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ORIGINAL ARTICLE

Stroke Risk Following Infection in Patients with Continuous-Flow Left Ventricular Assist Device

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Abstract

Background: Infection has been associated with stroke in patients with left ventricular assist devices (LVAD); however, little data exist on the timing, type and mortality impact of infection-related stroke.

Methods: Prospectively collected data of HeartMate II ($N = 332$) and HeartWare ($N = 70$) LVAD patients from a single center were reviewed. Only strokes (ischemic or hemorrhagic) that occurred within 6 weeks following a LVAD infection were considered in analyses. The association between LVAD infections (wound, pump pocket, driveline and/or bloodstream infection [BSI]), specific pathogens and ischemic and hemorrhagic strokes was evaluated using multivariable logistic regression analysis. The impact of infection-related stroke on cumulative survival was assessed using Kaplan–Meier analysis.

Results: Of 402 patients, LVAD infection occurred in 158 (39%) including BSI in 107 (27%), driveline infection in 67 (17%), wound infection in 31 (8%) and pump pocket infection in 24 (6%). LVAD infection-related stroke occurred in 20/158 (13%) patients in a median of 4 days (0–36 days) from documented infection. In multivariable analysis, ischemic stroke was associated with wound infection (aOR 9.0, 95% CI 2.4–34.0, $P = 0.001$) and BSI (aOR 7.7, 95% CI 0.9–66.0, $P = 0.064$), and hemorrhagic stroke was associated with BSI in 100% of cases ($P = 0.01$). There was no association with driveline or pump pocket infection. The cumulative survival rate among patients with infection-related stroke was significantly lower compared to those with LVAD infection but no stroke (log-rank $P < 0.001$). There was a trend toward shorter stroke-free survival among patients with LVAD infection.

Conclusions: LVAD infections, particularly BSI, are significantly associated with stroke, and infection-related stroke conferred significantly lower cumulative survival.

Keywords: Left ventricular assist device (LVAD), HeartWare (HVAD), HeartMate II (HM II), Stroke, Ischemic stroke, Hemorrhagic stroke, Infection

Introduction

Infection is one of the most common complications with left ventricular assist devices (LVAD) as more devices are being implanted as destination therapy [1]. Among various infections, pump pocket and driveline infections are the most common, followed by bloodstream infection (BSI) [2]. LVAD infections are associated with significant morbidity and mortality due to their association with an increased risk of pump thrombosis, bleeding events, and disqualification or delays in heart transplant [3]. Infection is known to be a causal factor for stroke even among patients without a LVAD [4]. Common mechanisms for infection-related stroke in the general population include septic emboli from cardiac sources, infectious vasculitis,

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rupture of mycotic aneurysms and inflammation-related hypercoagulable states [5–9]. While some studies have described a relationship between BSI and both ischemic and hemorrhagic strokes in LVAD patients [10–13], the association of stroke with other types of infections (wound, pump pocket, and driveline), the timing of the stroke in proximity to the infection and the type of infectious pathogen has not been previously explored.

We aimed to evaluate the association of the timing and type of infection with each subtype of stroke among LVAD patients. We also aimed to evaluate mortality rates associated with infection-related stroke.

Methods

Study Design and Population

We reviewed prospectively collected data of HeartMate II ($N=332$) and HeartWare ($N=70$) patients admitted to a single, tertiary center between October 21, 2004, and May 19, 2015 [10]. We included all adult patients (age > 18) with placement of continuous-flow pump (HeartMate II or HeartWare LVAD) for either bridge to transplant or destination therapy. Infection-related strokes were defined as ischemic or hemorrhagic strokes (subarachnoid hemorrhage [SAH], intraparenchymal hemorrhage or intraventricular hemorrhage [IVH] not due to trauma) occurring within 6 weeks following a documented infection. This time frame was selected to maximize the likelihood that the stroke event was pathophysiologically related to the LVAD infection and because the existing literature suggests the highest risk of stroke occurs in the first month following infective endocarditis [14]. Patients with a LVAD infection and a stroke outside of the prescribed time window (e.g., either before or > 6 weeks after documented LVAD infection) were coded as *not* having a LVAD infection-related stroke. Exclusion criteria were as follows: placement of a biventricular assist device, total artificial heart or temporary/short-term mechanical assist circulatory device, traumatic intracranial hemorrhage (including subdural hematoma, traumatic SAH or brain contusion), and lack of informed consent. This study was approved by the Cleveland Clinic Institutional Review Board, and all patients or their surrogates consented to participation.

