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Early adverse events as predictors of 1-year mortality during mechanical circulatory support

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BACKGROUND: Ventricular assist devices (VADs) provide effective treatment for end-stage heart failure; however, most patients experience ≥1 major adverse events (AEs) while on VAD support. Although early, non-fatal AEs may increase the risk of later death during VAD support, this relationship has not been established. Therefore, we sought to determine the impact on 1-year mortality of AEs occurring during the first 60 days of VAD support.

METHODS: A retrospective analysis was performed using prospectively collected data from a single-site database for patients aged ≥18 years receiving left ventricular or biventricular support during 1996 to 2008 and who survived >60 days on VAD support. Fourteen major classes of AEs occurring during this 60-day period were examined. One-year survival rates of patients with and without each major AE were compared.

RESULTS: The study included 163 patients (80% men; mean age, 49.5 years), of whom 87% were European American, 72% had left ventricular support, and 83% were bridge to transplant. The occurrence of renal failure, respiratory failure, bleeding events, and reoperations during the first 60 days after implantation significantly increased the risk of 1-year mortality. After controlling for gender, age, VAD type, and intention to treat, renal failure was the only major AE significantly associated with later mortality (hazard ratio, 2.96; $p = .023$).

CONCLUSIONS: Specific AEs, including renal failure, respiratory and bleeding events, and reoperations, significantly decrease longer-term survival. Renal failure conferred a 3-fold increased risk of 1-year mortality. Peri-operative management should focus on strategies to mitigate risk for renal failure in order to maximize later outcomes.

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Ventricular assist devices (VADs) provide effective treatment for end-stage heart failure and can be used as bridges to transplantation,[1–5] bridges to myocardial recovery,[6,7] or as destination therapy for patients who are not transplant candidates.[8–12] The field of mechanical circulatory support is rapidly evolving with the development of more durable devices, leading to an increasing interest in using VADs for extended support. To maximize patient

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outcomes, it is critical to have a comprehensive understanding of the variety of factors that adversely affect survival, particularly beyond the first several months after implantation. Although previous reports have documented the influence of patient characteristics before implantation on patient mortality,[13–16] the patient's clinical course while on mechanical support also has a substantial effect on survival.[17–22] In particular, the effect of early, non-fatal adverse events (AEs) on longer-term survival has yet to be examined.

Currently, there is a high incidence of clinically significant AEs during VAD support: approximately 80% to 90% of patients experience some type of clinically significant AE.[15,23] The most common AEs are bleeding, infection, cardiac arrhythmias, and reoperations,[3,4,15,23] and most occur within the first 1 to 2 months after implantation.[3,15,24,25] Analyses of these early AEs are largely limited to the effect of a single AE[18–20,26–29] on immediate patient mortality. However, the lasting consequences of these early, non-fatal AEs on longer-term survival have not been explored.

We hypothesized that clinically significant, but non-fatal, AEs that occur during the first 60 days after VAD implantation would negatively affect later-term survival. Therefore, using standardized Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) AE definitions,[23,30] we sought to study patients on extended VAD support to determine the separate and combined effects of early AEs on 1-year survival.

Methods

This retrospective study of prospectively collected data was approved by the University of Pittsburgh Institutional Review Board.

Patients

The study included all patients aged ≥18 years who received left or biventricular mechanical support at the University of Pittsburgh Medical Center (UPMC) between January 1996 and December 2008. To capture a cohort with the potential for longer-term VAD implantation, we required that patients survive on VAD support for at least 60 days. Pulsatile devices included the Novacor LVAS (WorldHeart Corp, Oakland, CA), the HeartMate XVE LVAS (Thoratec Corp, Pleasanton, CA), and the Thoratec paracorporeal or implantable VAD, used as either an LVAD or BiVAD (Thoratec Corp). Continuous-flow devices implanted were the HeartMate II LVAD (Thoratec Corp), the VentrAssist LVAD (Ventracor, Brisbane, Queensland, Australia), and the Jarvik 2000 LVAD (Jarvik Heart Inc, New York, NY).

