Journal of the American Heart Association

ORIGINAL RESEARCH

# Identifying Temporal Relationships Between In-Hospital Adverse Events After Implantation of Durable Left Ventricular Assist Devices

Arman Kilic, MD; Laura Seese, MD; Francis Pagani, MD; Robert Kormos, MD

**BACKGROUND:** This study evaluated the impact of adverse events (AEs) on the development of subsequent AEs after left ventricular assist device (LVAD) surgery.

**METHODS AND RESULTS:** The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) was used to identify primary durable LVADs implanted between 2006 and 2016. The temporal relationships between AEs occurring during the index hospitalization were evaluated using separate risk-adjusted Cox proportional hazard models. LVADs were implanted in 18 763 patients. The strongest positive relationships were renal failure leading to hepatic dysfunction (hazard ratio [HR], 6.62; 95% CI, 5.12–8.54; $P<0.001$), respiratory failure leading to renal failure (HR, 5.51; 95% CI, 4.79–6.34; $P<0.001$), respiratory failure leading to hepatic dysfunction (HR, 4.36; 95% CI, 3.25–5.83; $P<0.001$), renal failure leading to respiratory failure (HR, 4.18; 95% CI, 3.76–4.64; $P<0.001$), and renal failure leading to right ventricular assist device implant (HR, 3.70; 95% CI, 2.31–5.90; $P<0.001$). Although bleeding, infection, and right ventricular assist device implant were each associated with several subsequent AEs, the magnitude of association was less substantial. The lowest 1-year post-LVAD survival was associated with the primary AEs of renal failure (68.1%) and respiratory failure (70.7%) (log-rank $P<0.001$).

**CONCLUSIONS:** Most in-hospital AEs after LVAD implantation have a significant association with the development of subsequent AEs, with the most profound impact associated with primary renal or respiratory failure, which are also associated with the lowest 1-year survival. Targeting the reduction of renal or respiratory failure as the primary AE after LVAD surgery would likely yield the greatest reductions in overall AE burden and subsequent mortality.

**Key Words:** complications ■ heart failure ■ left ventricular assist device

Although the survival of patients undergoing left ventricular assist device (LVAD) implantation has markedly improved over the past decades, adverse events (AEs) remain a major hurdle to wider adoption of LVAD therapy. Certain AEs, such as stroke, multisystem organ failure, infection, right heart failure, and device malfunction, have all been shown to deter the likelihood of early postoperative recovery and long-term survival.[1] More important, AEs often are markers of major morbidity, requiring frequent hospital readmission, and lead to overall reductions in patient quality of life.[2,3] In efforts to reduce the occurrence and minimize the impact of LVAD-related AEs, many studies have evaluated preoperative predictors and longitudinal outcomes after isolated AEs.[4–7] However, in the clinical setting, there is a proclivity for AEs to occur in a clustered manner. These relationships between AEs remain to be

Correspondence to: Arman Kilic, MD, Division of Cardiac Surgery, University of Pittsburgh Medical Center, 200 Lothrop St, Ste C-700, Pittsburgh, PA 15213. E-mail: kilica2@upmc.edu

Supplementary Materials for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015449

For Sources of Funding and Disclosures, see page 10.



*JAHA* is available at: www.ahajournals.org/journal/jaha

## CLINICAL PERSPECTIVE

### What Is New?

- This is a large, multicenter study evaluating the temporal relationships between adverse events (AEs) after left ventricular assist device surgery.
- Renal and respiratory failure are associated with the greatest magnitude of impact on the development of subsequent AEs, and with the lowest 1-year survival.

### What Are the Clinical Implications?

- Most in-hospital AEs occurring after left ventricular assist device surgery are associated with the development of subsequent AEs.
- Renal and respiratory failure should be targeted for quality improvement efforts to reduce the overall burden of AEs and subsequent mortality in left ventricular assist device surgery.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AEs** | Adverse Events |
| **BTT** | Bridge to Transplant |
| **INTERMACS** | Interagency Registry for Mechanically Assisted Circulatory Support |
| **LVAD** | Left Ventricular Assist Device |
| **RHF** | Right Heart Failure |
| **RVAD** | Right Ventricular Assist Device |

elucidated. The aim of this study was to examine if specific AEs were the main drivers of subsequent AEs after LVAD implantation.

## METHODS

### Data Source

The authors declare that all supporting data are available within the article and its online supplementary files. The data source for this study was the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) multicenter database. The INTERMACS data set is a North American registry formed in 2005 that is used to evaluate clinical outcomes in patients receiving a durable, implantable mechanical circulatory support device to treat advanced heart failure. This study was approved by the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center as well as the institutional review board at the University of Pittsburgh (Pittsburgh, PA). The need for patient informed consent for participation in the study was waived.

### Study Population

Adults (aged ≥18 years) registered in the INTERMACS database who underwent primary implantation of a durable continuous flow LVAD from 2006 to 2016 were included. Patients supported with total artificial heart devices, temporary devices, pulsatile devices, and isolated right ventricular assist devices (RVADs) and patients undergoing LVAD exchange were excluded from the analysis. We also excluded patients who had any missing data on occurrence or timing of any of the major AEs that were included in the study (3.0%; n=631). Those requiring concomitant RVAD support during LVAD implantation were included. Patients in the study were stratified on the basis of their first chronologic postoperative AE.

### Baseline Characteristics

Baseline demographics, including age, sex, race, and cause of heart failure, were evaluated. The clinical status of patients was evaluated using the INTERMACS profiles, and bridging strategy (bridge to transplant versus destination therapy) was also examined. Mean and SD and number with percentage were reported for continuous and noncontinuous data, respectively.

### Outcomes

The primary outcome was subsequent AEs after the occurrence of an initial primary AE after LVAD implantation. Only AEs occurring during the index hospitalization after LVAD surgery were analyzed. The categories of AEs included in the analysis were bleeding, cardiac arrhythmias, device malfunction attributable to pump thrombosis, hepatic dysfunction, infection, neurological dysfunction attributable to ischemic or hemorrhagic strokes, renal failure with or without dialysis, respiratory failure, and right ventricular failure requiring RVAD implantation. The criteria for defining these AEs were derived from the clinical definitions prespecified by the INTERMACS data registry.

### Statistical Analysis

To evaluate the temporal relationships between AEs, each event was chronologically ordered and defined as a primary AE if it was the first in the series or as a subsequent AE if the AE occurred after the primary AE. For each patient, all AEs occurring during their index hospitalization after LVAD implant were included. The associations between AEs were evaluated using separate multivariable, risk-adjusted Cox proportional

hazards models for each category of AEs. Each AE was analyzed as a time-varying covariate to account for the temporality and chronological proximity between associated AEs. The index AE was treated as the categorical variable, and the hazards for the development of subsequent AEs were evaluated for each primary AE. The mathematical notation for the Cox model used for the analysis is $\lambda(t|\bar{Z}) = \lambda_0(t)e^{\beta' Zt}$ where $\beta'$ denotes the 9 different index AEs and Z(t) denotes the time-varying associated AEs.

Kaplan-Meier survival curves were also generated and stratified by primary AE. Survival curves were compared with the log-rank test. Continuous data are presented as mean±SD, and all categorical data are presented as number (percentage). The statistical analyses were performed using version 9.4 of SAS software (SAS Institute, Cary, NC).