Patient Assessments

All patients were enrolled in a local, prospective database (EDIT: Electronic Data Interface for Transplantation) which included pre-implant demographic data, medical history, social history, type of device, pre- and post-implant clinical status variables and adverse event variables. Additional data detailing the types of infection, and microorganisms were retrospectively collected from the hospital electronic medical record. Patients were followed up from the time of implant until death or transplant with mandatory follow-up visits at 1 week and 1, 3, 6 and 12 months post-implant. Among patients who died, the cause of death was prospectively coded in the EDIT database and adjudicated by the treating physicians at the time of death.

Both ischemic and hemorrhagic strokes were defined using INTERMACS adverse event criteria [1] in conjunction with a review of all computed tomography (CT) brain imaging. Transient ischemic attacks and ischemic strokes, including those with hemorrhagic conversion, were grouped together as "ischemic strokes." Hemorrhagic stroke included SAH, intracerebral hemorrhage (ICH) and IVH. Patients with traumatic brain injury, including subdural hematoma, traumatic SAH and traumatic contusions, were excluded from analysis. We included only acute, symptomatic strokes with radiographic evidence of infarction or hemorrhage in the appropriate corresponding vascular territory. Transient ischemic attacks consisting of focal neurological deficits conforming to anatomic vascular territories and lasting < 24 h without radiographic evidence of infarction were also included (as defined by INTERMACS adverse event definitions) [15]. Silent strokes identified by imaging alone were not included in analysis since the timing of such strokes in relation to LVAD infection could not be definitively ascertained. All patients diagnosed with stroke were evaluated by the Cleveland Clinic vascular neurologists and underwent CT imaging as part of routine clinical care. CT images were interpreted by an independent neuroradiologist, and both images and reports for all patients were reviewed by a single neurology investigator (S.-M.C.). Magnetic resonance imaging (MRI) was not performed due to MRI incompatibility of LVAD devices.

The types of LVAD-specific infections included wound infection, driveline, pump pocket and BSI [10]. These infections were defined following the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) adverse event definitions [16]. Wound infection was defined as localized infection of the surgical wound site without systematic involvement. Driveline infection was defined as infection involving the soft tissues surrounding the driveline exit site, accompanied by erythema, warmth, and purulent discharge accompanied by positive site culture. Pump pocket infection was defined as infection involving the skin and/or tissue surrounding the LVAD pump with clinical signs such as pain, fever, drainage, or leukocytosis accompanied by positive site culture. BSI was defined using Centers for Disease Control and Prevention/National Healthcare Safety Network criteria [17]. Patients could be coded as having multiple infection types. The date

and time of infection diagnosis and stroke occurrence were collected, and the specific pathogen type was recorded. When driveline, pump pocket and wound infection occurred within 7 days preceding a BSI, the original infection was considered as an etiology of BSI. Specific analyses were performed for *Pseudomonas* species and *Staphylococcus aureus* infections based on prior literature suggesting an association with stroke in LVAD patients [12]. All types of infections were confirmed by infectious disease specialty consultations at the Cleveland Clinic.

