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Mortality following Durable Left Ventricular Assist Device Implant by Timing and Type of First Infection

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Abstract

Purpose: While infections are common following left ventricular assist device (LVAD) implant, the relationship between timing and category of first infection and mortality is less well understood.

Methods: The Society of Thoracic Surgeons Intermacs patients receiving a primary LVAD from 4/2012 to 5/2017 were included, with follow-up through 10/2017. The primary exposure was defined in 3 ways: any infection, timing of first infection (early: < 90 days; intermediate: 91–180 days; late: >180 days), and type of first infection (VAD-specific, VAD-related, non-VAD). The association between first infection and all-cause mortality was estimated using Cox proportional hazards regression, adjusting for comorbidities & post-implant adverse events.

Results: The study cohort included 12,957 patients (228,742 person-months) implanted (destination therapy: 47.4%, bridge-to-transplant: 41.2%) at 166 centers. First infections were most often non-VAD (54.2%), followed by VAD-specific (25.4%) & VAD-related (20.4%). Rates of first infection (per 100 person-months) were highest in the early interval (10.7) versus intermediate (3.7), or late (2.7), $p < 0.001$. Relative to patients without infection, patients with any infection had a significantly higher adjusted hazard of death [HR 2.63 (2.46, 2.86)]. First infection in the intermediate interval was associated with the largest increase in adjusted hazard of death

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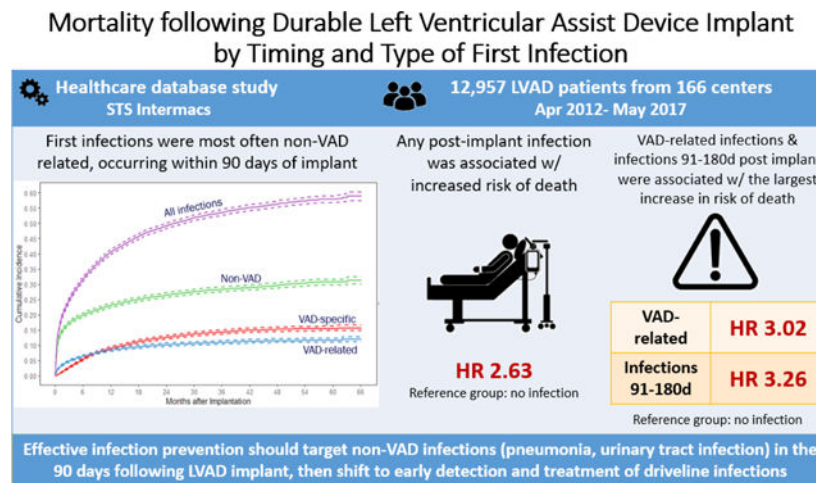
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[HR 3.26 (2.82–3.78)], followed by late [HR 3.13 (2.77, 3.53)] and early intervals [HR 2.37 (2.16, 2.60)]. VAD-related infections were associated with the largest increase in hazard of death [HR 3.02 (2.69, 3.40)], followed by VAD-specific [HR 2.92 (2.57, 3.32)], and non-VAD [HR 2.42 (2.20, 2.65)].

Conclusions: Relative to those without infection, patients with any post-implant infection had an increased risk of death. VAD-related infections and infections occurring in the intermediate interval were associated with the largest increase in risk of death.

Graphical Abstract

Central Picture Legend: First infections were most often non-VAD related, occurring within 90 days of implant



Keywords

mechanical circulatory support; ventricular assist device; infection; mortality

INTRODUCTION

Left ventricular assist devices (LVAD) provide life-saving and quality of life benefits for patients with advanced heart failure.¹ Large-scale interhospital variability exists in infections and associated spending, both of which hinder broad dissemination of this therapy.² Newer LVAD pump technology has significantly reduced the risk of post-implant pump thrombosis and stroke, yet the risk of infections remains a leading cause of morbidity and mortality over the duration of a patient's LVAD support.¹ At 2 years, major infections occurred among 58% of HeartMate 3 and 56% HeartMate II patients ($p=0.57$) in the recent MOMENTUM 3 (Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™) trial³ and 52% of all patients in the most recent The Society of Thoracic Surgeons Interagency Registry for Mechanically Assisted Circulatory Support ("STS-Intermacs") experience.⁴

Despite higher mortality rates at hospitals with high versus low infection rates,⁵ further investigation is warranted to account for other contributing factors. First, prior reports

have not fully adjusted for the effect of a patient's comorbid conditions and other post-implant adverse events.^{3,6} Second, the role of timing and VAD-relatedness (VAD-specific, VAD-related, non-VAD) of a first infection on subsequent mortality has not been fully evaluated.^{3,6} Addressing these knowledge gaps would both inform targets for infection prevention and treatment strategies, as well as advance efforts to more broadly disseminate this life-saving therapy to diverse target populations.

