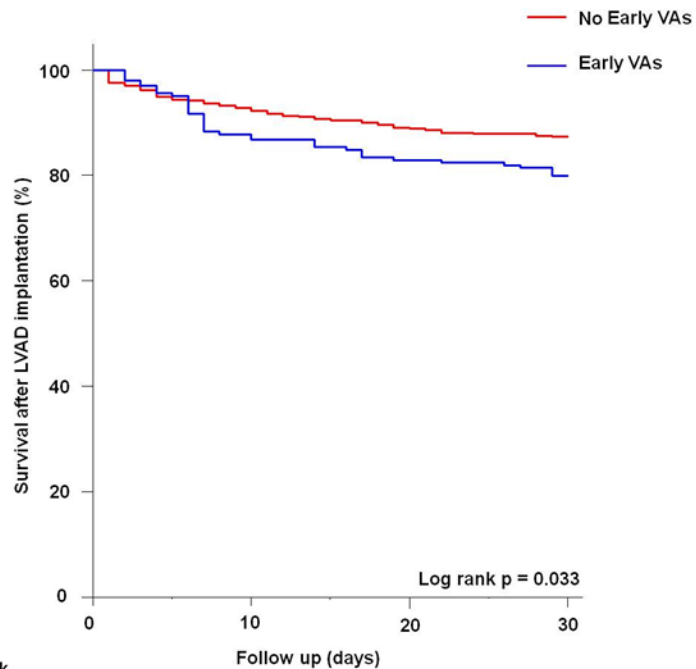
AF = atrial fibrillation; CI = confidence interval; ECLS = extracorporeal life support; ICD = implantable cardioverter-defibrillator; ICU = intensive care unit; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; OR = odds ratio; VA = ventricular arrhythmia.

Table 4: Characteristics between patients with early ventricular arrhythmias and with or without the occurrence of early electrical storm

	Early VA without electrical storm (n=123)	Early VA with electrical storm (n=39)	p Value
Age. Yrs	59.5 (53.4-65.5)	59.5 (53.3-65.3)	0.770
Men	111 (90.4)	32 (82.1)	0.971
Body mass index. kg/m ²	26.7 (23.8-25.6)	26.3 (23.7-29.)	0.634
Heart failure etiology			0.290
Ischemic	74 (60.2)	28 (71.8)	
Idiopathic	38 (30.9)	7 (17.9)	
Other	11 (8.9)	4 (10.3)	
Heart failure duration. months	76.4 (11.9-176.0)	91.0 (26.5-215.2)	0.259
LVEDD prior to LVAD. mm	72.3±9.2	71.2±8.3	0.543
LVEF prior to LVAD. %	20.0 (15.0-25.0)	20.0 (15.0-22.0)	0.732
History of VAs	62 (50.4)	25 (64.1)	0.190
ICD prior to LVAD	88 (71.5)	29 (74.4)	0.891
CRT prior to LVAD	39 (31.7)	12 (30.8)	0.930
Biology			
Serum creatinine. µmol/L	127.0 (92.0-156.7)	109.0 (96.7-151.7)	0.509
Serum sodium. mmol/L	135.0 (131.0-138.0)	135.0 (133.0-138.2)	0.546
Total bilirubin. µmol/L	16.0 (10.9-29.1)	19.0 (11.7-33.0)	0.355
Type of LVAD			0.734
HeartMate 2	89 (72.3)	29 (74.4)	
HeartWare	27 (22.0)	9 (23.1)	
Jarvik2000	7 (5.7)	1 (2.6)	
LVAD indication			0.468
Bridge to transplantation	74 (60.2)	23 (59.0)	
Destination therapy	47 (38.2)	14 (35.9)	
Bridge to decision / recovery	2 (1.6)	2 (5.1)	
Surgery combined with LVAD	26 (21.1)	6 (15.4)	0.578
Right ECLS during surgery	8 (6.5)	5 (12.8)	<0.001
Early ventricular fibrillation	22 (17.9)	18 (46.2)	<0.001
AF post LVAD in ICU	63 (51.2)	18 (46.2)	0.713