Statistical Analysis

The association between LVAD infections (wound infection, pump pocket infection, driveline infection and BSI), specific pathogens (*Pseudomonas and Staphylococcus aureus)* and ischemic and hemorrhagic stroke was evaluated using Mann–Whitney *U*, Chi-squared and Fisher's exact tests. All univariate variables with $P \leq 0.100$ were entered into multivariable, backward, stepwise logistic regression analyses to determine predictors of ischemic and hemorrhagic strokes. Backward elimination was continued if the resulting number of variables exceeded the 10:1 event-to-variable ratio that is recommended to avoid overfitting the model. Cumulative survival was compared between patients who suffered stroke within 6 weeks following a LVAD-specific infection and those with LVAD infection but no stroke using Kaplan–Meier analysis. An additional Kaplan–Meier analysis of stroke-free survival among patients with or without LVAD-specific infection was performed. Patients were censored at the time of transplant, death or at the end of the study period. Differences in the distribution of survival curves were assessed with the log-rank test. All analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY), and SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of 402 patients, 158 (39%) had a LVAD-specific infection within a median of 45 days (range 0–1642) from the time of implant and 132 (33%) patients had multiple LVAD-specific infections (Table 1). BSI (107 of 158 patients with infection or 68%) and driveline infection (67 of 158 patients with infection or 42%) were the most common sites of infection (Fig. 1). Gram-negative rods accounted for 42% (67 of 158) of LVAD-specific infections, while *S. aureus* was identified in 25% (39 of 158 patients). Stroke occurred in 20/158 (13%) patients in the 6 weeks following documented LVAD infection and in 33/244 (14%) of those without LVAD infection over a median follow-up time of 2.4 years ($P=0.802$). Of those with LVAD infection, 114/158 (72%) had no strokes before or any time after the documented LVAD infection, while another 16/158 (10%) patients had 19 strokes but outside of the study time frame (e.g., either before or >6 weeks after documented LVAD infection). Among those with LVAD infection, the stroke event rate (events-per-patient-year, EPPY) during the first 6 weeks following documented infection was 52.0 EPPY, while the stroke event rate per-patient-year among those without LVAD infection was 0.07 EPPY ($P=0.683$) from the time of LVAD implant to study end or death. Thus, the first 6 weeks post-LVAD infection represented a very high-risk time frame for stroke. The cumulative rate of stroke-free survival trended lower in patients with infection compared to those without (Fig. 2, log-rank $P=0.186$). Among infection-related strokes, ischemic stroke occurred in 11/20 (55%) and hemorrhagic stroke in 13/20 (65%). Four (20%) had both ischemic and hemorrhagic strokes. The most common type of hemorrhagic stroke was ICH ($N=8$) followed by SAH ($N=5$).

Table 1 List of any types of infections in the entire cohort ($N=402$)

	N (%)
Infection	
Any LVAD-specific infection	158 (39%)
Multiple LVAD-specific infections	132 (33%)
Location of infection	
Driveline infection	67 (17%)
Pump pocket infection	24 (6%)
Wound infection	28 (7%)
Bloodstream infection	107 (27%)
BSI due to driveline infection	25/107 (23%)
BSI due to wound infection	7/107 (7%)
BSI due to pump pocket infection	5/107 (5%)
BSI without any other documented LVAD infections	67/107 (63%)
Pathogen	
Pseudomonas	34 (8%)
Non-*Pseudomonas* GNR	42 (10%)
S. aureus	39 (10%)
Fungal	6 (1%)
Pathogen and location	
S. aureus BSI	20 (5%)
S. aureus driveline infection	20 (5%)
S. aureus pump infection	9 (2%)
Pseudomonas BSI	14 (3%)
Pseudomonas driveline infection	28 (7%)
Pseudomonas pump infection	7 (2%)

For a BSI to be attributed to a source it must be occurring within 7 days following or 1 day before the source infection

BSI bloodstream infection, *GNR* gram-negative rod, *LVAD* left ventricular assist device, *S. aureus staphylococcus aureus*

