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The HVAD Left Ventricular Assist Device

Risk Factors for Neurological Events and Risk Mitigation Strategies

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the risk factors for ischemic in hemorrhage cerebrovascular events in patients supported by the HeartWare ventricular assist device (HVAD).

BACKGROUND Patients supported with left ventricular assist devices are at risk for both ischemic and hemorrhagic cerebrovascular events.

METHODS Patients undergoing implantation with a HVAD as part of the bridge-to-transplant trial and subsequent continued access protocol were included. Neurological events (ischemic cerebrovascular accidents [ICVAs] and hemorrhagic cerebrovascular accidents [HCVAs]) were assessed, and the risk factors for these events were evaluated in a multivariable model.

RESULTS A total of 382 patients were included: 140 bridge-to-transplant patients from the ADVANCE (Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure) clinical trial and 242 patients from the continued access protocol. Patients had a mean age of 53.2 years; 71.2% were male, and 68.1% were white. Thirty-eight percent had ischemic heart disease, and the mean duration of support was 422.7 days. The overall prevalence of ICVA was 6.8% (26 of 382); for HCVA, it was 8.4% (32 of 382). Pump design modifications and a protocol-driven change in the antiplatelet therapy reduced the prevalence of ICVA from 6.3% (17 of 272) to 2.7% (3 of 110; $p = 0.21$) but had a negligible effect on the prevalence of HVCA (8.8% [24 of 272] vs. 6.4% [7 of 110]; $p = 0.69$). Multivariable predictors of ICVA were aspirin ≤81 mg and atrial fibrillation; predictors of HCVA were mean arterial pressure >90 mm Hg, aspirin ≤81 mg, and an international normalized ratio >3.0. Eight of the 30 participating sites had established improved blood pressure management (IBPM) protocols. Although the prevalence of ICVA for those with and without IBPM protocols was similar (5.3% [6 of 114] vs. 5.2% [14 of 268]; $p = 0.99$), those with IBPM protocols had a significantly lower prevalence of HCVA (1.8% [2 of 114] vs. 10.8% [29 of 268]; $p = 0.0078$).

CONCLUSIONS Anticoagulation, antiplatelet therapy, and blood pressure management affected the prevalence of cerebrovascular events after implantation of the HVAD. Attention to these clinical parameters can have a substantial impact on the occurrence of serious neurological events. (Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure [ADVANCE]; NCT00751972) (J Am Coll Cardiol HF 2015;3:818–28)

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Left ventricular assist devices (LVADs) are used with increasing frequency in patients with advanced systolic heart failure both as a bridge to transplant (BTT) and as destination therapy (1-3). The current generation of continuous flow devices provides excellent survival and quality of life, affords greater durability, and allows for less extensive surgical dissection and implantation in a wider variety of patients than the pulsatile technology these devices supplanted. However, despite these advances, patients remain at risk for serious adverse events such as infection, bleeding, thrombus, and stroke (4-14).

Cerebrovascular accidents (CVAs) can be especially devastating, and, if not fatal, they often lead to permanent disability, dramatically reducing quality of life and negatively affecting transplant candidacy. The reported prevalence of CVA after implantation of continuous flow LVADs ranges from 7% to 15% (15-19). CVAs, particularly hemorrhagic cerebrovascular accidents (HCVAs), often account for a significant proportion of deaths for patients on ventricular assist device (VAD) support. Other studies have implicated sepsis and excessive anticoagulation as risk factors for hemorrhagic stroke, but no comprehensive multivariable analysis of risk factors for stroke in patients with continuous flow VADs has been published (6,20,21). Given the morbidity and mortality of CVAs complicating VAD therapy, we examined the prevalence and rates of neurological events from the HeartWare BTT trial and continued access protocol (CAP). Our goal was to determine the impact that changes to device design had on CVAs and to identify modifiable risk factors.

METHODS

The design of the HeartWare HVAD BTT and CAP clinical trial has been described previously (22). Briefly, it was a prospective, multicenter, pivotal clinical trial evaluating the HVAD for BTT in the United States. The trial enrolled 140 patients with advanced heart failure who were eligible for heart transplantation. The study was reviewed and approved by the U.S. Food and Drug Administration (FDA) and conducted in compliance with regulations for Good Clinical Practice. Each of 30 participating sites received institutional review board approval, and all patients or their authorized representatives gave informed consent. A second arm of the study was a contemporaneous control group consisting of patients enrolled in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) who received a commercially available LVAD as a BTT. The results of the BTT trial were submitted to the FDA as part of the premarketing approval in December 2010. A CAP for the BTT indication was approved by the FDA, yielding 242 additional clinical trial patients enrolled until final FDA approval of the BTT indication in November 2012. In the present analysis, we present data on the entire 382-patient cohort from the final clinical database, which was locked in June 2013.

DEFINITIONS. All serious adverse events and those meeting the INTERMACS definitions were evaluated. All CVAs were adjudicated by the trial clinical events committee. The diagnosis of CVA was confirmed by any new, permanent, focal, or global neurological deficit ascertained by a standard neurological examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests (e.g., computed tomography scan) and consultation notes. These were further defined as ischemic cerebrovascular accidents (ICVAs) or HCVAs. Localization was based on clinical narratives and findings from computerized tomography scans. Scores on the modified Rankin scale (23) were recorded at the time of the neurological event and at 4 and/or 8 weeks' post-event.