Using STS-Intermacs data to identify patients who received a primary, durable LVAD from April 1, 2012, to May 4, 2017, the objectives of this study were to investigate: 1) the timing of first infection stratified by infection type, and 2) the risk of death associated with infection stratified by the timing and type of infection. It was hypothesized that post-implant infections would be associated with an increased risk of death and that the risk of death would vary as a function of the time of occurrence of the first infection and infection type (i.e., VAD-related or non-VAD related).

Methods

Data source

The structure and registry process for data collection and elements within STS-Intermacs have previously been reported.⁷ The study sample included adult patients 19 years of age implanted with a durable, primary continuous flow LVAD, with or without a right ventricular assist device (RVAD). Patients were excluded if they were implanted with a pulsatile device, received isolated RVAD placement, total artificial heart, or if the LVAD was not placed as a primary implant (Supplemental figure 1). Records were obtained between April 1, 2012 through May 4, 2017, with follow up through October 31, 2017, where available.

Using STS-Intermacs definitions, patient-level data were obtained, including demographics (e.g. age, sex, race/ethnicity), characteristics pre-implant (height, weight, Intermacs profile), VAD implant indication, comorbidities (e.g. hypertension, diabetes, history of stroke), and laboratory studies. Follow-up data of post-implant adverse events included the occurrence of infections, right heart failure, device exchange, re-operation for any reason, renal dysfunction (including new acute renal injury and dialysis), stroke, as well as cause and date of death.

Informed consent for registrant participation in STS-Intermacs was required until the implementation of protocol v4.0 (February 27, 2014). The research use of STS-Intermacs data was approved by the University of Michigan Medical School Institutional Review Board (HUM00155687, approved 2/4/2019).

Exposure and Clinical Outcomes

The exposure of interest was the first post-implant infection (using STS-Intermacs' definition for Major Infection Adverse Event). Infection types were categorized as: VAD-specific (exit cannula, pump pocket, pump interior, or driveline), VAD-related (positive blood culture, mediastinum, or line sepsis), and non-VAD (pulmonary, urine, gastrointestinal, peripheral wound, other, or unknown). A priority rule was *a priori*

implemented to classify multiple concomitant infections based on assumed infection severity: VAD-specific > VAD-related > non-VAD.

The timing of first infection following implant was divided into early (< 90 days), intermediate (91–180 days), and late (>180 days) intervals.

The primary outcome was all-cause mortality following the first infection. Patients were censored at transplant, explant (no new device) or device decommissioning (i.e., termination of pump support without removal), lost to follow-up, or at end of follow-up at study closure.

Statistical Analysis

Baseline patient characteristics were summarized as the mean (standard deviation) for continuous variables and number (%) for categorical variables. Group comparison for continuous and categorical variables was conducted using the nonparametric Kruskal-Wallis test and the Chi-square test, respectively. The crude incidence rates of first infection per 100 patient-months of support by timing and category of the first infection were calculated.

Crude cause-specific cumulative incidence functions of the first infection during the entire follow-up period were calculated, with death, transplant, and explant (no new device or decommissioning) treated as competing risks of the first infection. Stratified Cox proportional hazards models were used to study the effect of first infection (vs. no infection) on mortality, by timing and category of the first infection. The Cox models were stratified by hospitals and adjusted for baseline patient risk factors and post-implant time-dependent covariates including stroke, new right heart failure (in the 30d following implant), renal dysfunction or dialysis, device exchange, and re-operation (for any reason). The likelihood ratio test was used to examine whether the effect of first infection on mortality differed by timing and type of the first infection.

Analyses were conducted using R 3.2.5 and SAS 9.4 software. All statistical tests are two-sided with the significance level set at 0.05.

RESULTS

Patient demographics

The cohort included 12,957 patients at 166 centers who were enrolled in STS-Intermacs between April 1, 2012 through May 4, 2017, Supplemental Figure 1. Patients were predominantly male (78.4%) and white (66.1%) with a mean age of 57.3 (SD 12.8), Table 1. Intermacs Profile was 2 or 3 for the majority of patients (34.7% and 34.48%, respectively). The most common device strategy was destination therapy (47.4%) followed by bridge-to-transplant (41.2%). Axial flow devices were implanted in 73.8% of patients. There were statistical, although not clinically meaningful, differences between the first infection type and some baseline characteristics. The baseline characteristics for patients who did and did not have an infection in the follow-up period are reported in Supplemental Table 1.

Among the 6378 patients who developed an infection, 2,287 (35.86%) died. Neurological dysfunction was the most common cause of death for patients with VAD-specific and

VAD-related infections, while multisystem organ failure was the most common cause of death for Non-VAD infections (Supplemental Table 2).