Study design and measures

The data were extracted from the University of Pittsburgh Medical Center (UPMC) Cardiothoracic Transplantation Program's electronic database of prospectively collected data on all mechanical support patients, supplemented by review of patients' UPMC medical records.

The primary study outcome was 1-year actuarial survival while on ventricular support, assessed by time to patient death or to the end of patient follow-up, defined as cardiac transplantation, successful weaning of the device, or continued VAD support at 12 months. The actuarial survival rate adjusts for patients' varied mortality risk exposure due

Table 1 Patient Demographics and Presenting Clinical Characteristics

Characteristic	Descriptive statistic (N = 163)
Gender, %	
Male	79.8
Female	20.2
Age, years	
Mean ± SD	49.5 ± 13.1
Range	18–71
Race, %	
European American	86.5
African American	11.0
Other	2.5
Outcome by 12 mon, No. (%)	
Transplanted	96 (58.9)
Died on device	35 (21.5)
Still implanted	21 (12.9)
Weaned	11 (6.7)
Device type, %	
LVAD	72.4
Pulsatile	75.4
Continuous flow	24.6
BiVAD	27.6
Device, %	
Thoratec BiVAD	27.6
Thoratec LVAD	20.9
Novacor	20.9
HeartMate XVE	12.9
Ventrassist	10.4
HeartMate II	6.1
Jarvik 2000 LVAD	1.2
Diagnosis, %	
Ischemic cardiomyopathy	52.1
Idiopathic cardiomyopathy	38.7
Inflammatory	7.4
Congenital	1.2
Hypertrophic cardiomyopathy	0.6
Intention to treat, %	
Bridge to transplant	82.8
Recovery support	6.7
Destination therapy	6.1
Postcardiotomy failure	4.3
Implant era,[a] %	
1996–2003	51.5
2004–2008	48.5

BiVAD, biventricular assist device; LVAD, left ventricular assist device; SD, standard deviation.

[a]Implant era was divided at the beginning of 2004 due to the introduction of continuous-flow LVADs during 2004.

Table 2 Causes of Death While on Ventricular Assist Device Support

Cause of death	No. (%) ($N = 35$)
CNS event	13 (37.1)
Cerebrovascular accident, hemorrhagic	6 (17.1)
Cerebrovascular accident, ischemic	6 (17.1)
Intraoperative air embolism	1 (2.9)
Infection	11 (31.4)
Bacterial sepsis	8 (22.9)
Bacterial pneumonia	2 (5.7)
Mediastinitis	1 (2.9)
Multiorgan failure	4 (11.4)
Cardiovascular	3 (8.6)
Arrhythmia	1 (2.9)
Right ventricular failure	1 (2.9)
Allergic reaction	1 (2.9)
Pulmonary: respiratory failure	2 (5.7)
Malignancy: CNS	1 (2.9)
Accidental trauma	1 (2.9)

CNS, central nervous system.

to their different lengths of implantation, with censoring due to cardiac transplantation or weaning from the device.

Fourteen categories of clinically significant AEs occurring during the first 60 days after implant were examined as possible predictors of mortality during the remaining year. These AEs, defined using INTERMACS criteria,[30] have been detailed previously,[23] and include clinically significant infections, bleeding events, respiratory events, neurologic events, right ventricular (RV) failure, cardiovascular dysfunction, reoperations, cardiac tamponade, renal events, hepatic events, gastrointestinal events, thromboembolisms, hemolysis, and device malfunctions. Data on baseline patient demographics, clinical characteristics and causes of death were also collected.