STATISTICAL ANALYSIS. Survival was expressed by using the Kaplan-Meier method and through the

ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplant

CAP = continued access protocol

CVA = cerebrovascular accident

FDA = U.S. Food and Drug Administration

EPPY = events per patient-year

HCVA = hemorrhagic cerebrovascular accident

HR = hazard ratio

HVAD = HeartWare ventricular assist device

IBPM = improved blood pressure management

ICVA = ischemic cerebrovascular accident

INR = international normalized ratio

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support

LVAD = left ventricular assist device

MAP = mean arterial pressure

TTR = time in therapeutic range

VAD = ventricular assist device

Thoratec Inc. Dr. Goldstein has served on the Medical Advisory Board for Thoratec Inc. and HeartWare Inc.; has received payment as a surgical proctor for HeartWare Inc.; and has served as a consultant for Medtronic Inc. Dr. Starling has served as a steering committee member for the HeartWare MVAD trial. Dr. Malik has received funds for travel to a HeartWare Cardiology Scientific Advisory Meeting and Users Meeting; and has served as a consultant for HeartWare Inc. Drs. Silvestry and Jorde have served as consultants for HeartWare Inc. and Thoratec Inc. Dr. Naka has served as a consultant for Thoratec Inc., Biomet, and Medtronic; and as a member of the study steering committee for Transmedics Inc. Dr. Birks' spouse owns stock in HeartWare Inc. Mr. Najarian is an employee of and owns stock in HeartWare Inc. Dr. Hathaway is a former employee and has received consultant fees from HeartWare Inc. Drs. Aaronson and Pagani have received institutional research grant support from HeartWare Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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estimated hazard ratio (HR) from a Cox proportional hazards regression. Follow-up was censored at the time of heart transplantation, device explant for recovery, withdrawal of consent, or loss to follow-up. Descriptive statistics were used to evaluate prevalence and event rates as well as changes from baseline in clinical markers and adverse events. Both the percentage of subjects affected and the rate per subject-year of follow-up are reported. Descriptive statistics were used for the other secondary endpoints and for safety measures.

A multivariate analysis was conducted to determine if there were modifiable risk factors for stroke. Ischemic strokes occurring in the first 48 h after device implantation were thus classified as procedure related and were excluded from the multivariable analysis. Also excluded from the multivariate analysis of risk factors were HCVAs that were considered iatrogenic (due to use of thrombolytic agents with or without intravenous glycoprotein IIb/IIIa inhibitors for the treatment of VAD thrombus) and subdural hematomas associated with head trauma because these events had a clinically identified causality.

A total of 77 dichotomous covariates were considered as potential risk factors. The following variables were included in the model: age; etiology; BTT or CAP study; left ventricular apical wall thickness; aspirin dosage; baseline cardiac index; body mass index; body surface area; sex; history of atrial fibrillation, atrial flutter, diabetes, hypertension, stroke or transient ischemic attack, ventricular fibrillation, or ventricular tachycardia; prior sternotomy; mechanical ventilation; intra-aortic balloon pump; international normalized ratio (INR) values at event and at discharge; percent time in therapeutic range (TTR); prior infection within 7, 10, 14, or 30 days; sepsis before the event; cardiac arrhythmia within 7, 14, or 30 days prior; supraventricular arrhythmia before the event; venous thromboembolism within 7, 14, or 30 days prior; arterial thromboembolism within 7, 14, or 30 days prior; cardiac tamponade within 7, 14, or 30 days prior; bleeding within 7, 14, or 30 days prior; mean arterial pressure (MAP) on or before the event; MAP before the event; MAP within 7 days before the event; systolic blood pressure before the event or within 7 days; INTERMACS patient profile; New York Heart Association class; pump flow at baseline or at event; pump flow index (per body surface area); pump power at baseline; pump speed at baseline or at event; race; and use of a sintered pump.

The median values of continuous variables were used for assessment in a dichotomous manner. Each covariate was assessed independently as a predictor by using univariable analysis, and covariate influence was measured with odds ratios and accompanying p values by using the Cochran-Mantel-Haenszel test. To analyze the data related to warfarin, the method of Rosendaal et al. (24) was used to calculate the percent TTR or the overall time that INR values remained within the therapeutic range of 2.0 to 3.0. The INR within 24 h of a reported event was also reviewed. The aspirin dosage was examined by evaluating the dosage reported closest to, but within 7 days before, the event, compared with the mean overall aspirin dose in those patients without a CVA. MAP was examined as a continuous variable in patients with and without strokes, as well as the mean of all measures within 1 week of a stroke, both including and excluding the day of the event, compared with the mean overall MAP in patients without stroke events. Covariate reduction was performed on the basis of the univariable analysis results, using a p value limit of <0.15, as well as the impact of potential multicollinearity. The remaining covariate terms were modeled parametrically by using a logistic regression analysis.