First Infection by Type and Timing of Onset

A total of 6378 patients (49.2%) developed an infection during the follow-up period. Non-VAD infections were the most common first infection (54.2%), followed by VAD-specific (25.3%), and VAD-related (20.4%) infections (Table 1).

Overall, the rate (per 100 person-months) of the first infection was 4.54 (Table 2). Rates of first infections (per 100 person-months) were highest in the early interval (10.7), followed by the intermediate (3.7) and late intervals (2.7), $p < 0.001$.

In the early interval, the rate of first non-VAD infections (8.23/100 person-months) was significantly higher than both VAD-related (2.27/100 person-months) and VAD-specific infections (1.16/100 person-months), $p < 0.0001$. Pneumonia (rate:1.02/100 person-months) and urinary tract infections (rate:0.76/100 person-months) were the most common non-VAD infections.

In the intermediate interval, rates of first non-VAD infection remained highest among all infection categories (1.72/100 person-months), followed by VAD specific (1.43/100 person-months) and VAD-related (1.05/100 person-months) infections.

In the late interval, rates of first non-VAD infection were highest (1.22/100 person-months), followed by VAD specific (1.07/100 person-months) and VAD-related (0.68/100 person-months) infections.

The early interval (< 90d) had the highest first infection rates in all infection categories (VAD-specific, VAD-related, non-VAD). Compared to the early interval, rates of non-VAD and VAD-related first infections decreased in the intermediate interval (91–180d), with non-VAD infections seeing a much larger decline (8.23 to 1.72/100 person-months) compared to VAD-related (2.27 to 1.05/100 person-months). Conversely, rates of VAD-specific infection saw an increase from the early (1.16/100 person-months) to intermediate (1.43/100 person-months) interval, mostly driven by an increase in driveline infections ($p < .0001$, Table 2). In the late interval (>180d), infection rates decreased in all three categories.

The cumulative incidence of first infection by category over the post-implant follow-up period is displayed in Figure 1. Non-VAD infections had the highest cumulative incidence, followed by VAD-specific and VAD-related infections.

Impact of First Infection on Mortality

Compared to those without infection, patients who had any infection during the follow-up time had a significantly higher adjusted hazard of death (HR 2.63, 95% CI 2.46 – 2.86), Table 3. The adjusted hazard ratios of any infection, by timing and infection category, are displayed in Figure 2.

Compared to those without infection, patients whose first infection occurred in the intermediate interval had the highest increase in adjusted hazard of death (HR 3.26, 95%

CI 2.82 – 3.78), followed by the late interval (HR 3.13, 95% CI 2.77 – 3.53, Table 3). The adjusted hazard of mortality differed by the timing of first infection, $p < 0.001$. Of the three time intervals, an infection in the early interval carried the lowest adjusted hazard of death (HR 2.37, 95% CI 2.16 – 2.60).

Compared to patients without infection, those who had a VAD-related first infection had the highest increase in adjusted hazard of death (HR 3.02, 95% CI 2.69 – 3.40), followed by VAD-specific (HR 2.92 95% CI 2.57 – 3.32) infections, Table 3. The adjusted hazard of mortality differed by category of the first infection, $p < 0.001$). Of the three infection categories, non-VAD first infections carried the lowest adjusted hazard of death (HR 2.42, 95% CI 2.20 – 2.65).

DISCUSSION

Three key findings emerged from this large, population-based evaluation of mortality following the first infection after durable VAD implant. First, relative to patients without infection, patients with any infection had a significantly higher risk of death (HR 2.63). Second, first infections in the intermediate interval (90–180d post-implant) were associated with the largest increase in risk of death (HR 3.26), followed by late (>180d post-implant, HR 3.13) and early intervals (90d post-implant, HR 2.37). Third, VAD-related infections were associated with the largest increase in risk of death (HR 3.02), followed by VAD-specific (HR 2.92), and non-VAD infections (HR 2.42).

To our knowledge, this is the largest observational study evaluating the relationship between post-implant infections and long-term mortality. Previous work by Hannan and colleagues, using the International Society of Heart and Lung Transplantation Mechanically Assisted Circulatory Support (IMACS) registry, evaluated the epidemiology of infections among 10,171 patients undergoing VAD implant between January 2013 and December 2015.⁸ Among these patients, infection was associated with increased mortality; the 2-year unadjusted all-cause mortality of VAD patients with infection was 41.0% compared to 25.2% for those without infection.⁸ The present analysis advances this prior work by adjusting for baseline demographic and disease characteristics as well as post-implant adverse effects that might have accounted for some of the deaths among patients with infections. After doing so, patients with any infection following VAD implant had an associated adjusted risk of death more than twice as high (HR 2.6) as those without an infection.