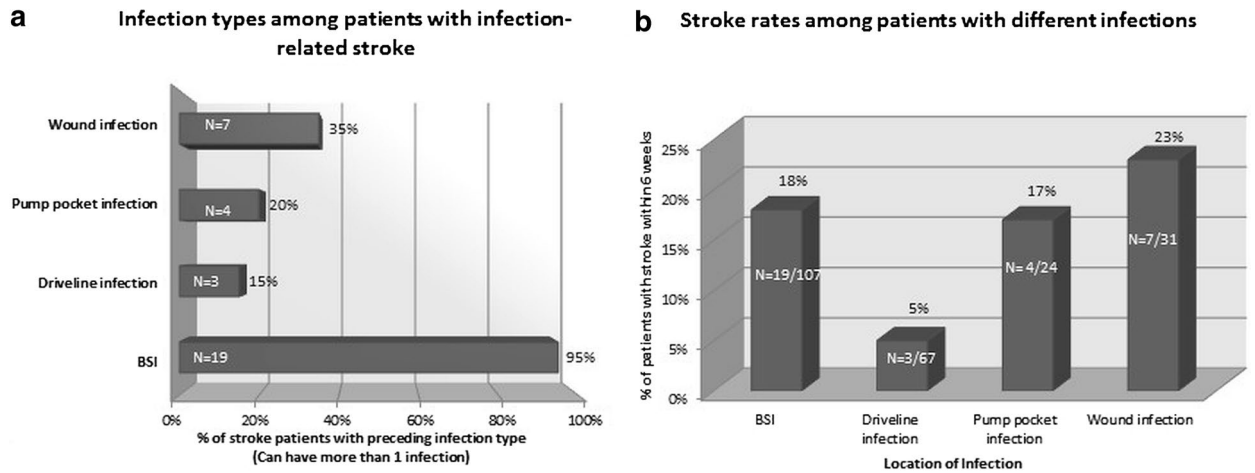

Fig. 1 Infection types among patients with stroke-related infection ($N=20$, A) and stroke rates among patients with different infection locations ($N=158$)

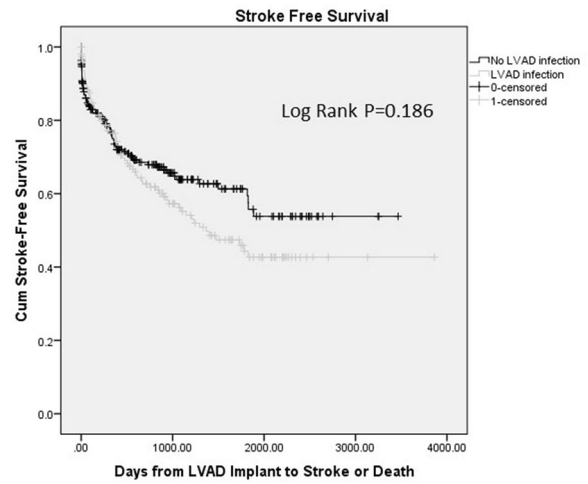

Fig. 2 Kaplan–Meier curve of cumulative stroke-free survival among patients with LVAD infections ($N=158$). Black line represents patients without LVAD-specific infection (bloodstream infection, pump pocket infection, driveline infection or wound infection), and gray line represents patients with LVAD-specific infection. Cross-hatching represents censored patients

The median time from infection diagnosis to stroke was 4 days (range 0–36), and 2/20 (10%) died due to infection-related stroke. There was no significant change in the LVAD infection rate or stroke rate over the 10-year course of the study. Of 20 patients with LVAD infection-related strokes, only 2 (10%) received heart transplant. This was significantly lower than the number of transplants in patients with LVAD infection without any strokes ($N=44/124$; (OR 5.0, 95% CI 1.1–22.3, $P=0.04$). The number of heart transplants did not differ between patients with LVAD infection-related stroke ($N=2/20$) versus strokes without any LVAD infections ($N=9/46$, $P=0.35$).

Univariate predictors of any type of stroke included BSI and fungal infection. BSI was also a predictor of hemorrhagic stroke specifically, while wound infection and fungal pathogens were associated with ischemic stroke (all $P<0.05$; Table 2). Traditional stroke risk factors including hypertension, tobacco use, diabetes and atrial fibrillation were not associated with post-infection stroke. Additionally, there were no differences in post-infection stroke between HeartWare and HeartMate II devices. When the analysis was restricted to the patients with multiple LVAD infections, the results were similar (Table 2).