# RESULTS

## Baseline Characteristics

A total of 18 763 LVAD device implants occurred during the study period (Figure 1). The average age of the eligible patients was 57±13 years, and most patients were men (78.6%) and white (67.1%) (Table 1). The most common causes of heart failure were ischemic cardiomyopathy (45.6%) and dilated cardiomyopathy (50.1%). Most patients were identified as INTERMACS profiles 2 (35.9%) and 3 (30.7%), whereas 16.4% were classified as INTERMACS profile 1. Destination therapy was used as the device strategy in 44.6% of patients, whereas the strategies bridge to transplant currently

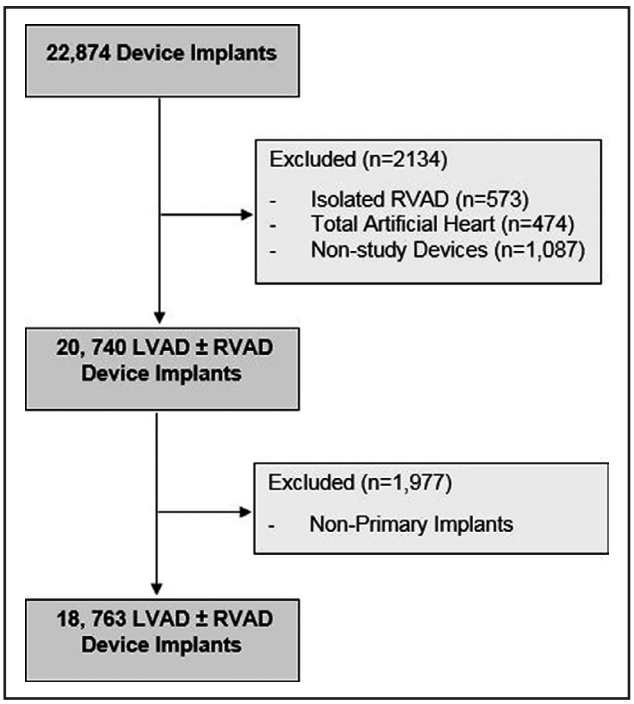


**Figure 1. Consort-like diagram demonstrating the inclusion and exclusion criteria of patients within the study.** LVAD indicates left ventricular assist device; and RVAD, right ventricular assist device.

**Table 1. Baseline Characteristics of the Study Population**

| Characteristic | Value |
|---|---|
| Age, y | 56.7±13.0 |
| Age group, y | |
| 19–29 | 866 (4.6) |
| 30–39 | 1381 (7.4) |
| 40–49 | 2696 (14.4) |
| 50–59 | 5110 (27.4) |
| 60–69 | 6153 (33.0) |
| 70–79 | 2358 (12.6) |
| >80 | 109 (0.6) |
| Female sex | 3992 (21.4) |
| Race | |
| White | 12 530 (67.1) |
| Black | 4425 (23.7) |
| Other | 1718 (9.2) |
| BMI, kg/m$^2$ | 28.7±7.0 |
| BMI group, kg/m$^2$ | |
| <18.5 | 757 (4.1) |
| 18.5–25 | 5098 (27.3) |
| 25–30 | 5953 (31.9) |
| 30–35 | 4011 (21.5) |
| >35 | 2854 (15.3) |
| Primary diagnosis | |
| Ischemic cardiomyopathy | 8523 (45.6) |
| Dilated cardiomyopathy | 9359 (50.1) |
| Restrictive cardiomyopathy | 349 (1.9) |
| Congenital heart disease | 442 (2.4) |
| INTERMACS profile | |
| 1: Critical cardiogenic shock | 3070 (16.4) |
| 2: Progressive decline | 6711 (35.9) |
| 3: Stable but inotrope dependent | 5726 (30.7) |
| 4: Resting symptoms | 2348 (12.6) |
| 5: Exertion intolerant | 420 (2.2) |
| 6: Exertion limited | 169 (0.9) |
| 7: Advanced NYHA class 3 | 115 (0.6) |
| Device strategy | |
| BTT* | 5030 (26.9) |
| Possible BTT† | 5163 (27.6) |
| Destination therapy‡ | 8334 (44.6) |
| Bridge to recovery | 146 (0.8) |

Data are given as mean±SD or number (percentage). BMI indicates body mass index; BTT, bridge to transplant; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.

*Currently listed for transplant.

†Likely eligible for transplant or moderate likelihood of becoming eligible for transplant.

‡Destination therapy or BTT, unlikely to become eligible.

**Table 2. Overall Rates of AEs and Frequency of Index AEs**

| Type of AE | No. (%) |
|---|---|
| Overall rates of AEs | |
| Bleeding | 3824 (20.5) |
| Cardiac arrhythmia | 3286 (17.6) |
| Device malfunction: pump thrombosis | 219 (1.2) |
| Hepatic dysfunction | 371 (2.0) |
| Infection | 3510 (18.7) |
| Neurologic (ischemic or hemorrhagic stroke) | 522 (2.8) |
| Renal failure | 1509 (8.1) |
| Respiratory failure | 2643 (14.1) |
| RVAD implant | 699 (3.8) |
| Rates of index AEs | |
| Bleeding | 4036 (31.4) |
| Cardiac arrhythmia | 2730 (21.2) |
| Device malfunction: pump thrombosis | 1373 (10.7) |
| Hepatic dysfunction | 73 (0.6) |
| Infection | 2577 (20.0) |
| Neurologic (ischemic or hemorrhagic stroke) | 743 (5.8) |
| Renal failure | 324 (2.5) |
| Respiratory failure | 566 (4.4) |
| RVAD implant | 439 (3.4) |

AE indicates adverse event; and RVAD, right ventricular assist device.

listed and bridge to transplant likely or moderate eligibility occurred in 26.9% and 27.6% of patients, respectively.

## Incidence of AEs

The median length of hospitalization was 18.8 days, with an interquartile range of 12.8 to 27.6 days. The highest overall rates of AEs were bleeding (20.5%), infection (18.7%), and cardiac arrhythmias (17.6%) (Table 2). The incidence of the remaining AEs in descending order of frequency was respiratory failure in 14.1%, renal failure in 8.1%, RVAD implantation in 3.8%, stroke in 2.8%, hepatic dysfunction in 2.0%, and device malfunction secondary to pump thrombosis in 1.2% (Figure 2). Bleeding (31.4%), cardiac arrhythmia (21.2%), and infection (20.0%) were most frequently the primary AEs in the AE sequences that were identified. An evaluation of events during the preimplant hospitalization and other key characteristics of patients experiencing no major AEs compared with those experiencing each specific type of AE demonstrated significant differences in preimplant events, laboratory values, and cardiopulmonary bypass times (Table 3). An expanded version of this table with more in-depth demographic and baseline characteristics is found in Table S1.

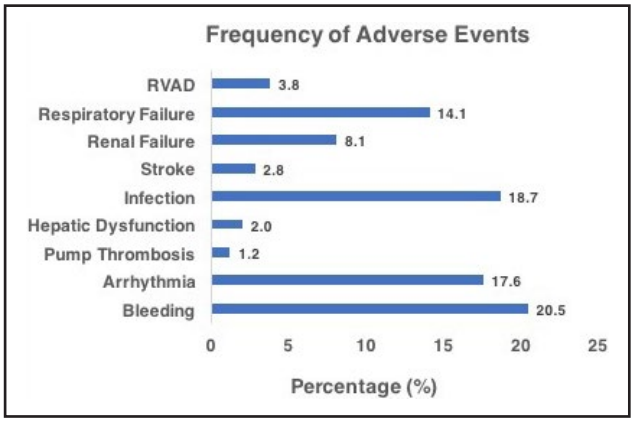


**Figure 2. Bar graph demonstrating the percentage of each adverse event category.**
RVAD indicates right ventricular assist device.