Statistical analysis

Descriptive information (including proportions, means, medians, and ranges) on patient demographics, VAD-related characteristics, and causes of death while on VAD support were examined. The incidence of each type of major AE in the first 60 days of VAD implant was determined. The association between the occurrence of AEs during the first 60 days of support and subsequent time to death was examined by survival analysis using the Kaplan-Meier procedure and the log-rank test, with $\alpha = 0.05$. All AEs that were at least marginally associated with survival ($p < 0.10$) were entered into a Cox proportional hazards model, which was then fit to the data to determine each AE's unique predictive effect within the context of other AEs. Thus, the main effects of each AE were first entered into the model. The interaction terms between pairs of AEs were added on a subsequent step to evaluate possible synergistic effects of combinations of AEs. Four baseline characteristics were controlled in the model: gender, age, intention to treat (bridge to transplant vs other indications for implant), and type of VAD implanted (BiVAD, pulsatile LVAD, or continuous-flow LVAD). The VAD type was controlled in the Cox model because survival may be altered by the implantation of an LVAD vs a BiVAD.[12,14,15,31] Moreover, by entering device flow pattern (pulsatile vs continuous) in the model, we controlled for significant changes in patient management that occurred over recent years with the development of VAD technology. Before fitting this model, the predictors were examined and met all analytical assumptions adequately. An $\alpha = 0.05$ was used to determine statistical significance.

Table 3 Incidence of Non-fatal Clinically Significant Adverse Events During the First 60 Days After Implant

Clinically significant AE	Patients (%) with ≥1 AE ($N = 163$)
Infection	73 (44.8)
• Driveline	
• Blood Stream	
• Pulmonary	
• Mediastinum	
• Pocket	
Bleeding	72 (44.2)
• Coagulopathy	
• Mediastinum	
• Pocket	
• Thorax	
• Gastrointestinal	
Cardiovascular dysfunction	62 (38.0)
• Ventricular (VT/VF)	
• Atrial (SVT/AF)	
Reoperations	54 (33.1)
• Bleeding	
• Infection	
• Wound dehiscence	
• Wound debridement	
• Flaps	
Neurologic events	46 (28.2)
• Hemorrhagic CVA	
• Ischemic CVA	
• TIA	
• Seizure	
• Coma	
Tamponade	43 (26.4)
Respiratory	42 (25.8)
• Tracheostomy	
• Reintubation	
Right ventricular failure (LVAD only, $n = 118$)	32 (19.6)
Acute renal failure	22 (13.5)
Device malfunction	14 (8.6)
Thromboembolism	10 (6.1)
Hepatic events	7 (4.3)
Hemolysis	5 (3.1)
Gastrointestinal events	0 (0)
• Bowel perforation	
• Ischemic bowel	

AE, adverse events; AF, atrial fibrillation; CVA, cerebrovascular accident; LVAD, left ventricular assist device; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Results

Cohort characteristics

A total of 163 patients (118 LVAD, 45 BiVAD) met inclusion criteria. The cohort was demographically similar to previously published cohorts of VAD patients in the United States.[3,4,12,15] Approximately 52% of patients presented with ischemic cardiomyopathy, and 83% were implanted as a bridge to transplantation. Further details of the cohort's baseline characteristics are listed in Table 1.

One-year mortality while on VAD support

The actuarial survival of the cohort through 1 year (ie, adjusted for censoring in the observed duration of implantation due to transplantation or weaning from the device) was 60.2% (standard error, 5.9%). There were 35 deaths, and their causes were classified into 7 broad categories, as summarized in Table 2. Central nervous system events, mainly hemorrhagic and ischemic strokes, were responsible for 37% of deaths; infectious events, mainly sepsis and pneumonia, caused 31%, and multiorgan failure caused 11%.

Incidence of clinically significant AEs

As reported in Table 3, the most frequently occurring AEs during the first 60 days after VAD implant were infection (experienced by 44.8% of patients), bleeding (44.2%), reoperations (33.1%), and cardiovascular dysfunction (38.0%). In comparison, hemolysis, mechanical, gastrointestinal, hepatic, and thromboembolic events were AEs that occurred infrequently (<10% incidence rate) and therefore were excluded as predictors of survival. The AEs from Table 3 with incidence rates of at least 10% were examined in relation to 1-year survival in both the univariable and multivariable analyses.