In multivariable analyses, infection-related stroke was associated with preceding BSI (adjusted odds ratio [aOR] 11.1, 95% confidence interval [CI] 1.4–87.4, $P=0.023$) and fungal pathogens (aOR 6.5, 95% CI 1.7–25.3, $P=0.007$). Examining specific stroke subtypes, ischemic stroke was associated with wound infection (aOR 9.0, 95% CI 2.4–34.0, $P=0.001$) and there was a trend toward an association with BSI (aOR 7.7, 95% CI 0.9–66.0, $P=0.064$), and hemorrhagic stroke was associated with BSI in 100% of cases ($P=0.01$). Driveline infection, pump pocket infection and *S. aureus* and *Pseudomonas* species were not associated with stroke in multivariable analyses.

Next, we evaluated the association of infection-related stroke and all-cause mortality. Kaplan–Meier curves demonstrate significantly worse cumulative survival among patients with infection-related stroke (log-rank $P<0.001$; Fig. 2) compared to patients with a LVAD infection but no stroke ($N=158$). Among all

Table 2 Univariate analyses of predictors of stroke within the 6 weeks following infection (*N* = 158)

	Any stroke within 6 weeks after infection	No stroke within 6 weeks after infection	*P* value	Hemorrhagic stroke	No hemorrhagic stroke	*P* value	Ischemic stroke	No ischemic stroke	*P* value
Count (*N*, %)	20 (13%)	138 (87%)		13 (8%)	145 (92%)		11 (7%)	147 (93%)	
Demographics and medical history									
Age (median, range)	55 (33–75)	55 (17–74)	0.798	57 (33–70)	55 (17–75)	0.924	58 (35–75)	55 (17–74)	0.349
Sex (female)	6 (30%)	28 (20%)	0.382	2 (15%)	32 (22%)	0.736	4 (36%)	30 (20%)	0.252
HeartWare versus HeartMate II, *N* (%)	4 (20%)	20 (15%)	0.511	4 (31%)	20 (14%)	0.113	1 (9%)	23 (16%)	1.00
Hypertension, *N* (%)	15 (75%)	82 (59%)	0.224	9 (69%)	88 (61%)	0.768	8 (73%)	89 (61%)	0.532
Tobacco use, *N* (%)	14 (70%)	75 (54%)	0.232	9 (69%)	80 (55%)	0.392	9 (82%)	80 (54%)	0.115
Diabetes, *N* (%)	7 (35%)	48 (35%)	1.00	4 (31%)	51 (35%)	1.00	4 (36%)	51 (35%)	1.00
Atrial fibrillation, *N* (%)	6 (30%)	47 (34%)	0.805	5 (39%)	48 (33%)	0.762	3 (27%)	50 (34%)	1.00
Location of infection									
Multiple infections, *N* (%)	17 (85%)	115 (83%)	1.00	10 (77%)	122 (84%)	0.437	11 (100%)	121 (82%)	0.214
Driveline infection, *N* (%)	5 (25%)	74 (54%)	**0.029**	3 (23%)	75 (52%)	0.079	3 (27%)	75 (51%)	0.210
Pump pocket infection, *N* (%)	4 (20%)	20 (15%)	0.511	3 (23%)	21 (15%)	0.420	2 (18%)	22 (15%)	0.674
BSI, *N* (%)	19 (95%)	88 (64%)	**0.004**	13 (100%)	94 (65%)	**0.010**	10 (91%)	97 (66%)	0.106
LVAD wound infection, *N* (%)	7 (35%)	21 (15%)	0.054	3 (23%)	25 (17%)	0.703	6 (55%)	22 (15%)	**0.005**
Pathogen									
Any GNR infection, *N* (%)	11 (55%)	83 (60%)	0.788	7 (54%)	87 (60%)	1.00	6 (55%)	88 (60%)	0.712
Any Pseudomonas infection, *N* (%)	5 (25%)	35 (25%)	0.765	3 (23%)	37 (26%)	1.00	3 (27%)	37 (25%)	0.413
Any non-Pseudomonas GNR infection, *N* (%)	5 (25%)	44 (32%)	1.00	4 (31%)	45 (31%)	1.00	2 (18%)	47 (32%)	1.00
Any *S. aureus* infection, *N* (%)	7 (35%)	40 (29%)	0.253	5 (39%)	42 (29%)	0.505	3 (27%)	44 (30%)	0.684
Any fungal infection, *N* (%)	5 (25%)	7 (5%)	**0.009**	2 (15%)	10 (7%)	0.258	3 (27%)	9 (6%)	**0.039**
Pathogen and location									
S. aureus BSI, *N* (%)	3 (15%)	17 (12%)	0.721	3 (23%)	17 (12%)	0.216	1 (9%)	19 (13%)	1.00
S. aureus driveline infection, *N* (%)	1 (5%)	19 (14%)	0.471	1 (8%)	19 (13%)	1.00	1 (9%)	20 (14%)	0.363
S. aureus pump infection, *N* (%)	1 (5%)	8 (6%)	1.00	1 (8%)	8 (6%)	0.553	1 (9%)	8 (5%)	0.458