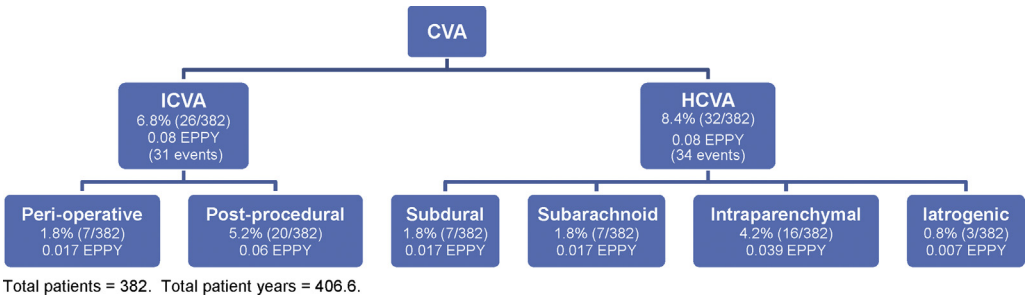
Given the impact of blood pressure on outcomes, a post-hoc review of sites' blood pressure management strategies was performed by using site surveys and interviews. Sites were then separated into those that used strict monitoring, treatment, and long-term management protocols for hypertension (e.g., improved blood pressure management [IBPM]) versus those sites that did not have an established systematic approach to blood pressure management. An analysis of events occurring at sites with and without IBPM protocols was performed.

A site was considered to have IBPM protocols if they: 1) set strict limits for MAP maintenance, not to exceed 90 to 100 mm Hg; 2) used a progressive, incremental blood pressure-driven antihypertensive therapy protocol; and 3) maintained close surveillance of blood pressure weekly or more often via home monitoring and telephone or clinic visits until MAP was under control. Monitoring was accomplished with home monitoring, which included a blood pressure cuff or combination of a cuff and Doppler probe, the use of a referring physician for MAP monitoring, and/or a nurse practitioner who recorded all MAP findings and followed up patients with hypertension.

RESULTS

A total of 382 patients were included in the study. As shown in **Figure 1**, the overall prevalence of ICVA was 6.8% (26 of 382); for HCVA, it was 8.4% (32 of 382). Seven patients experienced periprocedural (within

FIGURE 1 Breakdown of Strokes Occurring in BTT + CAP



BTT = bridge to transport; CAP = continued access protocol; CVA = cerebrovascular accident; EPPY = events per patient-year; ICVA = ischemic cerebrovascular accident; HCVA = hemorrhagic cerebrovascular accident.

48 h after implantation) ICVAs (1.8%), and 20 patients (5.2%) had 24 nonprocedural ICVAs (1 patient had a periprocedural event as well as a later ICVA). Of the 4 patients who experienced a second ICVA, 3 fully recovered from both events, and 1 patient died 1 month after the second ICVA 3 months after his first event. In addition, 2 patients experienced a second HCVA; 1 patient died after a second HCVA occurring 1 year after his first event, and a second patient had 2 HCVAs after falls (1 subdural and 1 subarachnoid) occurring >5 months apart, eventually fully recovering. Of the 34 HCVAs, 7 were subdural hematomas, and 7 were subarachnoid hemorrhages. Two of the 7 subdural bleeding events occurred as a direct result of a fall with head trauma. Three HCVAs were considered iatrogenic, occurring within days of treatment with a lytic agent (e.g., tissue plasminogen activator) for a VAD thrombus or hemolysis event (Table 1). One HCVA had an undefined location/origin.

The ICVAs were equally distributed on both the right (10 events) and left (9 events) hemispheres, whereas 1 was diffuse/bilateral. HCVAs primarily occurred in the right hemisphere (18 events), with 5 events on the left. There were 4 bilateral/diffuse HCVAs. Three events (1 ICVA and 2 HCVAs) were located in the pontine/posterior fossa, whereas 4 events (3 ICVAs and 1 HCVA) were unknown/not recorded. Finally, 7 of 28 HCVAs involved a midline shift, and 6 of those were suspected as a hemorrhagic conversion.

A comparison of baseline demographic characteristics and other characteristics of patients with and without a CVA revealed no significant differences between those with ICVA or HCVA versus those who were stroke free (Table 1).

Survival at 6 months in patients after an ICVA was similar to those without a stroke (91% vs. 93%, respectively; $p = 0.82$). Conversely, those patients with an HCVA had significantly worse 6-month survival (72% vs. 93%; $p < 0.0001$) (Figure 2). Complete functional recovery, defined as a score of 0 on the modified Rankin scale, occurred in 55% (11 of 20) of patients with ICVAs but in only 15% (5 of 34) of patients with HCVAs. Furthermore, 63% (15 of 24) of all ICVA events were nondisabling (defined as a score of ≤2 on the modified Rankin scale) compared with 26.5% (9 of 34) of HCVAs. The 1- and 2-year freedom from any ICVA was 93.2% and 88.3%, and the 1- and 2-year freedom from any HCVA was 90.4% and 86.4% (Figure 3).

In mid-2011, several HVAD design changes were introduced in an effort to reduce the rate of VAD thrombus; these changes included introduction of a larger-diameter coring tool to reduce apical tissue puckering at the device insertion site and texturing (sintered titanium beads) of a segment of the pump inflow cannula intended to promote tissue ingrowth and enhance healing. In addition, anticoagulation recommendations were reinforced at an investigator meeting in March 2011 to achieve a target INR of 2.0 to 3.0 and to administer higher aspirin dosage (325 mg daily). These design enhancements and changes in anticoagulation led to a decrease in pump thrombus events requiring an exchange (18). When periprocedural ICVAs were excluded, these changes resulted in a nonsignificant reduction in the prevalence of ICVA from 6.3% (17 of 272) to 2.7% (3 of 110; $p = 0.21$) and no significant decrease in the rate of ICVA (0.06 vs. 0.05 event per patient-year [EPPY]; $p = NS$). These changes did not significantly affect