Univariable analysis of survival while on VAD support

The cohort's 1-year actuarial survival rates, stratified by the presence or absence of each of the 9 AEs, are listed in Table 4. The presence of some AEs conferred a significantly increased risk of mortality. For example, 1-year survival among patients who experienced early, acute renal failure was only 32% compared with 65% ($p < 0.001$) for those without renal failure. The survival curves for those with and without acute renal failure are shown in Figure 1A, demonstrating that the effect of early renal failure on later-term mortality begins immediately: the mortality curves begin to diverge at the start of the observation period and continue to separate over time. Respiratory events, bleeding events, and reoperations were also associated with a significant decrease in cumulative survival through 1 year of VAD support; their respective survival curves are shown in Figure 1B-D.

We also examined 1-year actuarial survival as a function of the total number of the 9 different types of AEs each patient experienced (ie, a simple count of how many unique types of AEs a patient had, ranging from 0–9). The patients were grouped into 4 categories depending on whether they experienced 0 to 1 AE, 2 to 3 AEs, 4 to 5 AEs, or 6 to 8 AEs. None of the patients experienced all 9 types of AEs in the first 60 days of implant. Figure 2 demonstrates that a dose-response relationship emerged, with survival significantly decreasing as the number of types of AEs experienced by a patient increased.

Multivariable analysis of survival while on VAD support

Two sets of Cox models were examined: one was fit for the entire cohort of BiVAD and LVAD patients, and a separate model was fit for only LVAD patients to examine incident RV failure in this sub-group.

Beginning with the entire cohort, the main effects for all AEs with values of $p < 0.10$ in the univariable analysis

Table 4 Actuarial Survival at 12 Months by Kaplan-Meier Analysis with Stratification by the Presence or Absence of Early Non-fatal Adverse Events

	Surviving on device, %		Test of significance[a]	
Adverse event	≥1 AEs	No AE	Chi-square	*p*-value
Renal	32.0	65.1	15.464	<0.001
Respiratory	35.3	68.7	8.623	0.003
Bleeding	48.3	70.9	4.945	0.026
Reoperation	47.9	67.7	4.343	0.037
RV failure	43.0	66.7	3.714	0.054
Infection	53.9	65.2	2.717	0.099
Neurologic	57.3	60.6	1.026	0.311
Tamponade	58.0	61.2	0.001	0.980
CV dysfunction	57.7	62.1	0.000	0.984

AE, adverse event; CV, cerebrovascular; RV, right ventricular.
[a]Statistical test: log-rank analysis.