Table 2 (continued)

	Any stroke within 6 weeks after infection	No stroke within 6 weeks after infection	*P* value	Hemorrhagic stroke	No hemorrhagic stroke	*P* value	Ischemic stroke	No ischemic stroke	*P* value
Pseudomonas BSI, *N* (%)	3 (15%)	11 (8%)	0.390	2 (15%)	12 (8%)	0.323	2 (18%)	12 (8%)	0.252
Pseudomonas driveline infection, *N* (%)	3 (15%)	25 (18%)	1.00	3 (23%)	25 (17%)	0.704	1 (9%)	27 (18%)	0.692
Pseudomonas pump infection, *N* (%)	1 (5%)	6 (4%)	1.00	1 (8%)	6 (4%)	0.463	1 (9%)	7 (5%)	1.00
Stroke analysis on patients with multiple LVAD infections	**Any stroke within 6 weeks after multiple infections**	**No stroke within 6 weeks after multiple infections**	***P* value**	**Hemorrhagic stroke**	**No hemorrhagic stroke**	***P* value**	**Ischemic stroke**	**No ischemic stroke**	***P* value**
Count (*N*, %)	17 (13%)	115 (87%)		10 (8%)	122 (92%)		11 (8%)	121 (92%)	
Driveline infection, *N* (%)	6 (35%)	70 (61%)	**0.046**	4 (40%)	72 (59%)	0.24	4 (36%)	72 (60%)	0.14
Pump pocket infection, *N* (%)	4 (24%)	19 (17%)	0.48	3 (30%)	20 (16%)	0.28	2 (18%)	21 (17%)	0.95
BSI, *N* (%)	16 (94%)	76 (66%)	**0.02**	10 (100%)	82 (67%)	**0.03**	10 (91%)	82 (68%)	0.11
Wound infection, *N* (%)	7 (41%)	18 (16%)	**0.01**	3 (30%)	22 (18%)	0.35	6 (55%)	19 (16%)	**0.002**
Any fungal infection, *N* (%)	5 (29%)	4 (3%)	**<0.001**	2 (20%)	7 (6%)	0.09	3 (27%)	6 (5%)	**0.005**

BSI bloodstream infection, *GNR* gram-negative rod, *S. aureus staphylococcus aureus*. Note that some GNR infections are not identified. Bold indicates $P < 0.05$

patients in the cohort with stroke ($N = 69$), there was no significant difference in survival between those with or without LVAD infection (log-rank $P = 0.548$).