TABLE 1 Baseline Demographic and Clinical Characteristics: No CVA, ICVA, and HCVA

	No CVA (n = 324)	ICVA (n = 26)	p Value*	HCVA (n = 32)	p Value*
Age, yrs	52.9 ± 11.6	57.1 ± 11.4	0.08	53.4 ± 12.4	0.82
Male	72.2	57.7	0.12	71.9	>0.99
Race			0.49		>0.99
White	67.0	84.6		68.8	
Black/African American	26.9	15.4		28.1	
Other	6.1	0.0		3.1	
Body mass index, kg/m^2	28.1 ± 6.0	27.4 ± 5.9	0.60	29.9 ± 6.6	0.10
Body surface area, m^2	2.00 ± 0.29	1.90 ± 0.33	0.051	2.10 ± 0.35	0.30
Ischemic cause of heart failure	38.5	30.8	0.53	37.5	>0.99
Left ventricular ejection fraction	17.1 ± 7.3	18.3 ± 7.5	0.44	18.1 ± 6.9	0.47
Arterial blood pressure, mm Hg					
Systolic	103 ± 16	109 ± 12	0.12	103 ± 14	0.74
Diastolic	63 ± 10	68 ± 11	0.07	62 ± 11	0.56
Mean	77 ± 11	82 ± 10	012	78 ± 12	0.89
Cardiac index, l/min/m^2	2.1 ± 0.5	2.3 ± 0.5	0.50	2.3 ± 0.5	0.33
Pulmonary artery pressure, mm Hg					
Systolic	49 ± 15	46 ± 15	0.47	51 ± 12	0.60
Diastolic	24 ± 9	23 ± 7	0.57	23 ± 7	0.33
NYHA functional class			0.21		0.68
I	0	0		0	
II	0.3	3.8		0	
III	4.0	0.0		0	
IV	95.4	96.2		100	
INTERMACS profile level			0.73		0.82
1	6.4	0		0	
2	33.3	42.3		43.8	
3	41.0	38.5		40.6	
4–7	19.3	19.2		15.6	
Medical history					
Smoker	52.3	53.8	>0.99	50.0	0.85
Diabetic	33.3	38.5	0.67	50.0	0.08
Arrhythmia	71.9	65.4	0.50	78.1	0.54
Stroke/TIA	10.1	7.7	>0.99	15.6	0.36
Cancer	5.2	7.7	0.64	6.3	0.68
Hypertension (requiring medication)	60.2	50.0	0.31	56.3	0.71
IABP	32.4	23.1	0.39	40.6	0.43
BUN, mmol/l	8.8 ± 5.1	9.2 ± 5.5	0.69	10.6 ± 5.3	0.06
LDH, U/l	315 ± 188	316 ± 198	0.99	349 ± 194	0.37
Creatinine, mg/dl	1.30 ± 0.38	1.10 ± 0.38	0.12	1.40 ± 0.42	0.27

Values are mean ± SD or %. Data are stratified according to the occurrence of any cerebrovascular accident (CVA). Significance testing was performed by using the Fisher exact test for categorical data and a 2-sample *t* test for quantitative data. *P values are for the comparison of the patients with either an ischemic cerebrovascular accident (ICVA) or hemorrhagic cerebrovascular accident (HCVA) versus patients with no CVAs.

BUN = blood urea nitrogen; IABP = intra-aortic balloon pump; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LDH = lactate dehydrogenase; NYHA = New York Heart Association; TIA = transient ischemic attack.

the prevalence of HVCAs unrelated to either falls or use of thrombolytic agents (7.4% [20 of 272] vs. 6.4% [7 of 110]; p = 0.69) or the rate of HCVAs (0.06 vs. 0.09 EPPY; p = NS) (Table 2).