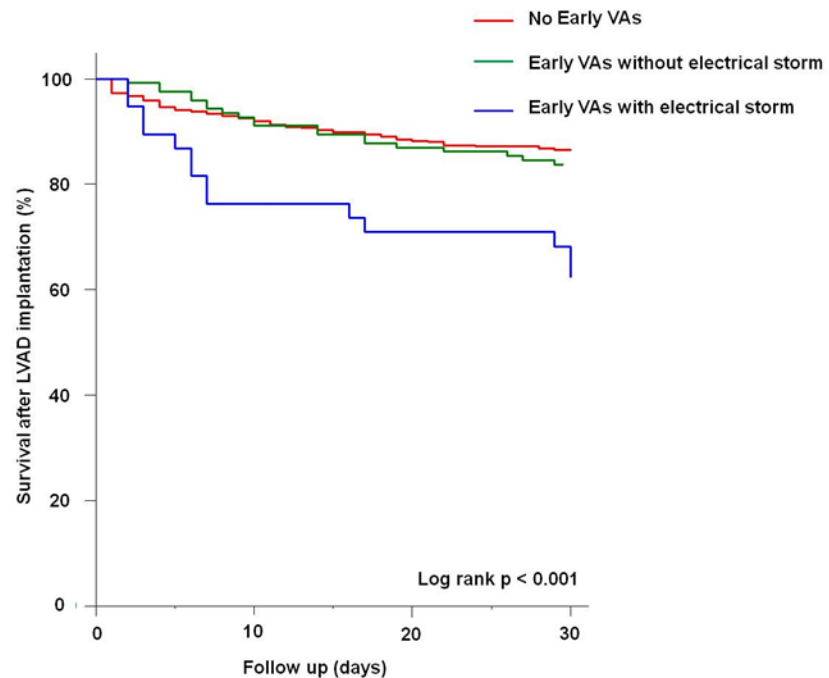
Values are median (interquartile range), n (%), or mean ± standard deviation. AF = atrial fibrillation; CRT = cardiac resynchronization therapy; ECLS = extracorporeal life support; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; VAs = ventricular arrhythmias; VF = ventricular fibrillation