## Relationships Between AEs

Each type of AE was found to be uniquely associated with specific subsequent AEs. After bleeding, right heart failure requiring RVAD (hazard ratio [HR], 2.4; 95% CI, 2.1–2.7; $P<0.001$), respiratory failure (HR, 2.2; 95% CI, 1.9–2.4; $P<0.001$), and renal failure (HR, 1.9; 95% CI, 1.7–2.1; $P<0.001$) had the highest hazards to occur as subsequent AEs (Table 4) (Figure 3). If cardiac arrhythmia was the primary AE, there was a 2-fold increased hazard for respiratory failure (HR, 2.2; 95% CI, 2.0–2.5; $P<0.001$), infection (HR, 1.7; 95% CI, 1.5–1.9; $P<0.001$), and bleeding (HR, 1.6; 95% CI, 1.5–1.8; $P<0.001$). Patients with initial pump thrombosis had a 3-fold increased hazard for right heart failure requiring an RVAD (HR, 2.9; 95% CI, 1.9–4.4; $P<0.001$) and a 2-fold increased hazard for renal failure (HR, 1.7; 95% CI, 1.1–2.6; $P=0.02$). Patients with hepatic dysfunction had a 7-fold increased hazard for developing renal failure (HR, 6.6; 95% CI, 5.1–8.5; $P<0.001$), a 4-fold increased hazard for respiratory failure (HR, 4.4; 95% CI, 3.3–5.8; $P<0.001$), and a 2-fold increased hazard for developing bleeding (HR, 2.0; 95% CI, 1.6–2.6; $P<0.001$). After infection, the highest hazards for subsequent AEs were for respiratory failure (HR, 2.9; 95% CI, 2.7–3.2; $P<0.001$), bleeding (HR, 1.8; 95% CI, 1.7–1.9; $P<0.001$), and cardiac arrhythmias (HR, 1.7; 95% CI, 1.5–1.8; $P<0.001$). Neurological dysfunction was most commonly associated with subsequent respiratory failure (HR, 3.1; 95% CI, 2.4–4.0; $P<0.001$), right heart failure requiring RVAD placement (HR, 1.7; 95% CI, 1.2–2.3; $P=0.001$), and renal failure (HR, 1.4; 95% CI, 1.0–1.9; $P=0.02$). Patients with renal failure had a 6-fold increase in the hazard for subsequent respiratory failure (HR, 5.5; 95% CI, 4.8–6.3; $P<0.001$), a 3-fold increased hazard for hepatic dysfunction (HR, 3.4; 95% CI, 2.5–5.4; $P<0.001$), and a

**Table 3. Key Preimplant Events and Characteristics Stratified by Primary AE Group**

| Variable | No AE (n=8400) | Bleeding (n=4164) | Arrhythmia (n=2815) | Hepatic Dysfunction (n=78) | Infection (n=2615) | Neurological Dysfunction (n=749) | Renal Dysfunction (n=355) | Respiratory Dysfunction (n=592) | Right Heart Failure (n=468) | Device Malfunction (n=1424) | *P* Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Preimplant hospital events | | | | | | | | | | | |
| Cardiac arrest | 366 (4.4) | 206 (4.9) | 155 (5.5) | 6 (7.7) | 106 (4.1) | 26 (3.5) | 28 (7.9) | 59 (10.0) | 20 (4.3) | 56 (3.9) | <0.001 |
| Mechanical ventilation | 885 (10.5) | 457 (11.0) | 355 (12.6) | 13 (16.7) | 314 (12.0) | 84 (11.2) | 62 (17.5) | 145 (24.5) | 31 (6.6) | 122 (8.6) | <0.001 |
| Sepsis with positive blood cultures | 207 (2.5) | 98 (2.4) | 72 (2.6) | 3 (3.8) | 72 (2.8) | 26 (3.5) | 20 (5.6) | 34 (5.7) | 9 (1.9) | 34 (2.4) | <0.001 |
| Intra-aortic balloon pump | 1601 (19.1) | 867 (20.8) | 569 (20.2) | 12 (15.4) | 488 (18.7) | 181 (24.2) | 86 (24.2) | 118 (19.9) | 94 (20.1) | 257 (18.1) | 0.003 |
| Dialysis | 209 (2.5) | 141 (3.4) | 42 (1.5) | 1 (1.3) | 98 (3.7) | 15 (2.0) | 26 (7.3) | 33 (5.6) | 8 (1.7) | 26 (1.8) | <0.001 |
| ECMO | 315 (3.8) | 143 (3.4) | 79 (2.8) | 7 (9.0) | 97 (3.7) | 30 (4.0) | 23 (6.5) | 48 (8.1) | 7 (1.5) | 40 (2.8) | <0.001 |
| Cardiopulmonary bypass time, min | 93.76±47.93 | 101.69±53.85 | 94.61±45.81 | 102.57±45.77 | 93.07±46.18 | 95.61±54.07 | 107.10±54.12 | 105.27±60.26 | 101.99±52.50 | 92.10±51.90 | <0.001 |
| Creatinine, mg/dL | 1.39±0.71 | 1.46±0.71 | 1.40±0.67 | 1.51±1.04 | 1.41±0.80 | 1.40±0.70 | 1.94±1.19 | 1.51±0.86 | 1.39±0.55 | 1.42±0.92 | <0.001 |
| INR | 1.34±0.49 | 1.36±0.47 | 1.37±0.49 | 1.43±0.44 | 1.37±0.52 | 1.35±0.52 | 1.40±0.51 | 1.38±0.49 | 1.37±0.45 | 1.48±0.65 | <0.001 |
| Prealbumin, mg/dL | 18.74±7.34 | 18.21±7.50 | 18.92±7.56 | 17.91±7.91 | 18.36±7.43 | 18.50±7.38 | 17.17±8.27 | 16.23±7.50 | 17.74±6.68 | 19.52±7.55 | <0.001 |

Data are given as number (percentage) or mean±SD. AE indicates adverse event; ECMO, extracorporeal membrane oxygenation; and INR, international normalized ratio.