Discussion

In this cohort, we found that LVAD-related infections occurred in nearly 40% of patients and more than one in eight patients with an LVAD-related infection had a stroke within the following 6 weeks. The first 6 weeks following LVAD infection represented a high-risk period for strokes with an event rate of 52 EPPY among those with LVAD infection, compared to a baseline rate of 0.07 strokes EPPY for those without LVAD infection. Post-LVAD infection ischemic and hemorrhagic stroke occurred at a similar frequency, and the most significant type of infection predisposing to stroke was BSI. Possible mechanisms for BSI-related stroke include endocarditis of either the native heart or the LVAD hardware with subsequent septic emboli, mycotic aneurysm rupture, or vasculitis. The risk of stroke in patients with non-LVAD associated endocarditis is as high as 35% during the first 10 days of antibiotic therapy and declines thereafter [18, 19]. Additionally, cerebral septic emboli due to endocarditis are prone to hemorrhagic conversion [20]. LVAD patients may be particularly susceptible to embolic stroke since device-related microbial biofilms have reduced antibiotic penetrance and can serve as a nidus for thrombus or abscess [21].

Others have reported an association of BSI with both ischemic and hemorrhagic strokes in LVAD patients [10–13]. However, the causal implications of BSI leading to stroke were limited in these studies due to inclusion of stroke occurring at any time point before or after BSI [12], or up to 6 months [11] or 2 years following a BSI [13]. Because stroke predisposes patients to infection and because infection may be a marker for other factors that may lead to stroke, the temporal relationship between the index infection and the stroke event is crucial to demonstrating causality. We selected a very narrow time frame (6 weeks) following infection both to improve the plausibility of causality and to underscore the implications of patient monitoring and treatment in the acute time frame following BSI [14]. While our previous work [10] identified a hypothesis-generating association between BSI, pump pocket infection and stroke, using stricter definitions for LVAD

infection-related stroke demonstrated a significant association of stroke with BSI and fungal pathogens in the current analysis. Examining stroke subtypes, we found that LVAD infection-related ischemic stroke was significantly associated with wound infection and that 100% of patients with LVAD infection-related hemorrhagic stroke had preceding BSI. We did not confirm the previously identified association with pump pocket infection. Interestingly, we found that the median time from infection to acute stroke was only 4 days, indicating there is a casual relationship between acute infection and acute stroke. We also explored other types of LVAD infection including driveline, wound and pump pocket infections. Though wound infection was associated with ischemic stroke in multivariable analysis, neither pump pocket nor driveline infection was associated with stroke. This is consistent with prior literature showing that driveline infection is not a significant factor in pump thrombosis or stroke occurrence [2, 22, 23]. We did, however, find that nearly 23% of BSIs were immediately preceded by or occurred at the time of acute driveline infection, implying some degree of indirect association with stroke. The association of LVAD wound infection and ischemic stroke has not been reported in the past, and the pathophysiology is unclear. Because patients did not routinely get transthoracic or transesophageal echocardiogram at the time of acute wound infection, it is difficult to determine if wound infection was a marker for coexistent endocarditis (Fig. 3).

In regard to specific pathogens, while we hypothesized that *S. aureus* and *Pseudomonas* would be more virulent pathogens in terms of stroke risk based on the existing literature [12], fungal infections were found to be of higher risk. Systemic angioinvasive fungal infection can cause severe inflammation and infectious cerebral vasculitis [6], as well as ICH. It is possible that endothelial dysfunction due to non-physiologic flow in LVAD [24] mediates the formation of a fibrin and platelet bed that allows for fungal adhesion, which may predispose these patients to invasive fungal infections [25].

Another important finding in our paper was the association of infection-related stroke and death. While others have shown that stroke and BSI are each independently associated with mortality in LVAD patients [11, 12, 26], our paper is the first to demonstrate that infection-related stroke is associated with reduced rates of cumulative survival. Additionally, we found a trend toward reduced cumulative stroke-free survival among patients with any type of LVAD infection (including wound, driveline, pump pocket or BSI), though we were underpowered to demonstrate statistical significance. Strategies to mitigate the risk of infection-related stroke may include early antibiotic administration, surveillance for