A

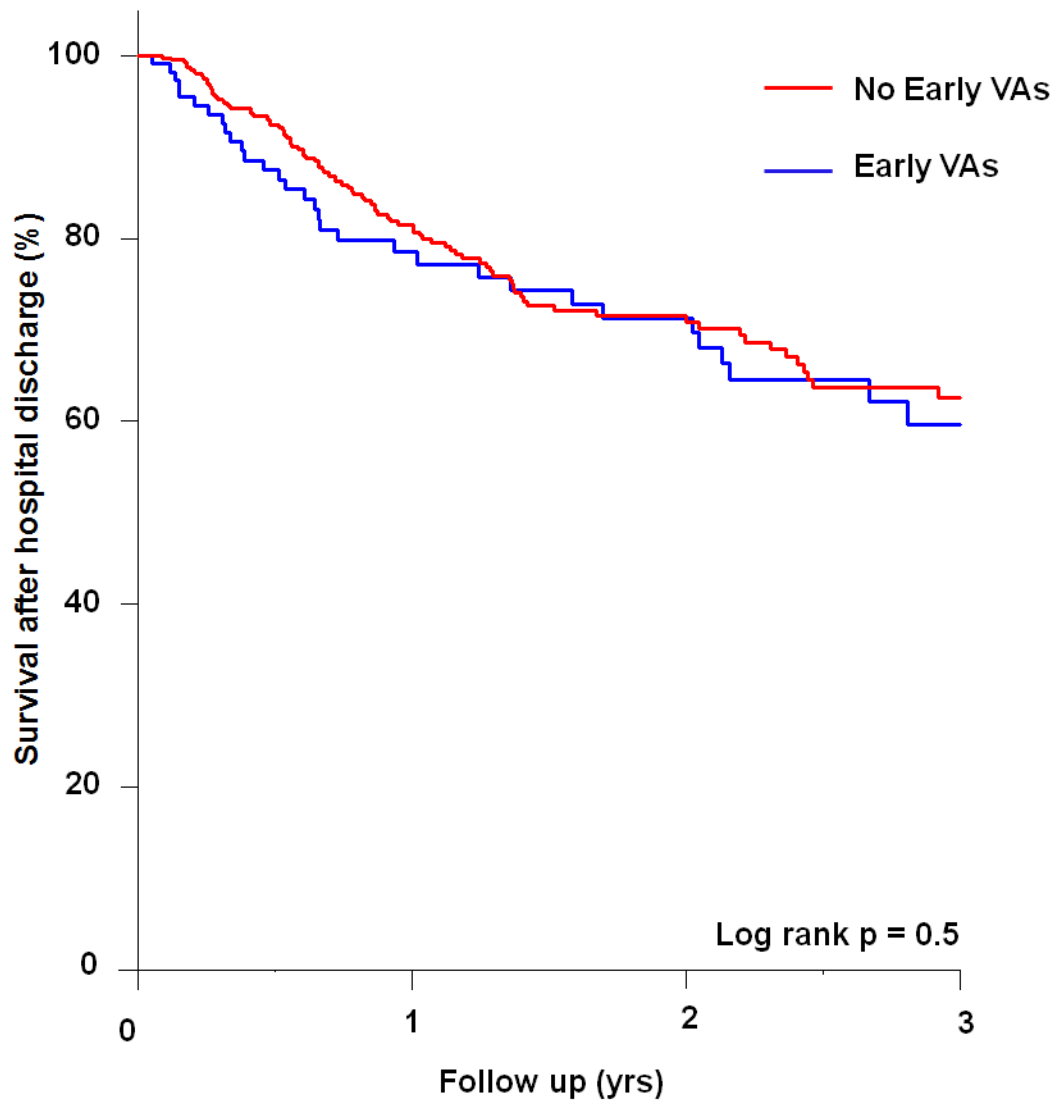
Number at risk

	0	10	20	30
Early VAs	162	144	134	129
No early VA	490	450	429	419

B

Number at risk

	0	10	20	30
Early VAs and AS	39	31	25	24
Early VAs and no AS	123	116	108	104
No early VA	490	450	429	417



Number at risk

Early VAs	111	59	44	22
No early VA	396	204	105	53

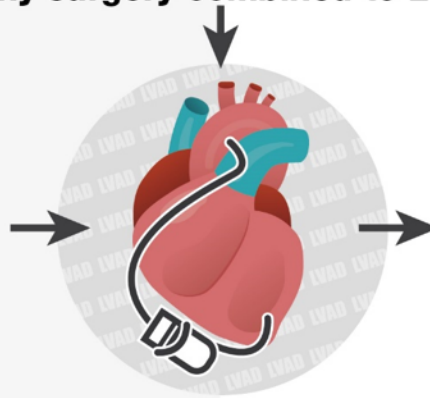
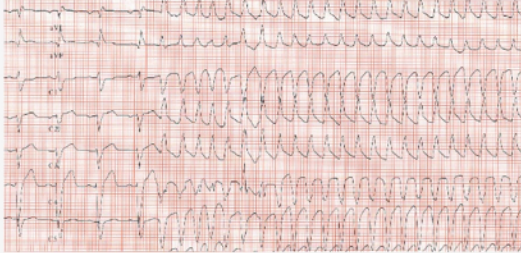
PRE-OPERATIVE PERIOD

PERIOPERATIVE PERIOD

POST-OPERATIVE PERIOD

Any surgery combined to LVAD

History of VA



2

fold increase
risk of VA and
arrhythmic storm

7

fold increase
in post-operative
mortality

LVAD Medical Team



Cardiac surgeon
Anesthesiologist
Heart failure specialist
LVAD nurse



Electrophysiologist

ACTIONS



Check patient file
for a history of VA



VA ablation prior to LVAD
should be discussed
in selected patients



Discuss the need
for a combined surgery



Close contact between ICU and Electrophysiologist
if early VA occur



Aggressive arrhythmia management

- Anti-arrhythmic drugs
- VA ablation