**Table 4. Multivariable Cox Proportional Hazards Models With Time-Varying Covariates Demonstrating the Relationships Between AEs***

| Subsequent AEs | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Primary AE: bleeding | | | |
| Cardiac arrhythmia | 1.57 | (1.42, 1.73) | <0.001 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 1.05 | (0.70, 1.44) | 0.746 |
| Infection | 1.73 | (1.55, 1.93) | <0.001 |
| Neurologic | 0.55 | (0.39, 0.77) | 0.001 |
| Renal failure | 1.86 | (1.65, 2.11) | <0.001 |
| Respiratory failure | 2.17 | (1.94, 2.43) | <0.001 |
| RVAD implant | 2.38 | (2.12, 2.66) | <0.001 |
| Primary AE: cardiac arrhythmia | | | |
| Bleeding | 1.59 | (1.45, 1.75) | <0.001 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 0.94 | (0.66, 1.34) | 0.740 |
| Infection | 1.71 | (1.50, 1.91) | <0.001 |
| Neurologic | 0.56 | (0.38, 0.82) | 0.002 |
| Renal failure | 1.50 | (1.30, 1.71) | <0.001 |
| Respiratory failure | 2.22 | (1.96, 2.49) | <0.001 |
| RVAD implant | 1.05 | (0.90, 1.23) | 0.518 |
| Primary AE: pump thrombosis | | | |
| Bleeding | 0.97 | (0.67, 1.41) | 0.884 |
| Cardiac arrhythmia | 0.85 | (0.50, 1.27) | 0.435 |
| Hepatic dysfunction | 1.28 | (0.64, 2.52) | 0.482 |
| Infection | 1.42 | (0.95, 2.10) | 0.080 |
| Neurologic | 1.12 | (0.59, 2.12) | 0.730 |
| Renal failure | 1.68 | (1.08, 2.60) | 0.019 |
| Respiratory failure | 1.14 | (0.74, 1.75) | 0.534 |
| RVAD implant | 2.91 | (1.94, 4.35) | <0.001 |
| Primary AE: hepatic dysfunction | | | |
| Bleeding | 2.04 | (1.59, 2.60) | <0.001 |
| Cardiac arrhythmia | 1.28 | (0.99, 1.63) | 0.052 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Infection | 1.62 | (1.25, 2.09) | <0.001 |
| Neurologic | 0.81 | (0.42, 1.53) | 0.514 |
| Renal failure | 6.62 | (5.12, 8.54) | <0.001 |
| Respiratory failure | 4.36 | (3.25, 5.83) | <0.001 |
| RVAD implant | 1.55 | (1.10, 2.13) | 0.007 |
| Primary AE: infection | | | |
| Bleeding | 1.79 | (1.65, 1.94) | <0.001 |
| Cardiac arrhythmia | 1.65 | (1.51, 1.80) | <0.001 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 1.03 | (0.79, 1.34) | 0.826 |
| Neurologic | 1.23 | (0.98, 1.53) | 0.062 |
| Renal failure | 1.53 | (1.37, 1.71) | <0.001 |
| Respiratory failure | 2.93 | (2.67, 3.21) | <0.001 |
| RVAD implant | 1.31 | (1.1, 1.49) | <0.001 |
| Primary AE: stroke | | | |
| Bleeding | 1.18 | (0.93, 1.49) | 0.159 |

(*Continued*)

**Table 4. Continued**

| Subsequent AEs | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Cardiac arrhythmia | 1.05 | (0.82, 1.35) | 0.683 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 1.04 | (0.58, 1.83) | 0.896 |
| Infection | 1.17 | (0.90, 1.52) | 0.239 |
| Renal failure | 1.39 | (1.04, 1.85) | 0.024 |
| Respiratory failure | 3.09 | (2.39, 3.99) | <0.001 |
| RVAD implant | 1.68 | (1.23, 2.28) | 0.001 |
| Primary AE: renal dysfunction | | | |
| Bleeding | 1.86 | (1.64, 2.11) | <0.001 |
| Cardiac arrhythmia | 1.44 | (1.25, 1.65) | <0.001 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 3.40 | (2.54, 4.53) | <0.001 |
| Infection | 1.88 | (1.62, 2.17) | <0.001 |
| Neurologic | 0.27 | (0.14, 0.51) | <0.001 |
| Respiratory failure | 5.51 | (4.79, 6.34) | <0.001 |
| RVAD implant | 1.72 | (1.44, 2.05) | <0.001 |
| Primary AE: respiratory failure | | | |
| Bleeding | 2.29 | (2.09, 2.51) | <0.001 |
| Cardiac arrhythmia | 1.96 | (1.78, 2.15) | <0.001 |
| Device malfunction: pump thrombosis | IE | IE | IE |
| Hepatic dysfunction | 0.84 | (0.58, 1.20) | 0.334 |
| Infection | 3.31 | (3.01, 3.64) | <0.001 |
| Neurologic | 3.12 | (2.54, 3.83) | <0.001 |
| Renal failure | 4.18 | (3.76, 4.64) | <0.001 |
| RVAD implant | 1.64 | (1.43, 1.87) | <0.001 |

AE indicates adverse event; IE, insufficient evidence; and RVAD, right ventricular assist device.
*Variables used for risk adjustment are delineated in Table S2.

2-fold increased hazard for infection (HR, 1.9; 95% CI, 1.6–2.2; *P*<0.001) and bleeding (HR, 1.9; 95% CI, 1.6–2.1; *P*<0.001). Patients with respiratory failure had the highest hazards to have renal failure (HR, 4.2; 95% CI, 3.8–4.6; *P*<0.001), infection (HR, 3.3; 95% CI, 3.0–3.6; *P*<0.001), and neurological dysfunction (HR, 3.1; 95% CI, 2.5–3.8; *P*<0.001) as subsequent AEs. Patients with right heart failure requiring an RVAD had the highest hazards for renal failure (HR, 3.7; 95% CI, 2.3–5.9; *P*<0.001), bleeding (HR, 2.7; 95% CI, 2.2–3.3; *P*<0.001), and respiratory failure (HR, 2.5; 95% CI, 1.5–4.1; *P*=0.001). These general relationships and sequences persisted after stratifying patients on the basis of INTERMACS category 1 versus 2 to 7.

## Impact of Primary AEs on Survival

The impact of primary AEs on survival post-LVAD implantation varied significantly according to the specific type of primary AE (Table 5) (Figure 4). Moreover, the highest 1-year survival was seen in those patients with primary device malfunction (89.3%), infection (87.9%), or RVAD implant (85.1%). The lowest 1-year survival was seen in those patients with the primary AEs of renal failure (68.1%) and respiratory failure (70.7%). The negative effects of AEs in patients compared with those without AEs was not appreciated in early follow-up (91.1% versus 91.1%; *P*=0.125 at 3 months) but had a significant impact on survival at 1 year (82.6% versus 80.9%; *P*=0.012) (Figure S1).

# DISCUSSION

The principal hindrance to wider adoption of LVAD therapy is no longer survival or device durability but instead the longitudinal burden of AEs that negatively impacts hospital readmission rates and quality of life, and may disqualify patients for cardiac transplantation. Although solitary AEs and their impact on early and longer-term outcomes have been extensively studied in LVAD patients, most complications after LVAD implantation rarely occur as isolated events and often progress as a series of associated AEs.[8–12] Most prior AE studies in LVADs have lacked insight into the