Further, this study is among the first to evaluate the relationship between later-developing post-implant infections and mortality. Holman and colleagues reported the relationship between first infections and mortality among 593 patients undergoing VADs (LVAD with or without RVAD) among 88 centers participating in STS-Intermacs between 2006–2008.⁶ Patients developing an infection within one month of implant had significantly lower survival than those developing an infection between one to three months after implant ($p = 0.04$). In the present analysis, early interval infections were associated with a 2.37-fold associated increased risk of death. Compared to the other pre-defined time intervals, early infections had the lowest associated risk of death. A higher risk of death associated with

late occurring infections, likely because the intermediate and late intervals had a larger proportion of VAD-related and VAD-specific infections, both of which have been previously identified with elevated risks of death.⁹

Last, this study further advances the relationship between the type of first infection and mortality. Hannan and colleagues also observed that patients with infections varied by the location of infection, with the highest mortality occurring among patients developing VAD pump/cannula infections (60.1% at 18 months) and VAD pocket infections (54.8% at 2 years); both VAD-specific infections. In another study from the IMACS registry, Aslam and colleagues evaluated the impact of bloodstream infections (BSIs) on 10,171 patients undergoing mechanical circulatory support device implant between January 2013 and December 2015.¹⁰ Patients with BSI within the first 3 months of implant had increased risk of death compared to those without BSI (HR 2.56). In the present analysis, the largest increase in risk of death was observed among VAD-related infections, 95% of which are bloodstream infections (HR 3.02), followed closely by VAD-specific (HR 2.92), then by non-VAD infections (HR 2.42).⁵

Further, neurological dysfunction was the most common cause of death among those developing VAD-specific and VAD-related infections, while multisystem organ failure was the most common cause of death among patients developing non-VAD infections. These findings suggest that a very different pathway between VAD-specific and VAD-related infections and death relative to non-VAD infections. It has been postulated that some of the increase in mortality following BSIs may be attributed to strokes and device thrombosis subsequent to the infection.^{11–13} In the work by Hannan, the five most common primary causes of death among all VAD patients were multisystem organ failure, cardiovascular causes, neurologic causes, withdrawal of support, and major infection. These were also the same five most common causes of death among our cohort of patients.

These findings have important implications for patients and providers. As an example, these findings can be used to enhance a patient's understanding of the changing risk of death associated with early, intermediate, and late-occurring first infections. We believe that our findings can be used to inform different strategies to prevent infections across the spectrum of the patient's post-implant course. For example, during the early interval when rates of non-VAD infections are highest, infection prevention efforts may be appropriately directed towards healthcare-associated infection, such as implementing bundles to prevent hospital-acquired urinary and pulmonary infections (e.g., expedited extubation, expeditious removal of post-implant urinary catheters). In the intermediate post-implant period, when rates of all infections decreased except for that of driveline infections, close surveillance of the driveline site through routine VAD clinic visits, adoption of innovative wound care techniques, and aggressive treatment upon first symptoms may be beneficial. Improvements in device technology with adoption of totally implantable systems, eliminating the need for the percutaneous lead, may therefore have significant impact on later mortality related to device infection.¹⁴

Future directions

Further work is needed to make these data more actionable to individual institutions seeking to improve infection practices. A mixed-methods exploration of infection practices at higher performing hospitals could help identify and elucidate best practices for infection prevention and treatment, which may be generalized and implemented at other institutions.¹⁵ We believe a similar approach may be helpful to define best practices for prevention of post-VAD infections across the spectrum of post-VAD care.

Benchmarking rates of health-care associated infections (e.g. pneumonia, surgical site infection, urinary tract infection) following coronary artery bypass grafting (CABG) surgery is standard practice. Prior work in the CABG and thoracic surgery literature has shown that collaborative quality improvement initiatives have led to large-scale reductions in healthcare-associated infections.^{16,17} Our prior analysis of variability of infections between VAD centers showed that higher tertile hospitals had more than four times higher bacterial infections, as well as higher device and non-device related infections compared to the low tertile hospitals. The creation of similar benchmarks in VAD patients for bloodstream infection and driveline infections using a standardized infection ratio, as well as provision of institution-specific rates of infection to various hospitals would create more transparency regarding the variability of HAI rates between centers, and highlight local opportunities for targeted interventions and quality improvement.