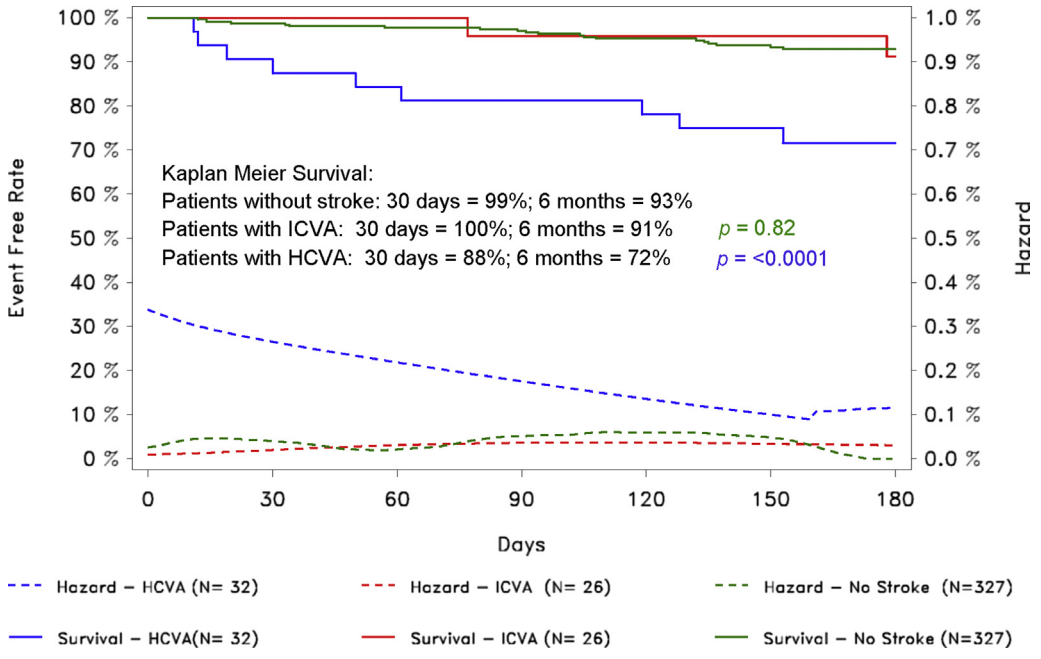
A univariable analysis was performed to identify variables for evaluation in a multivariable risk model to determine if there were modifiable risk factors for either ICVA or HCVA that excluded periprocedural ICVAs (n = 7) and HCVAs associated with a fall (n = 3) or thrombolytic agents (n = 3). Starting with >50 pre-implantation and post-implantation variables, the univariable model yielded 7 model candidates for developing an ICVA and 7 candidate factors significant for developing an HCVA (Table 2). ICVA factors from the univariable model with a p value <0.10 included age >56 years, race (white), history of atrial fibrillation, aspirin dosage ≤81 mg (7 days before the event), MAP >90 mm Hg (before event), flow ≤5.1 l/min, and baseline cardiac index >2.1 l/min/m^2. HCVA risk factors with a p value <0.10 included body mass index >27.6 kg/m^2, aspirin dosage ≤81 mg (7 days before the event), INR >3.0, MAP >90 mm Hg (average of measures over 7 days before the event [including day of event]), pump speed >2,750 or ≤2,750 rpm, intra-aortic balloon pump, and TTR ≤40%. These candidate factors were then entered into the multivariable model for determination of independent risk factors for developing strokes. As shown in Figure 4A, multivariable predictors of ICVA were aspirin ≤81 mg (HR: 7.1) and atrial fibrillation (HR: 2.9). As shown in Figure 4B, the multivariate predictors for HCVA were MAP >90 mm Hg (HR: 9.9), aspirin ≤81 mg (HR: 6.8), and INR >3.0 (HR: 5.1). Significant predictors with a p value <0.10 in the univariable model but that fell out of the multivariable model included a TTR ≤40% and pump speed >2,750 rpm.

The overall MAP of patients without any stroke (81.4 ± 5.93 mm Hg) compared with MAP at the time of an ICVA (83.1 ± 9.71 mm Hg) and MAP at the time of an HCVA (86.1 ± 17.92 mm Hg) were not significantly different (according to the Wilcoxon rank sum test) with p values of 0.49 and 0.39, respectively. A survey of blood pressure management practices at the 30 enrolling sites showed that 8 had established IBPM protocols. The occurrence of MAP measures >100 mm Hg at IBPM sites was less frequent compared with non-IBPM sites (Figure 5).

At those sites with IBPM protocols, there was also a significant reduction in the prevalence of HCVAs (9.3% vs. 1.8%; p = 0.003) and a trend for a reduction in HCVA rates (0.08 vs. 0.02 EPPY; p = 0.072). However, the prevalence of ICVA in those with and without IBPM was similar at 5.3% (6 of 114) versus 5.2% (14 of 268; p = 0.99), as was the rate (0.05 vs. 0.08 EPPY; p = NS) (Table 3). Both HCVAs (3.0% at 0.04 EPPY) and ICVAs (0% at 0.00 EPPY) were infrequent in 33 patients at IBPM sites after the design modifications.

Although there was no difference in the baseline incidence of hypertension in patients with and without stroke, given the data observed in the

FIGURE 2 Kaplan-Meier Survival Curve of Patients With and Without Any CVA



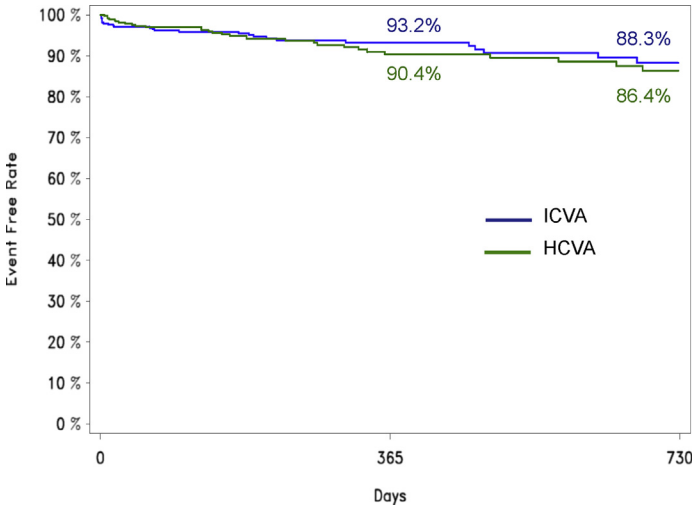
Survival in patients who had either an ischemic **(red)** or hemorrhagic **(blue)** stroke was compared with patients who did not experience a stroke **(green)** event **(solid lines)**. The p values represent the comparison according to the log-rank test of the ICVA or HCVA survivals versus survival in those patients not experiencing a stroke event. The **dashed lines** indicate the hazard over time in each of the respective cohorts. Abbreviations as in Figure 1.

multivariable analysis and the sites with IBPM, we further evaluated the mean MAP for patients with and without a history of hypertension. Those with a history of hypertension had a mean MAP of 82.2 ± 5.96 mm Hg (n = 228) versus 80.3 ± 5.59 mm Hg (n = 153) for those with no history of hypertension. This difference was statistically significant (p = 0.0016).