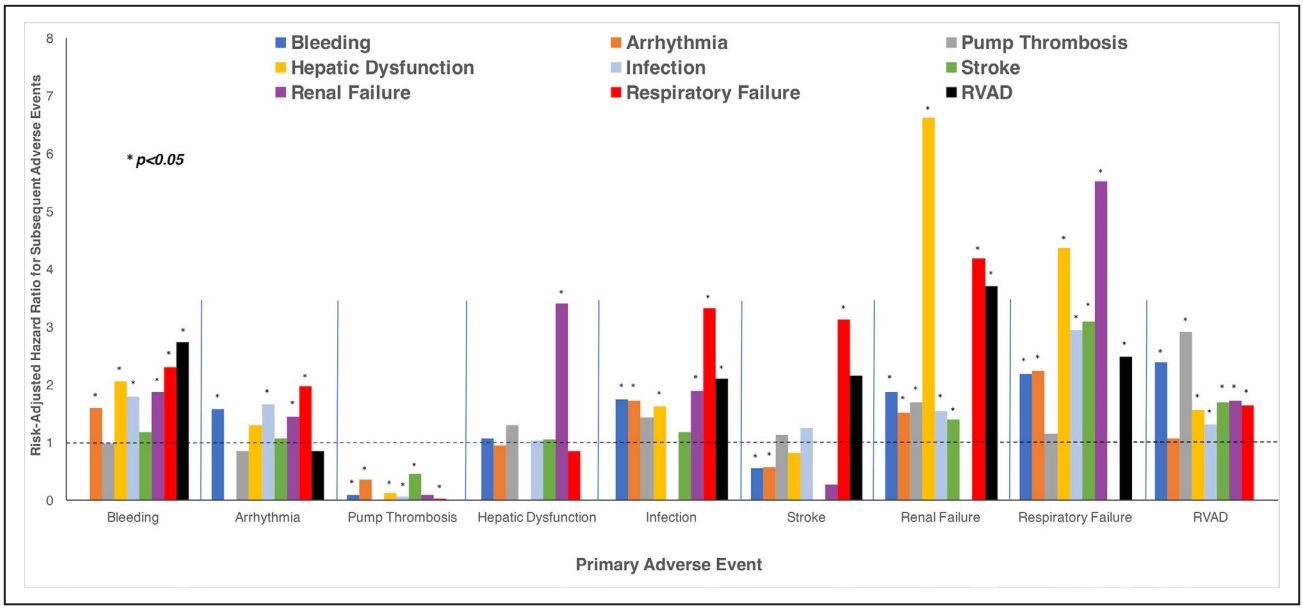


**Figure 3. Bar graph demonstrating the risk-adjusted hazards of developing subsequent adverse events stratified by primary adverse events.**
RVAD indicates right ventricular assist device.

sequential relationships between the index primary and subsequent AEs that can occur in this patient population. We propose that knowledge of the most common subsequent AEs that follows an index AE may allow for anticipatory management that may impede the sequence of further AEs.

## Study Implications

The current study adds to the literature by reporting the associations between AEs in a large, multicenter cohort of LVAD-supported patients. There are several implications of the study findings. Foremost, this study establishes that most major AEs occurring after LVAD implantation lead to subsequent AEs. Of the 9 primary AEs that we analyzed, all were significantly associated with the development of at least 2 subsequent major AEs, with some associated with upwards of 7 subsequent AEs. Another important implication relates to the specific sequences of AEs that we identified. These sequences provide clinical insights into patterns that are important for clinicians to recognize, and potentially target to reduce the overall burden of AEs in the LVAD population. Some of the sequences that were identified are clinically intuitive. The primary AE of major bleeding, for instance, was most strongly associated with the subsequent development of RVAD implantation. Major bleeding typically requires multiple blood product transfusions. The volume load from these transfusions in addition to hemodynamic instability that can accompany bleeding can certainly lead to right heart failure and a requirement for mechanical support. Hepatic dysfunction leading to renal failure was found to be a strong sequence, with an HR of 6.62. This is also intuitive in that liver failure can lead to hepatorenal syndrome, but also can be a consequence of hemodynamic instability, poor perfusion, and/or right heart failure, all of which can lead to renal compromise as well. Infection most strongly led to respiratory failure. Although various types of infections can occur, pneumonia or sepsis with hemodynamic instability often will lead to intubation and respiratory failure. Similarly, with stroke, there is often a need for airway protection and intubation. Stroke was found to be most closely associated with the subsequent AE of respiratory failure. Renal dysfunction led most strongly

**Table 5. Survival After LVAD Implantation, Stratified by Primary AE**

| Primary AE | Time, y | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Bleeding | 79.2 | 64.9 | 57.5 | 48.8 |
| Cardiac arrhythmia | 84.5 | 70.5 | 62.7 | 55.0 |
| Device malfunction | 89.3 | 77.1 | 70.6 | 64.3 |
| Hepatic dysfunction | 75.7 | 58.7 | 49.9 | 45.0 |
| Infection | 87.9 | 73.0 | 62.1 | 53.4 |
| Neurologic (ischemic or hemorrhagic stroke) | 80.3 | 63.0 | 54.9 | 49.8 |
| Renal failure | 68.1 | 53.0 | 49.2 | 44.8 |
| Respiratory failure | 70.7 | 59.3 | 52.1 | 44.4 |
| RVAD implant | 85.1 | 76.9 | 67.8 | 59.2 |
| *P* value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Data are given as percentages. AE indicates adverse event; LVAD, left ventricular assist device; and RVAD, right ventricular assist device.

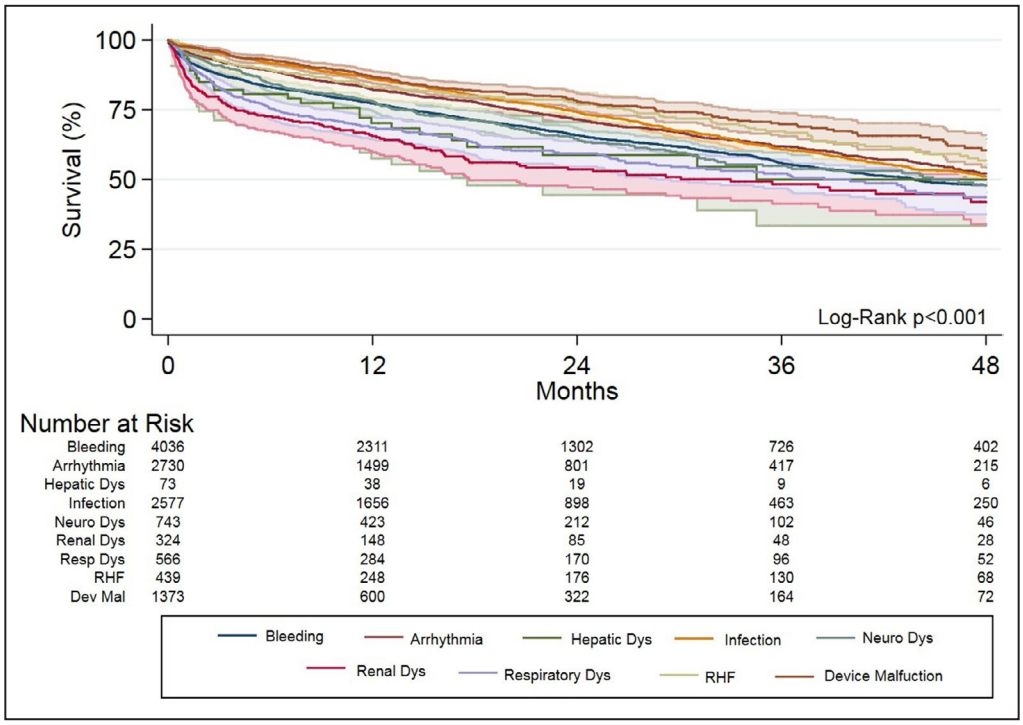


**Figure 4. Kaplan-Meier survival curves with 95% CIs, stratified by type of primary adverse event.** Dev indicates device; Dys, dysfunction; Mal, malfunction; Neuro, neurological; Resp, respiratory; and RHF, right heart failure.

to respiratory failure. In the setting of renal failure, effective diuresis can become challenging and lead to volume overloaded states causing respiratory failure. Interestingly, respiratory failure was most strongly associated with subsequent renal failure. Whether this reflects a similar scenario as above where a patient becomes volume overloaded and is then intubated but worsens his/her renal failure is unclear, but this represents one likely cause of this association.