Limitations

Several limitations are worthy of discussion. First, while the dataset used in this study reflects practice between 2012–2017 with limited inclusion of newer HeartMate3 devices, the rate of post-implant infection in this cohort (49.2%) is comparable to that of the HeartMate 3 arm of MOMENTUM 3 (58.3%) clinical study.^{1,3} Second, while a large, multicenter North American experience, findings from this study may not reflect experiences among non-FDA approved devices. Nonetheless, rates of infection and device exchange are largely consistent with the existing literature. It is also important to note that the STS-Intermacs registry does not collect data on microbiology, susceptibility, and antibiotic therapy for patients with infections. In our cohort, the overall bacterial infections were by far the most common, similar to previous studies.^{18–20} Last, as with any observational study, it is important to recognize the potential influence of unmeasured confounding. While we took into account pre-implant characteristics and a number of post-implant adverse events that may affect the relationship between first infection and mortality, we recognize that other confounders may remain.

CONCLUSION

In this large, multinational cohort of VAD patients, first infections were most often non-VAD related and rates were highest in the early interval after implant. We found that compared to those without infection, patients with any infection post-implant had an increased risk of death in the follow-up time. VAD-related infections and infections occurring in the intermediate interval were associated with the largest increase in risk of death. These findings suggest that the focus of infection prevention in the early interval

should be directed towards non-VAD related infections, but shift to VAD-specific and VAD-related infections as the patients come to the intermediate/late intervals following VAD implant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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Glossary of abbreviations:

CI	confidence interval
FDA	US Food and Drug Administration
HR	hazard ratio
Intermacs	Interagency Registry for Mechanically Assisted Circulatory Support
STS	The Society of Thoracic Surgeons
VAD	ventricular assist device

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Central message:

Effective infection prevention should target non-VAD infections in the 90 days following LVAD implant, then shift to early detection and treatment of driveline infections.

Perspective Statement:

Patients with any infections post durable implantation had a higher all-cause mortality compared to those without infections after adjusting for other post-implant factors (HR 2.63). VAD-related first infections (HR 3.02) and first infections occurring in the intermediate interval (HR 3.26) were associated with the largest increase in risk of death.