DISCUSSION

Stroke is arguably one of the most devastating adverse events associated with mechanical circulatory support. The addition of a complex blood-mechanical surface interface into the prothrombotic milieu of heart failure and the requisite use of potent anticoagulant agents and antiplatelet therapies highlights the challenges faced by multidisciplinary teams managing these patients. To the best of our knowledge, the present study is the first comprehensive analysis of neurological injury in patients supported with the HeartWare HVAD. In a group of 382 patients undergoing BTT, the overall prevalence of ischemic stroke and hemorrhagic stroke was 6.8%

FIGURE 3 Kaplan-Meier Freedom From Any ICVAs and HCVAs



Freedom from occurrence of either an ICVA **(blue line)** or HCVA **(green line)** over 2 years was analyzed by using Kaplan-Meier methods. Abbreviations as in Figure 2.

TABLE 2 Univariable Predictors of Strokes

	Risk	p Value
ICVA univariable factor		
Aspirin (7 days before the event)	≤81 mg	<0.0001
MAP (before event)	>90 mm Hg	0.0012
History of atrial fibrillation	Yes	0.0145
Age	>56 yrs	0.0227
Race	White	0.0409
Baseline cardiac index	>2.1 l/min/m^2	0.0558
Flow	≤5.1 l/min	0.1038
HCVA univariable factor		
Aspirin (7 days before the event)	≤81 mg	<0.0001
MAP (7 days before the event, including day of event)	>90 mm Hg	<0.0001
Pump speed	>2,750 rpm	0.0089
TTR using the Rosendaal method	≤40%	0.0383
INR	>3.0	0.0388
BMI	>27.6 kg/m^2	0.1162
IABP	Yes	0.1181

A univariable analysis was performed to identify significant variables for evaluation in a multivariable risk model to determine risk factors for either ICVA or HCVA. ICVA patients experiencing a procedural event (within ≤48 h of implantation, n = 7) and patients with HCVAs that were either iatrogenic (n = 3) or the result of a fall (n = 2 patients with 3 events) were excluded.

BMI = body mass index; INR = international normalized ratio; MAP = mean arterial pressure; TTR = time in therapeutic range; other abbreviations as in Table 1.

and 8.4%, respectively. The 6-month survival for those with an ICVA was similar to those who did not have a CVA (91% vs. 93%; p = 0.51). Conversely, hemorrhagic stroke was associated with significantly worse survival (72% vs. 93%; p < 0.0001) and a greater burden of residual neurological dysfunction. Pre-implantation patient characteristics, laboratory values, hemodynamics, and INTERMACS profiles were not useful predictive markers of stroke risk or type (ICVA or HCVA). Multivariate modeling showed that low aspirin dosage and atrial fibrillation were independent risk factors for ICVA, whereas hypertension, low aspirin dosage, and INR >3.0 were risk factors for HCVA. Importantly, changes in HVAD design and patient management strategies that were focused on blood pressure control and intensified anticoagulation that were implemented during the conduct of the trial significantly reduced the overall stroke rate by exclusively decreasing the prevalence of HCVA.

Somewhat counterintuitively, a low aspirin dosage was also a risk factor for HCVA. One possible explanation may be that these HCVAs were preceded by an ICVA that then underwent hemorrhagic conversion. This hypothesis seems reasonable considering the preponderance of right-sided strokes found in this analysis. Kim et al. (25) reported that right hemispheric infarctions are associated with cardiogenic embolism, whereas left hemispheric infarctions are associated more with emboli originating in the aorta. In addition, we noted that 7 of 28 HCVAs involved a midline shift, and 6 of those were suspected as a conversion. Okada et al. (26) described a tendency for large infarctions and those that caused midline shift to be more frequently associated with hemorrhagic conversion. Cardiogenic emboli typically flow to the right brain via the innominate artery. Kim et al. also described a propensity of aortic plaques in their patients with right-sided strokes and noted that this outcome was likely due to aortic flow turbulence resulting in a backward flow in the aorta and into the right hemisphere. The placement of the outflow graft along the descending aorta to the aortic arch and consequent influence on complex flow patterns and potential thrombogenesis have also been described in the setting of continuous flow VADs (27).