Another important implication of our study is that the primary AEs with the strongest associations for subsequent AEs were renal and respiratory failure. In addition, primary renal or respiratory failure was associated with the lowest 1-year survival after LVAD implantation. Therefore, this analysis would suggest that targeted efforts for better prediction and preimplant risk modification, along with early recognition and aggressive treatment for renal and respiratory failure, would likely be most effective in lessening the overall AE burden and subsequent mortality in LVAD patients. However, the mere number of AEs does not necessarily correlate with quality of life. A devastating stroke is more likely to impact functional ability, for example, than acute renal failure not requiring long-term dialysis. Despite the associations that our study has established between primary and secondary AEs, the importance of preoperative clinical status and existing comorbidities cannot be overemphasized. Each of the primary AE categories had unique preoperative comorbidities and preimplant hospital events, which may have contributed to the development of specific sequences of postimplant AEs. Patient selection and mitigating risk before durable LVAD surgery are therefore essential. For higher-risk patients, such as those presenting in decompensated shock or in a debilitated or malnourished state, intermediary interventions, such as temporary percutaneous support or prehabilitation with nutritional supplementation and functional improvement if possible, can be important factors in reducing the overall likelihood and burden of these AEs.

## Prior Studies Evaluating LVAD AEs

Prior studies have corroborated some of the AE sequences we identified in this analysis. A study evaluating the impact of renal failure on LVAD outcomes demonstrated higher rates of associated respiratory failure and right heart failure.[6] Another association that has been demonstrated in the post-LVAD population is the clustered occurrence of renal and hepatic dysfunction. This may be related to patients in hepatic failure developing hepatorenal syndrome, or patients with hemodynamic compromise having poor perfusion to end organs that results in ischemic insult.[13] Another association that has been documented is the development of right heart failure in patients experiencing major bleeding and

receiving multiple blood transfusions, likely as a result of the volume load in addition to hemodynamic insult that often accompanies bleeding.[12]

Infections in LVAD patients have been associated with stroke, such that wound infections and bloodstream infections were associated with ischemic strokes and bloodstream infections were associated with hemorrhagic strokes, with no association between stroke and driveline or pump pocket infections.[10] Another study showed that gastrointestinal bleeding was associated with subsequent thromboembolic complications, at a median time interval of 5 months.[14] This may be related to cessation of anticoagulation during periods of gastrointestinal bleeding. A retrospective study of 351 LVAD patients identified risk factors for gastrointestinal bleeding and used these risk factors to develop a composite risk score, with severe right heart dysfunction being identified as a predictor that was included in the score.[15] Another analysis demonstrated that post-LVAD infection and gastrointestinal bleeding were significantly associated with subsequent stroke.[4]

## Limitations

This is a retrospective study with limitations inherent to its design. Although this study evaluates broadly defined categories of AEs, differing results may occur if the study used more granular details about specific AEs, such as distinguishing mediastinal versus gastrointestinal bleeding, ischemic versus hemorrhagic strokes, or wound infection versus pneumonia versus indwelling line infection. The reason we chose to retain broadly defined categories was to have a reasonable number of patients in each group and to reduce the propensity for type II statistical error. In addition, the severity of the AEs is not available within the INTERMACS database and as such we could not adjust for this in our analysis, although it likely has an impact on outcomes. As with other multicenter registries, there is the potential for error in data entry as well. We also chose to not use a multiple events analysis, such as the Wei Lin Weissfeld method, as the focus of the current analysis was to identify which primary AEs specifically lead to other distinct AEs, although it is likely that the occurrence of an AE can lead to the subsequent occurrence of the same AE. For example, major bleeding that resolves can lead to the occurrence of another major bleeding episode at a subsequent time interval. This lack of adjustment can increase the risk of type I error.

# CONCLUSIONS

This study evaluated 18 763 LVAD patients and demonstrated that AEs occurring during the index hospitalization have significant associations with the development of subsequent AEs. Specific sequences and patterns of AE were identified. The most profound sequences were found to be associated with the primary AEs of respiratory or renal failure. Targeted efforts to reduce, recognize, and effectively treat respiratory or renal failure after LVAD implantation may be useful in reducing the overall AE burden and subsequent mortality in this patient population.

## ARTICLE INFORMATION

Received November 27, 2019; accepted February 27, 2020.

### Affiliations

From the Division of Cardiac Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA (A.K., L.S., R.K.); and Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI (F.P.).

### Acknowledgments

This article was prepared using INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) research materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of INTERMACS or the NHLBI.

### Sources of Funding

None.

### Disclosures

Dr Kilic is on the Medical Advisory Board for Medtronic, Inc, and Robert Kormos is an employee of Abbott, Inc. The remaining authors have no disclosures to report.