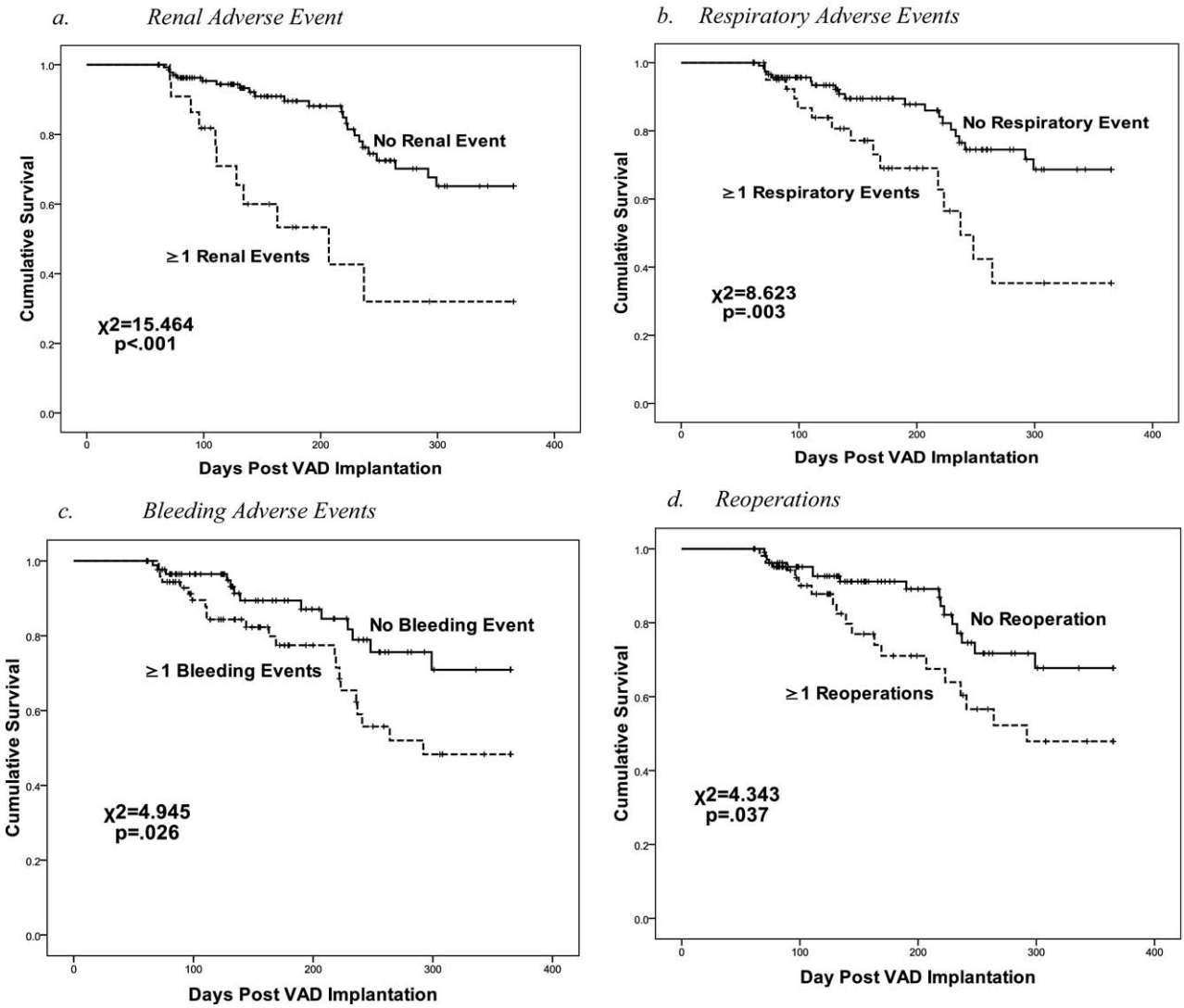

Figure 1 Cumulative patient survival through 12 months after ventricular assist device (VAD) implantation stratified by absence (solid line) or presence (dashed line) of clinically significant adverse events, including (A) renal events, (B) respiratory events, (C) bleeding events, and (D) reoperations.

were entered into the model (ie, renal, respiratory, bleeding, reoperation, and infection AEs), controlling for gender, age, intention to treat, and type of VAD implanted. The results (Table 5) indicate that the occurrence of acute renal failure was the only significant predictor of 1-year mortality, after controlling for baseline characteristics and the other AEs. Acute renal failure after implantation conferred a 3-fold increased risk of 1-year mortality while on VAD support (hazard ratio, 2.96; $p = 0.023$).

A second Cox model was fit for LVAD patients alone, in the same manner as the first model, to examine the effect of RV failure on mortality within the context of other AEs and baseline characteristics. The model (controlling for gender, age, intention to treat, and VAD type) included renal failure, respiratory AEs, bleeding events, reoperation, infections, and RV failure, with chi-square = 19.97 and $p = 0.03$. Within this model, RV failure did not significantly increase 1-year mortality ($p = 0.177$).

In both models, interaction terms between pairs of AE variables were added to determine if unique combinations of AEs conferred greater risk for mortality. None of the interaction terms was significant (all $p > 0.05$).

Discussion

Few studies have investigated the effect of early, non-fatal AEs on longer-term VAD mortality.[21] Moreover, reports examining mortality generally focus on the effect of a limited group of AEs.[18–20,26–29,32,33] The current study thus provides a unique investigation of the critical role of a full range of clinically significant, post-implant complications on longer-term mortality. Survival was significantly decreased at 1 year in patients who experienced non-fatal episodes of renal failure, respiratory failure, bleeding events, and reoperations within the first 60 days of VAD support. Furthermore, our multivariable analysis demonstrated that early, acute renal failure while on VAD support was the strongest predictor of later-term mortality, conferring a 3-fold increased risk of death through the first year after implantation.