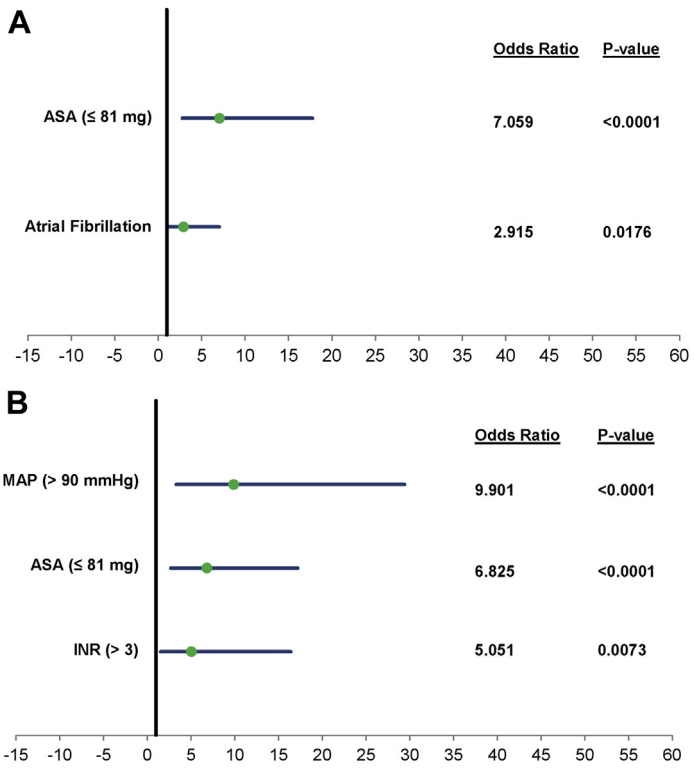
Current-generation LVADs have improved survival outcomes and reduced major adverse events, including stroke. However, the persistent risk of stroke as well as its impact on survival, functionality, and quality of life remain a target for intervention. Freedom from stroke in >5,000 continuous flow LVAD patients registered in INTERMACS was 93% at 6 months and 89% at 12 months (14), which is similar to the rates we report. In an 18-month follow-up of 281 HeartMate II BTT patients, the rate of ICVA was 0.09 EPPY and HCVA was 0.05 EPPY during 181.8 patient-years of support (17).

The etiology of stroke in LVAD patients is multifactorial, and no single intervention can completely abrogate the risk of stroke. Although the LVAD itself confers risk, some of the stroke risk can be attributed to patient characteristics. The Framingham Heart Failure Study reported that in patients with heart failure, there was a statistically significant 4-fold excess in strokes compared with subjects without cardiac disease (28). In patients with atrial fibrillation, the risk of stroke increased with age, ranging from 1.5% in the 50- to 59-year-old age group to 9.9% in the 70- to 79-year-old age group. However, the greatest attributable risk of stroke, independent of age, occurred in patients with hypertension, with an attributable risk of approximately 50% (25). Interestingly, we found no association between pre-implantation patient characteristics and stroke risk, suggesting that the patient-VAD interface as well as post-implantation comorbidities and management are drivers of this adverse event rather than patient selection. The multivariable analysis further showed that aspirin

dosage and anticoagulation play an important role in preventing ICVAs. The presence of atrial fibrillation was also predictive of ischemic strokes. In fact, atrial fibrillation has previously been shown to be an independent risk factor for strokes (28). Early clinical experience with continuous axial flow LVADs suggested that texturing (e.g., sintering) worked best in areas of high, unobstructed flow, such as the inflow cannula (29). The addition of sintering, a larger coring tool, and improved anticoagulation reduced the incidence of ICVAs. Despite this more robust anticoagulation and antiplatelet therapy, there was no increase in HCVAs. Bleeding events in general were also similar, in that 51% (93 of 181) of patients who were more frequently out of therapeutic range (i.e., with a TTR ≤45%) had bleeding events compared with 45% (85 of 191) of patients with a TTR >45%.

We observed that the strongest predictor of HCVAs was elevated MAP. This finding is not surprising because elevated blood pressure has been identified as a major risk factor for HCVA in the general population. A survey of study sites revealed a subset of sites that had procedures in place that ensured attentive monitoring and management of blood pressure in patients with VAD. A review of the HCVA prevalence and rates among sites with IBPM strategies demonstrated a significant reduction in the prevalence of HCVAs (8.4% vs. 2.6%; p = 0.037). Common practices among these sites included: having a targeted MAP of 90 mm Hg; the utilization of a progressive, pressure-driven drug therapy protocol; and close surveillance of blood pressure (weekly or more often) via home monitoring and telephone or clinic visits until MAP was under control. Blood pressure measurement can be challenging in patients with continuous flow LVADs secondary to markedly reduced pulse pressure. Monitoring was accomplished by using either a cuff or Doppler probe, and local physicians were intermittently engaged in blood pressure management. Although blood pressure in patients with a continuous flow device can be measured accurately with a regular blood pressure cuff, it has been shown that the success rate for obtaining a measurement is much higher when a Doppler probe is used (30). Regardless of the method of determining blood pressure, the measured pressures have been correlated to the systolic blood pressure, which in a low pulsatility setting closely approximates the MAP. It is noteworthy that Lampert et al. (31) recently reported the feasibility and effectiveness of an aggressive outpatient blood pressure regimen in patients with continuous flow LVADs.

FIGURE 4 Forest Plots of Multivariable Risk Factors

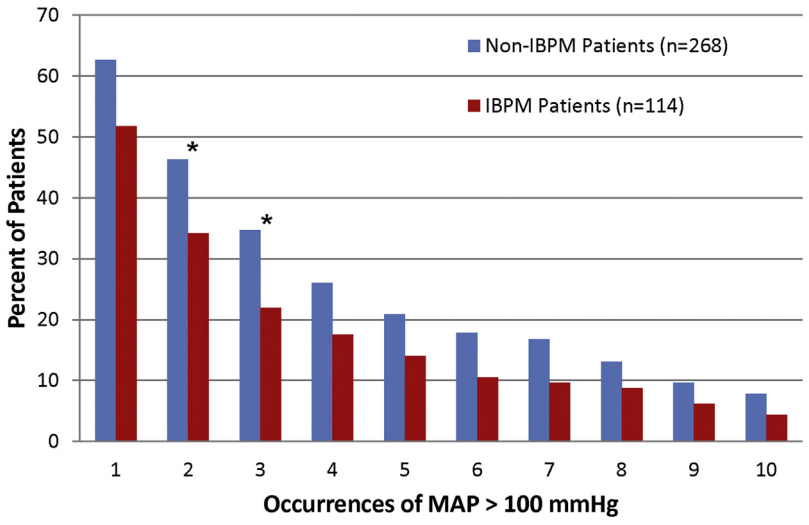


Forest plots are presented illustrating the hazard ratios and relative influence of the top risk factors emerging from the multivariate analysis. The hazard ratio is indicated by the **dot**, and the **lines** represent 95% confidence intervals. **(A)** Forest plot of multivariable ICVA events, and **(B)** Forest plot of multivariable HCVA risk factors. ASA = aspirin; INR = international normalized ratio; MAP = mean arterial pressure; other abbreviations as in Figure 2.