### Supplementary Materials

**Tables S1 and S2**
**Figure S1**

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# SUPPLEMENTAL MATERIAL

**Table S1. A comparison of baseline characteristics stratified by type of adverse event.**

| | No AE n= 8400 | Bleeding n=4164 | Arrhythmia n=2815 | Hepatic Dys n=78 | Infection n=2615 | Neuro Dys n=749 | Renal Dys n=355 | Respiratory Dys n=592 | Right Heart Failure n=468 | Device Malfunction n=1424 | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age Groups** | | | | | | | | | | | <0.001 |
| 19-29 | 481 (5.7%) | 107 (2.6%) | 89 (3.2%) | 7 (9.0%) | 162 (6.2%) | 22 (2.9%) | 8 (2.3%) | 28 (4.7%) | 30 (6.4%) | 94 (6.6%) | |
| 30-39 | 723 (8.6%) | 193 (4.6%) | 197 (7.0%) | 4 (5.1%) | 238 (9.1%) | 42 (5.6%) | 19 (5.4%) | 44 (7.4%) | 48 (10.3%) | 172 (12.1%) | |
| 40-49 | 1352 (16.1%) | 423 (10.2%) | 430 (15.3%) | 8 (10.3%) | 439 (16.8%) | 109 (14.6%) | 58 (16.3%) | 76 (12.8%) | 63 (13.5%) | 223 (15.7%) | |
| 50-59 | 2320 (27.6%) | 1044 (25.1%) | 837 (29.7%) | 23 (29.5%) | 677 (25.9%) | 208 (27.8%) | 95 (26.8%) | 174 (29.4%) | 127 (27.1%) | 424 (29.8%) | |
| 60-69 | 2515 (29.9%) | 1618 (38.9%) | 936 (33.3%) | 24 (30.8%) | 782 (29.9%) | 252 (33.6%) | 125 (35.2%) | 202 (34.1%) | 148 (31.6%) | 366 (25.7%) | |
| 70-79 | 967 (11.5%) | 743 (17.8%) | 314 (11.2%) | 12 (15.4%) | 298 (11.4%) | 111 (14.8%) | 49 (13.8%) | 64 (10.8%) | 51 (10.9%) | 130 (9.1%) | |
| 80+ | 42 (0.5%) | 36 (0.9%) | 12 (0.4%) | 0 (0.0%) | 19 (0.7%) | 5 (0.7%) | 1 (0.3%) | 4 (0.7%) | 1 (0.2%) | 15 (1.1%) | |
| Caucasian | 5678 (67.6%) | 2795 (67.12%) | 1955 (69.5%) | 53 (67.9%) | 1709 (65.4%) | 538 (71.8%) | 221 (62.3%) | 351 (59.3%) | 302 (64.5%) | 971 (68.2%) | 0.007 |
| Female Sex | 1786 (21.3%) | 942 (22.6%) | 514 (18.3%) | 16 (20.5%) | 630 (24.1%) | 178 (23.8%) | 80 (22.5%) | 139 (23.5%) | 100 (21.4%) | 295 (20.7%) | <0.001 |
| **Diagnosis** | | | | | | | | | | | <0.001 |
| Ischemic | 3616 (43.8%) | 2144 (52.7%) | 1283 (46.1%) | 40 (51.3%) | 1128 (44.2%) | 367 (50.0%) | 163 (46.6%) | 282 (48.9%) | 200 (43.5%) | 575 (41.2%) | |
| Dilated Cardiomyopathy | 4477 (54.3%) | 1864 (45.8%) | 1449 (52.1%) | 37 (47.4%) | 1381 (54.1%) | 355 (48.4%) | 184 (52.6%) | 286 (49.6%) | 255 (55.4%) | 793 (56.8%) | |
| Restrictive Cardiomyopathy | 106 (1.3%) | 46 (1.1%) | 35 (1.3%) | 0 (0.0%) | 27 (1.1%) | 8 (1.1%) | 0 (0.0%) | 6 (1.0%) | 4 (0.9%) | 23 (1.6%) | |
| Congenital Cardiomyopathy | 49 (0.6%) | 14 (0.3%) | 14 (0.5%) | 1 (1.3%) | 18 (0.7%) | 4 (0.5%) | 3 (0.9%) | 3 (0.5%) | 1 (0.2%) | 5 (0.4%) | |
| **INTERMACS Profile** | | | | | | | | | | | <0.001 |
| 1 Critical | 1377 (16.4%) | 671 (16.1%) | 475 (16.9%) | 18 (23.1%) | 455 (17.4%) | 126 (16.8%) | 105 (29.6%) | 165 (27.9%) | 67 (14.3%) | 178 (12.5%) | |
| 2 Progressive Decline | 2763 (32.9%) | 1219 (29.3%) | 810 (28.8%) | 12 (15.4%) | 797 (30.5%) | 232 (31.0%) | 76 (21.4%) | 138 (23.3%) | 134 (28.6%) | 478 (33.7%) | |
| 3 Stable but Inotrope Dependent | 2929 (34.9%) | 1552 (37.3%) | 1007 (35.8%) | 31 (39.7%) | 930 (35.6%) | 255 (34.0%) | 140 (39.4%) | 214 (36.1%) | 214 (45.7%) | 493 (34.7%) | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 Resting Symptoms | 1001 (11.9%) | 568 (13.6%) | 380 (13.5%) | 11 (14.1%) | 323 (12.4%) | 94 (12.6%) | 28 (7.9%) | 61 (10.3%) | 39 (8.3%) | 209 (14.7%) | |
| 5 Exertion Intolerant | 167 (2.0%) | 82 (2.0%) | 91 (3.2%) | 1 (1.3%) | 62 (2.4%) | 25 (3.3%) | 3 (0.8%) | 8 (1.4%) | 7 (1.5%) | 28 (2.0%) | |
| 6 Exertion Limited | 74 (0.9%) | 26 (0.6%) | 38 (1.3%) | 1 (1.3%) | 29 (1.1%) | 8 (1.1%) | 2 (0.6%) | 0 (0.0%) | 5 (1.1%) | 15 (1.1%) | |
| 7 Advanced NYHA | 45 (0.5%) | 20 (0.5%) | 9 (0.3%) | 3 (3.8%) | 10 (0.4%) | 6 (0.8%) | 0 (0.0%) | 5 (0.8%) | 1 (0.2%) | 12 (0.8%) | |
| **Pre-Implant Hospital Events** | | | | | | | | | | | |
| Cardiac Arrest | 366 (4.4%) | 206 (4.9%) | 155 (5.5%) | 6 (7.7%) | 106 (4.1%) | 26 (3.5%) | 28 (7.9%) | 59 (10.0%) | 20 (4.3%) | 56 (3.9%) | <0.001 |
| Mechanical Ventilation | 885 (10.5%) | 457 (11.0%) | 355 (12.6%) | 13 (16.7%) | 314 (12.0%) | 84 (11.2%) | 62 (17.5%) | 145 (24.5%) | 31 (6.6%) | 122 (8.6%) | <0.001 |
| Sepsis with Positive Blood Cultures | 207 (2.5%) | 98 (2.4%) | 72 (2.6%) | 3 (3.8%) | 72 (2.8%) | 26 (3.5%) | 20 (5.6%) | 34 (5.7%) | 9 (1.9%) | 34 (2.4%) | <0.001 |
| Intra Aortic Balloon Pump | 1601 (19.1%) | 867 (20.8%) | 569 (20.2%) | 12 (15.4%) | 488 (18.7%) | 181 (24.2%) | 86 (24.2%) | 118 (19.9%) | 94 (20.1%) | 257 (18.1%) | 0.003 |
| Dialysis | 209 (2.5%) | 141 (3.4%) | 42 (1.5%) | 1 (1.3%) | 98 (3.7%) | 15 (2.0%) | 26 (7.3%) | 33 (5.6%) | 8 (1.7%) | 26 (1.8%) | <0.001 |
| Extracorporeal Membrane Oxygenation | 315 (3.8%) | 143 (3.4%) | 79 (2.8%) | 7 (9.0%) | 97 (3.7%) | 30 (4.0%) | 23 (6.5%) | 48 (8.1%) | 7 (1.5%) | 40 (2.8%) | <0.001 |
| **Laboratory Values** | | | | | | | | | | | |
| Creatinine (mg/dL) | 1.39 ± 0.71 | 1.46 ± 0.71 | 1.40 ± 0.67 | 1.51 ± 1.04 | 1.41 ± 0.80 | 1.40 ± 0.70 | 1.94 ± 1.19 | 1.51 ± 0.86 | 1.39 ± 0.55 | 1.42 ± 0.92 | <0.001 |
| Sodium (mEq/L) | 135.15 ± 4.71 | 135.05 ± 4.81 | 134.92 ± 4.78 | 135.53 ± 4.60 | 135.15 ± 5.02 | 135.38 ± 4.90 | 134.95 ± 5.07 | 135.67 ± 5.66 | 134.58 ± 4.66 | 135.66 ± 4.76 | <0.001 |
| INR | 1.34 ± 0.49 | 1.36 ± 0.47 | 1.37 ± 0.49 | 1.43 ± 0.44 | 1.37 ± 0.52 | 1.35 ± 0.52 | 1.40 ± 0.51 | 1.38 ± 0.49 | 1.37 ± 0.45 | 1.48 ± 0.65 | <0.001 |
| Albumin (mg/dL) | 3.42 ± 0.65 | 3.36 ± 0.64 | 3.40 ± 0.69 | 3.25 ± 0.78 | 3.38 ± 0.68 | 3.35 ± 0.68 | 3.21 ± 0.63 | 3.24 ± 0.70 | 3.38 ± 0.63 | 3.45 ± 0.66 | <0.001 |
| Prealbumin (mg/dL) | 18.74 ± 7.34 | 18.21 ± 7.50 | 18.92 ± 7.56 | 17.91 ± 7.91 | 18.36 ± 7.43 | 18.50 ± 7.38 | 17.17 ± 8.27 | 16.23 ± 7.50 | 17.74 ± 6.68 | 19.52 ± 7.55 | <0.001 |
| NYHA Class | | | | | | | | | | | |
| 1 | 69 (0.8%) | 22 (0.5%) | 27 (1.0%) | 0 (0.0%) | 14 (0.5%) | 1 (0.1%) | 1 (0.3%) | 5 (0.8%) | 8 (1.7%) | 32 (2.2%) | <0.001 |
| 2 | 178 (2.1%) | 83 (2.0%) | 60 (2.1%) | 0 (0.0%) | 69 (2.6%) | 16 (2.1%) | 5 (1.4%) | 14 (2.4%) | 11 (2.4%) | 65 (4.6%) | |
| 3 | 1455 (17.3%) | 657 (15.8%) | 474 (16.8%) | 17 (21.8%) | 423 (16.2%) | 131 (17.5%) | 44 (12.4%) | 83 (14.0%) | 87 (18.6%) | 240 (16.9%) | |