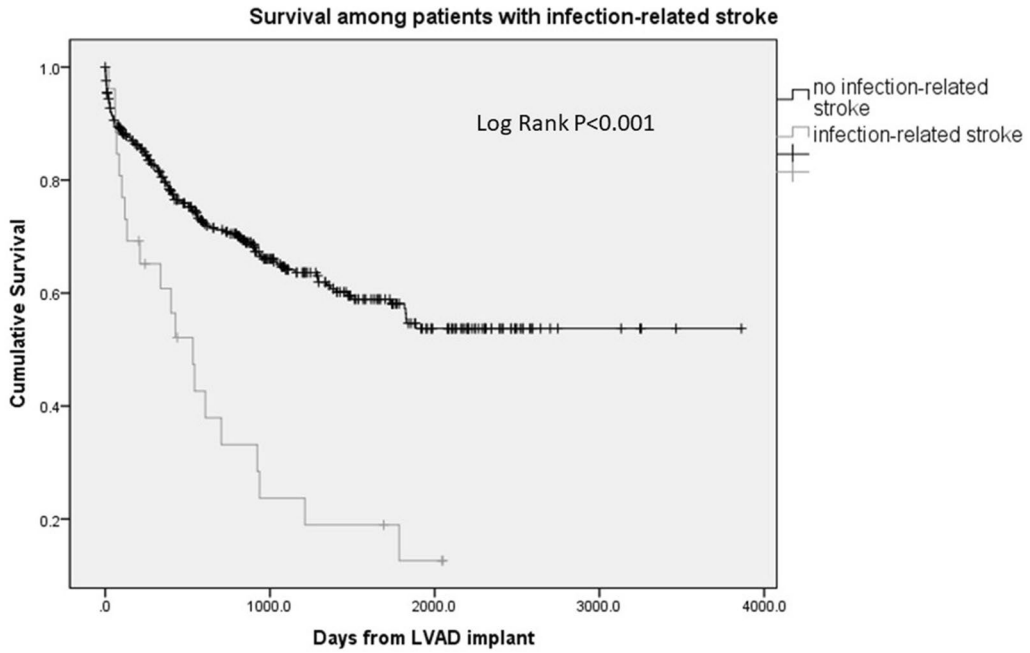

Fig. 3 Kaplan–Meier curve of cumulative survival among patients with infection-related stroke compared to the rest of the cohort ($N=402$). Black line represents patients without stroke within 6 weeks of infection, and gray line represents patients with infection-related stroke. Cross-hatching represents censored patients

endocarditis and embolic phenomenon (e.g., transcranial Doppler microemboli detection), vessel imaging for detection of mycotic aneurysms, along with close management of anticoagulation status may help ameliorate the risk of stroke following BSI.

Our study has several limitations. First, this was a retrospective review of prospectively collected data from a single center, which may be associated with selection bias. Though data on stroke severity (e.g., National Institutes of Health Stroke Scale) and long-term disability (e.g., Modified Rankin Scale scores) would have enhanced the findings of this study, the retrospective nature of the study and inconsistent collection of clinical scoring precluded this type of analysis. Second, the small sample size of patients with stroke is a limitation for statistical power. Third, though we limited inclusion to strokes occurring within 6 weeks of active infection, this still does not prove causality between infection and stroke given the limitations of retrospective study design.

Conclusions

Stroke occurred in one in eight patients in the acute time period (6 weeks) following LVAD infections, and the presence of an LVAD infection was associated with reduced stroke-free survival. BSI was most consistently associated with both hemorrhagic and ischemic stroke types. Infection-related stroke was associated with lower rates of cumulative survival. Precautions to mitigate infection risk may reduce stroke rates, but further research is necessary.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0662-1) contains supplementary material, which is available to authorized users.

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Author Contributions
SMC and JAF contributed to study concept and design. SMC and JAF contributed to data acquisition and analysis. JAF reviewed and finalized the statistical analysis. SMC prepared the first draft of the manuscript. SK, AB, NM and NKS contributed to drafting the manuscript. SMC and JAF finalized the manuscript.

Source of Support
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Compliance with Ethical Standards

Conflict of interest
The authors declare that they have no competing interests.

Ethical Approval
This study was approved by the Cleveland Clinic IRB, and all patients or their surrogates consented to participation.

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