The major risk factors for stroke derived from the present analysis were blood pressure, antiplatelet therapy, and intensity of anticoagulation. Fortunately, these risk factors are amenable to relatively straightforward changes to patient management, many of which have already become a standard part of numerous programs' post-LVAD protocols. The impact of these management practices is being prospectively assessed as a part of the ongoing HVAD destination therapy trial.

STUDY LIMITATIONS. This study included patients who received a HeartWare HVAD as a part of the BTT trial as well as the subsequent CAP. There were strict inclusion and exclusion criteria, patient's charts were audited, and a clinical events committee adjudicated all neurological adverse events. Because the design of the trial did not allow similar scrutiny of the control population, direct comparison of

FIGURE 5 Occurrences of MAP Measurements >100 mm Hg



Histogram showing the number of elevated mean arterial pressure (MAP) measurements in patients at sites with improved blood pressure management (IBPM) protocols versus non-IBPM sites. *Statistically significant comparisons.

neurological event rates may not be reliable. The BTT patient cohort included in this trial is not necessarily reflective of the larger destination therapy LVAD population, which is older and has a higher comorbidity burden. Thus, it is reasonable to anticipate that the stroke rate may be higher in these patients. Finally, blood pressure management was not prescribed as part of the trial, but patients who were included in the improved blood pressure control group had similar methods for assessing and treating blood pressure. However, blood pressure measurements can vary when measured by Doppler probe compared with a cuff as well as the subsequent determination of MAP. Although blood pressure was the strongest predictor of HCVA and those who were managed with IBPM had the lowest rates of HCVA, the impact of such protocols awaits prospective validation in ongoing clinical trials with the HVAD.

CONCLUSIONS

The use of HVAD as a BTT was associated with excellent outcomes and long-term survival. However, stroke after HVAD implantation remains a significant cause of morbidity and mortality and limits the overall effectiveness of the therapy. Nearly 10% of patients will experience either an ischemic or

TABLE 3 Effects of Improved Blood Pressure Management and Design Modifications on the Rate of CVA

	All HVAD (N = 382; (PY = 406.62)	Pre-Design Modifications (n = 272; PY = 330.07)	Post-Design Modifications (n = 110; PY = 76.55)	Non-IBPM HVAD (n = 268; PY = 316.64)	IBPM HVAD (n = 114; PY = 89.98)	Design Modifications + IBPM HVAD (n = 33; PY = 22.98)
ICVA						
No. (%) of patients	20 (5.2)	17 (6.3)	3 (2.7)	14 (5.2)	6 (5.3)	0
No. of events (EPPY)	24 (0.06)	20 (0.06)	4 (0.05)	17 (0.05)	7 (0.08)	0
HCVA						
No. (%) of patients	27 (7.1)	20 (7.4)	7 (6.4)	25 (9.3)	2 (1.8)*	1 (3.0)
No. of events (EPPY)	28 (0.07)	21 (0.06)	7 (0.09)	26 (0.08)	2 (0.02)†	1 (0.04)

ICVA patients having a procedural event (≤48 h of implantation, n = 7) and HCVAs that were either iatrogenic (n = 3) or the result of a fall (n = 2 patients with 3 events) were excluded.
*Indicates statistically significant difference between non-improved blood pressure management (IBPM) and IBPM, p = 0.008. †Indicates a trend from non-IBPM to IBPM, p = 0.056.
EPPY = events per patient-year; HVAD = HeartWare ventricular assist device; PY = patient-year; other abbreviations as in Table 1.

hemorrhagic stroke during the first year of HVAD support. Patients with hemorrhagic stroke have a greater degree of residual neurological deficit and mortality than those with an ischemic stroke. Although no pre-implantation variable was associated with stroke, low dosages of aspirin were associated with both hemorrhagic and ischemic stroke, and the presence of systemic hypertension was a predictor of hemorrhagic stroke. Focused programmatic efforts to lower MAP to <90 mm Hg seem to be associated with lower stroke rates. When combined with subtle changes in implantation technique and device design, maintaining blood pressure in the desired range was associated with fewer hemorrhagic strokes. Further validation of these principles is currently being prospectively tested in a randomized clinical study with pre-specified care incorporating these management practices.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Careful attention to antiplatelet therapy dosing, maintaining therapeutic anticoagulation and monitoring, and treating blood pressure for patients on a centrifugal flow LVAD were associated with lower rates of neurological adverse events.

TRANSLATIONAL OUTLOOK: The association between intensive blood pressure monitoring and control on the rates of neurological adverse events is currently being assessed in a prospective manner as part of the ongoing destination therapy trial for the HVAD.

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