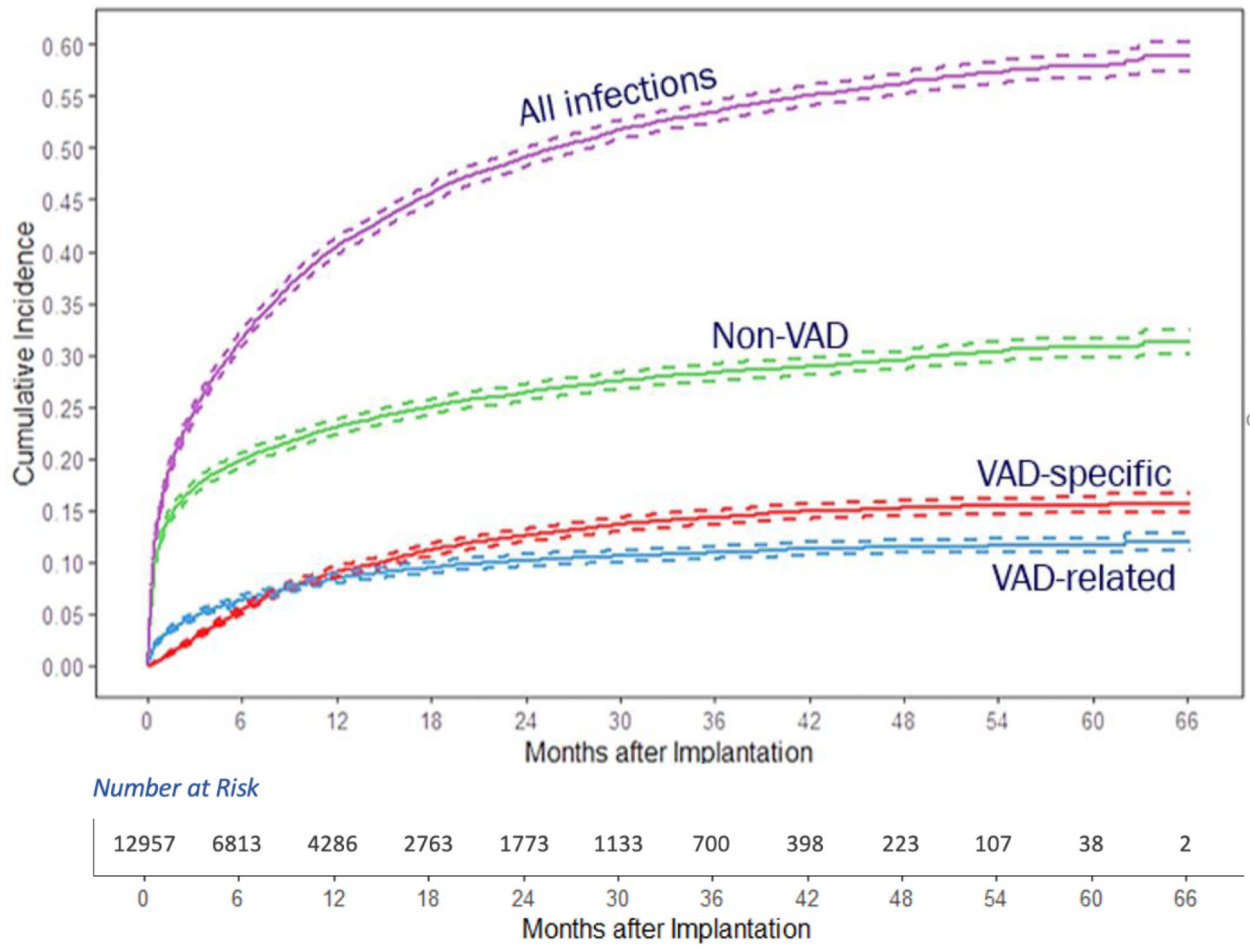


Figure 1. Cumulative Incidence of First Infection Following VAD Implant by Infection Type

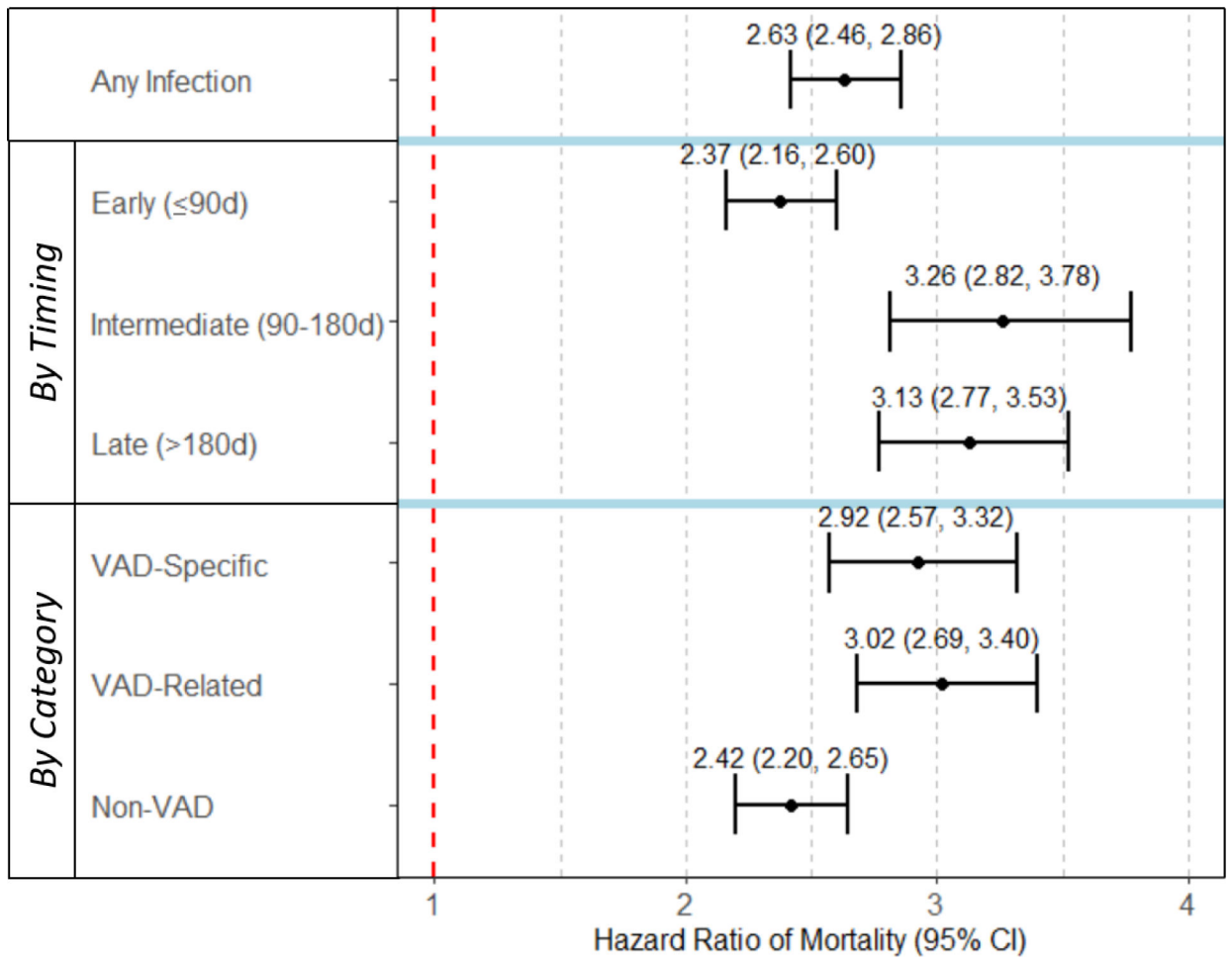


Figure 2.
The Effect of First Infection following LVAD-implant on Subsequent Mortality

Table 1.