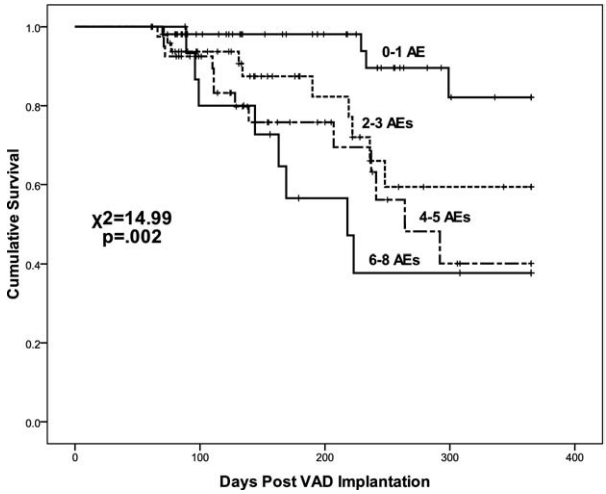

Figure 2 Cumulative patient survival through 12 months post ventricular assist device implantation, stratified by the number of types of major adverse events.

The finding that some major AEs, including neurologic events and RV failure, did not predict longer-term morality was unexpected. It has been well established that some of these AEs have a significant effect on peri-operative mortality. For example, many institutions, including our own, have shown that the development of RV failure is associated with a significant increase in mortality during the first 30 days after implant.[18,19,34] However, because we focused on patients who survived the first 60 days after VAD implant, patients who experienced these early, fatal events were excluded. Thus, we were able to demonstrate that only a few of these early, non-fatal AEs were associated with greater risk of mortality beyond the peri-operative period.

Among these AEs, early respiratory failure requiring reintubation or tracheostomy significantly decreased the likelihood of later survival. Respiratory failure occurred in 26% of our sample, and among these individuals, only 35% survived at 1 year (compared with 69% for those without respiratory failure). These respiratory AEs may be associated with episodes of decreased tissue oxygenation, increased RV afterload, risks of prolonged mechanical ventilation, and decreased mobility that contributes to deconditioning, all of which are likely to affect survival.

Bleeding remains one of the most common AEs after VAD implantation,[3,15,23,35] and in a previous study, we found that early bleeding events were particularly likely in BiVAD (compared with LVAD) patients.[23] The transfusions associated with significant bleeding events have been shown to increase infection risk, allosensitization, and acute lung injury.[36,37] The present study demonstrates that early, non-fatal bleeding events have a substantial effect on later-term mortality. Although patients with major bleeding events were successfully managed with transfusions or reoperations, or both, their 1-year survival rate of 48% was significantly poorer than the 71% survival rate in those without these events. Bleeding events often require multiple transfusions, which may lead to acute lung injury and, in turn, can compromise RV function, increase the risk of end-organ ischemia, and require reoperations to ensure hemostasis.

Reoperations also confer an increased risk of death, with a 48% 1-year survival in those who required a major reoperation compared with a 68% survival rate for those who did not. We defined clinically significant reoperations as procedures for bleeding events and severe infections requiring debridement or flaps, or both, and therefore, their correlation with decreased later survival may represent the effect of severe bleeding events and infections. Wound dehiscences indicate significant, chronic infections that are associated with a prolonged inflammatory response, deconditioning, and risk of sepsis, all which have longer-term consequences on patient outcomes.[28,38]

We also found that the development of acute renal failure early in VAD support was associated with a significantly decreased survival rate at 1 year. Chronic heart failure results in renal dysfunction through persistently elevated filling pressures, marginal cardiac output, and an adverse neurohormonal milieu.[39,40] Ventricular support restores end-organ perfusion, improves the neurohormonal milieu, and allows for more effective volume removal, all of which have salutary effects on renal function.[41–44] However, renal failure will still develop in a small percentage of patients (14%, in our sample), while on VAD support.[3,12,23,35] The development of renal failure after VAD implantation is particularly ominous: previous reports found a 6-month mortality rate of 71% to 100% in such patients.[20,32,33] The present study demonstrated a poor prognosis for later-term survival for patients who develop non-fatal, renal failure during the first 60 days of VAD support: only 50% of such patients are alive at 6 months and 30% at a year.