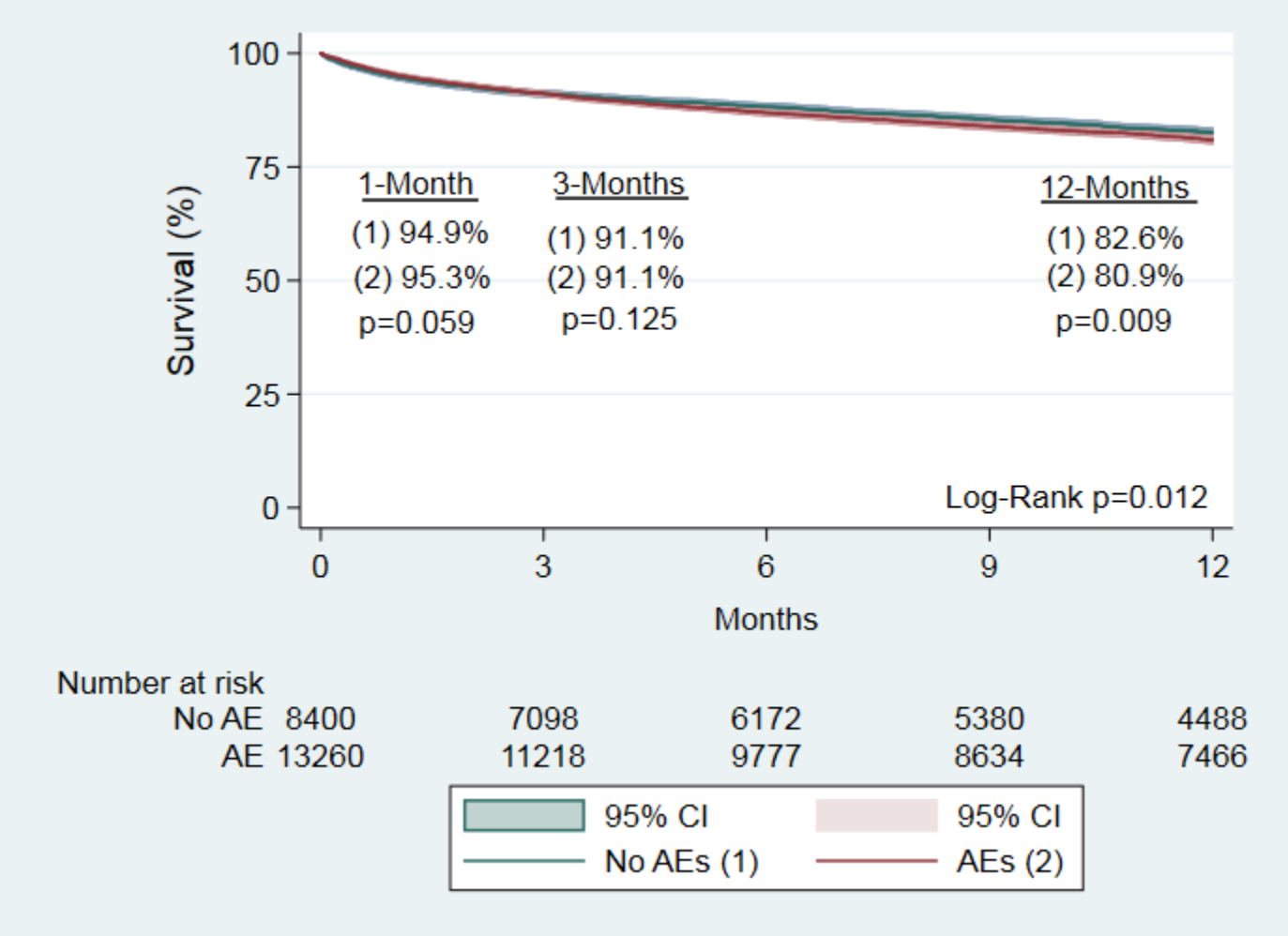
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 5916 (70.4%) | 3072 (73.8%) | 2017 (71.7%) | 59 (75.6%) | 1835 (70.2%) | 519 (69.3%) | 269 (75.8%) | 423 (71.5%) | 305 (65.2%) | 871 (61.2%) | |
| Cardiopulmonary Bypass Time | 93.76 ± 47.93 | 101.69 ± 53.85 | 94.61 ± 45.81 | 102.57 ± 45.77 | 93.07 ± 46.18 | 95.61 ± 54.07 | 107.10 ± 54.12 | 105.27 ± 60.26 | 101.99 ± 52.50 | 92.10 ± 51.90 | <0.001 |
| **Device Strategy** | | | | | | | | | | | 0.24 |
| BTT | 2004 (28.2%) | 921 (25.9%) | 678 (28.1%) | 11 (16.4%) | 615 (26.9%) | 156 (24.4%) | 79 (26.0%) | 141 (27.0%) | 144 (31.6%) | 336 (28.0%) | |
| Possible BTT | 1986 (28.0%) | 1025 (28.8%) | 688 (28.5%) | 20 (29.9%) | 647 (28.3%) | 192 (30.0%) | 96 (31.6%) | 153 (29.3%) | 128 (28.1%) | 313 (26.1%) | |
| Destination Therapy | 3059 (43.1%) | 1593 (44.7%) | 1035 (42.8%) | 36 (53.7%) | 1008 (44.1%) | 290 (45.3%) | 126 (41.4%) | 225 (43.1%) | 184 (40.4%) | 547 (45.5%) | |
| Bridge to Recovery | 45 (0.6%) | 22 (0.6%) | 16 (0.7%) | 0 (0.0%) | 18 (0.8%) | 2 (0.3%) | 3 (1.0%) | 3 (0.6%) | 0 (0.0%) | 5 (0.4%) | |

AE, adverse event; BTT, bridge-to-transplant; INR, international normalized ratio; Dys, dysfunction; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; mg/dL, milligram per deciliter; NYHA, New York Heart Association.

**Table S2. Variables Utilized for Risk-Adjustment in the Cox Proportional Hazards Models.**

| |
|---|
| Age, sex, heart failure etiology, interagency registry for mechanically assisted circulatory support profile, pre-Implant cardiac arrest, mechanical ventilation, sepsis, intra aortic balloon pump, dialysis, extracorporeal membrane oxygenator support, creatinine, prealbumin, cardiopulmonary bypass time and New York Heart Association class. |

**Figure S1. Kaplan-Meier survival curves with 95% confidence intervals, stratified by the presence or absence of adverse events.**




AE, adverse event.