Patient Characteristics for the Overall Cohort (N=12,957) and by Infection Type

	Overall	First Infection Type (n=6,378)			p-value
		VAD-specific	VAD-related	Non-VAD	
Number of Patients	12,957	1,617	1,303	3,458	
Demographics					
Age (years), mean (SD)	57.3 (12.8)	53.9 (13.7)	57.6 (12.9)	58.7 (12.4)	<.0001
Female Sex, n (%)	2765 (21.4)	352 (21.8)	245 (18.8)	864 (25.0)	<.0001
Race, n (%)					0.0009
White	8558 (66.1)	998 (61.7)	868 (66.6)	2291 (66.3)	
African-American	3181 (24.6)	482 (29.8)	326 (25.0)	843 (24.4)	
Other	1218 (9.4)	137 (8.5)	109 (8.4)	324 (9.4)	
Hispanic Ethnicity, n (%)	836 (6.6)	102 (6.4)	82 (6.4)	229 (6.7)	0.8510
Indication					
Device Strategy, n (%)					<.0001
Group 1 (Bridge to Transplant)	5338 (41.2)	663 (41.0)	508 (39.0)	1242 (35.9)	
Group 2 (Bridge to Candidacy)	1482 (11.4)	219 (13.5)	138 (10.6)	389 (11.3)	
Group 3 (Destination therapy)	6137 (47.4)	735 (45.5)	657 (50.4)	1827 (52.8)	
Device Brand, n (%)					0.0009
HeartMate II LVAS (Axial)	9562 (73.8)	1253 (77.5)	933 (71.6)	2617 (76.7)	
HeartWare HVAD (Centrifugal)	3395 (26.2)	364 (22.5)	370 (28.4)	841 (24.3)	
Patient Characteristics					
Body mass index (Kg/M2), mean (SD)	28.6 (7.2)	29.1 (7.4)	29.5 (8.4)	28.8 (7.0)	0.1164
INTERMACS Profile, n (%)					<.0001
Profile 1	1805 (13.9)	169 (10.5)	186 (14.3)	533 (15.3)	
Profile 2	4522 (34.9)	524 (32.4)	480 (36.8)	1273 (36.8)	
Profile 3	4563 (35.2)	653 (40.4)	453 (34.8)	1109 (32.1)	
Profile 4-7	2061 (15.9)	271 (16.8)	184 (14.1)	543 (15.7)	
Primary Diagnosis, n (%)					
Etiology 1	61 (0.5)	7 (0.4)	6 (0.5)	20 (0.6)	<.0001

	Overall	First Infection Type (n=6,378)			p-value
		VAD-specific	VAD-related	Non-VAD	
Number of Patients	12,957	1,617	1,303	3,458	
Etiology 2	5806 (45.2)	657 (40.3)	581 (44.9)	1670 (48.6)	
Etiology 3	6734 (52.4)	918 (57.2)	681 (52.7)	1679 (49.9)	
Etiology 4	258 (2.0)	32 (2.0)	25 (1.9)	67 (2.0)	
Left ventricular ejection fraction, n (%)					0.0014
>=50%	15 (0.1)	1 (0.1)	3 (0.2)	3 (0.1)	
40–49%	60 (0.5)	6 (0.4)	7 (0.5)	16 (0.5)	
30–39%	456 (3.5)	45 (2.8)	43 (3.3)	138 (4.0)	
20–29%	3173 (24.5)	352 (21.8)	364 (27.9)	899 (26.0)	
<20%	8569 (66.1)	1118 (69.1)	831 (63.8)	2213 (64.0)	
Not Recorded/Documented or Unknown	684 (5.3)	95 (5.9)	55 (4.2)	189 (5.5)	
Co-morbidities					
Severe diabetes, n (%)	1252 (9.7)	148 (9.2)	138 (10.6)	416 (12.1)	0.0078
Frailty, n (%)	840 (6.6)	60 (3.8)	96 (7.4)	263 (7.7)	<0001
Pulmonary disease, n (%)	1229 (9.6)	150 (9.4)	136 (10.5)	405 (11.9)	0.0251
Peripheral vascular disease, n (%)	604 (4.7)	71 (4.4)	66 (5.1)	211 (6.2)	0.0307
Laboratory Studies					
Serum creatinine (mg/dL), mean (SD)	1.4 (0.7)	1.3 (0.6)	1.5 (0.7)	1.4 (0.7)	<0001
Albumin (g/dL), mean (SD)	3.4 (0.6)	3.5 (0.6)	3.4 (0.6)	3.4 (0.6)	0.0306
Total bilirubin (mg/dL), mean (SD)	1.3 (1.8)	1.2 (1.1)	1.4 (1.8)	1.4 (2.1)	0.3743
Implant Year, n (%)					0.0003
2012	1593 (12.3)	266 (16.5)	164 (12.6)	501 (14.5)	
2013	2516 (19.4)	356 (22.0)	276 (21.2)	770 (22.3)	
2014	2615 (20.2)	375 (23.2)	280 (21.5)	752 (21.8)	
2015	2888 (22.3)	372 (23.0)	325 (24.9)	731 (21.1)	
2016	2568 (19.8)	211 (13.1)	206 (15.8)	573 (16.6)	
2017	777 (6.0)	37 (2.3)	52 (4.0)	131 (3.8)	