Because the set of AEs we examined are likely to be interrelated, we undertook further analysis to examine how the AEs act together to influence 1-year mortality. First, we discovered a dose-response relationship between mortality and the total number of different types of VAD AEs experienced by the patient. Second, after controlling for gender, age, VAD type, and intention to treat, we entered the subset of AEs that appeared to be the most important predictors of later death to determine the unique contribution of each AE. This model revealed that the strongest predictor of later-term mortality was the occurrence of renal failure within the first 60 days of VAD implant. Notably, the risk of death

Table 5 Multivariable Model of 12-Month Survival by Early Adverse Events, Controlling for Age, Gender, Intention to Treat, and Device Type[a]

Predictor variable	HR (95% CI)	*p*-value
Renal event	2.96 (1.16–7.57)	0.023
Bleeding event	1.52 (0.65–3.55)	0.337
Reoperation	1.19 (0.51–2.81)	0.689
Infection	1.17 (0.55–2.51)	0.681
Respiratory event	1.35 (0.56–3.25)	0.504

CI, confidence interval; HR, hazard ratio.
[a]Model fit: chi-square = 23.72; $p = 0.008$.

tripled in patients with acute renal failure during the study period.

The overriding effect of early renal AEs warrants further investigation into the mechanisms behind the development of acute renal failure after implantation to identify clinical targets to modify in daily practice. Other studies have suggested that the development of renal failure may be associated with a high-risk presentation,[45] where the insult to the renal system from prolonged periods of cardiogenic shock cannot be ameliorated by VAD support. We previously found that BiVAD support, an indicator of patient acuity, was significantly associated with increased renal failure.[23] Others have suggested that the development of renal failure after VAD implantation is the result of pre-existing diffuse vasculopathy[22,45] that limits renal reserve and contributes to increased mortality.

Several limitations to our study must be acknowledged. Because this study was restricted to a single medical center, the size of our cohort was relatively small. This limited our ability to perform more detailed analyses; for example, although a variety of VADs were implanted, we were only able to examine and control for general categories of device type (BiVAD, continuous-flow LVAD, or pulsatile LVAD) in our analyses. In addition, we evaluated the effects of early, non-fatal AEs largely assuming that each event occurred independently or could be examined while statistically controlling for the effect of other AEs. In reality, the occurrences of AEs are far more complex: multiple AEs may occur in a given patient, and a single event may occur multiple times. Such an analysis is considerably complex and will need a more detailed examination as the focus of a future study. These limitations notwithstanding, our cohort reflects the typical VAD population at major medical centers with regard to demographics, incidence of VAD AEs, and causes of death, and we thus believe our findings can be extrapolated to other VAD populations.

As mechanical circulatory support continues to be used as extended therapy, a complete understanding of the factors that predict longer-term survival is critical to maximizing patient outcomes. The analyses performed in the present study should be considered crucial in appreciating that even early AEs may have lasting effects that can reduce later-term survival. Future work should also build on the findings of this study to delineate interactions and cascades of AEs and their subsequent effect on mortality.

In conclusion, we have demonstrated that the occurrence of non-fatal acute renal failure, respiratory failure, significant bleeding events, and reoperations within the first 60 days of VAD implant are associated with decreased 1-year survival while on VAD support. Of these events, early renal failure is the strongest predictor of mortality, tripling the risk of death. Our findings also emphasize the important impact of the patient's early clinical course on longer-term outcomes, and thus, continued monitoring of the effect of VAD AEs is essential for future developments in ventricular support technology. The next logical step will be to closely examine how a full spectrum of pre-implant characteristics influences the risk of developing these critical AEs and what post-operative management practices are needed to minimize their effects.

Disclosure statement

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