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* Primary Diagnosis: Etiology 1 includes congenital heart disease. Etiology 2 includes coronary artery disease and ischemic dilated cardiomyopathy. Etiology 3 includes non-ischemic dilated cardiomyopathy (e.g., adriamycin, alcoholic, familial, idiopathic, myocarditis, post-partum, viral and valvular). Etiology 4 includes cancer and restrictive myopathies (e.g., amyloidosis, sarcoidosis, idiopathic, hypertrophic cardiomyopathy, and radiation).

* P-value refers to the comparison between the three first infection categories and calculated from Kruskal-Wallis test (continuous variables) and Pearson's Chi-squared test (categorical variables)

* A priority rule was established *a priori* to classify multiple concomitant infections based on assumed infection severity: VAD-specific > VAD-related > non-VAD.

Table 2.

Rates of First infection by Type, Location, and Timing

First VAD Infection Type	Location	Overall		Early (< 90 days)		Intermediate (91–180 days)		Late (> 180 days)		p-value
		Events (N)	Rate	Events (N)	Rate	Events (N)	Rate	Events (N)	Rate	
All First Infection		6378	4.54	3194	10.72	849	3.67	2335	2.66	<0001
VAD specific		1617	1.15	347	1.16	330	1.43	940	1.07	<0001
	Pump/Related: Driveline or Percutaneous Lead	1454	1.03	289	0.97	302	1.31	863	0.98	<0001
	Pump/Related: Pump Pocket	181	0.13	61	0.2	32	0.14	88	0.1	0.0002
	Pump/Related: Exit Cannula	30	0.02	11	0.04	5	0.02	14	0.02	0.1300
	Pump/Related: Pump Interior	23	0.02	5	0.02	3	0.01	15	0.02	0.9000
VAD related		1517	1.08	675	2.27	242	1.05	600	0.68	<0001
	Blood Cultures, Positive	1284	0.91	507	1.7	219	0.95	558	0.64	<0001
	Mediastinum	166	0.12	134	0.45	15	0.06	17	0.02	<0001
	Line Sepsis	145	0.1	83	0.28	18	0.08	44	0.05	<0001
Non-VAD		3921	2.79	2452	8.23	398	1.72	1071	1.22	<0001
	Pulmonary	1441	1.02	1036	3.48	95	0.41	310	0.35	<0001
	Urine	1062	0.76	676	2.27	102	0.44	284	0.32	<0001
	Gastrointestinal	433	0.31	257	0.86	55	0.24	121	0.14	<0001
	Peripheral Wound	145	0.1	65	0.22	22	0.1	58	0.07	<0001
	Other	847	0.6	411	1.38	132	0.57	304	0.35	<0001
	Unknown	222	0.16	150	0.5	20	0.09	52	0.06	<0001

* Infection rates are represented as per 100 person-months.

* P-value refers to the comparison between early, intermediate and late infection rates and calculated from the likelihood ratio test.

Table 3

Impact of First Infection on Mortality by 3 Primary Exposures: Any Infection, by First Infection Timing, and by First Infection Category

		HR (95% CI)	p-value
Model 1	Any infection	2.63 (2.46, 2.86)	<.0001
	(Any Infection)		
Model 2	Early interval first infection	2.37 (2.16, 2.60)	<.0001
	Intermediate interval first infection	3.26 (2.82, 3.78)	<.0001
	Late interval first infection	3.13 (2.77, 3.53)	<.0001
			LRT: p <.0001
Model 3	VAD-specific first infection	2.92 (2.57, 3.32)	<.0001
	VAD-related first infection	3.02 (2.69, 3.40)	<.0001
	Non-VAD first infection	2.42 (2.20, 2.65)	<.0001
			LRT: p <.0001

* The reference group is the group that had no infection in the entire follow up time period

* P-value is calculated from the Wald-test.

* LRT: likelihood ratio test, p value refers to the significance compare whether the effect of first infection on mortality is different by timing/by category.