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Clinical Investigation

Risk Factors for Development of Stroke in Patients With Continuous-Flow Left Ventricular Assist Device Support as Destination Therapy

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Abstract

Background: Continuous-flow left ventricular assist devices (LVADs) are increasingly used as destination therapy. Although postimplantation stroke rates have been described in the context of bridge-to-transplant or mixed cohorts, stroke development is not well evaluated in patients who receive continuous-flow LVAD with a destination therapy indication. This report characterizes the stroke profile of a modern institutional cohort of patients undergoing destination therapy and evaluates their risk factors for stroke onset.

Methods: Patients implanted with continuous-flow LVAD as destination therapy at the reporting institution between January 2010 and June 2020 were retrospectively reviewed and analyzed. Stroke was defined as any neurologic deficit caused by an abrupt disruption in cerebral blood flow that did not resolve within 24 hours and that was confirmed by imaging. Terminal outcomes of stroke development and death were assessed using a competing-risks model. Fine-Gray regression was used to evaluate potential predictors of stroke development.

Results: Patients who received continuous-flow LVAD (N = 311) were classified by device type: HeartMate II (Abbott; n = 97); HeartMate 3 (Abbott; n = 72); and HeartWare Ventricular Assist Device (Medtronic; n = 42). Thirty-five percent of patients (110/311) developed postoperative atrial fibrillation (AF). Estimated stroke incidence was 15% at 1 year, 24% at 3 years, and 27% at 5 years. According to multivariable Fine-Gray regression, receiving a HeartMate 3 device (subdistribution hazard ratio [HR], 0.41 [95% CI, 0.19-0.90]; P = .03) and amiodarone at discharge (HR, 0.55 [95% CI, 0.33-0.94]; P = .03) were associated with lower stroke risk. Postoperative AF (HR, 1.68 [95% CI, 1.03-2.73]; P = .04) was associated with increased stroke risk.

Conclusion: The HeartMate 3 was associated with decreased stroke rates, but risk remained high for patients who developed postoperative AF. Further investigation into protective strategies and use of amiodarone to treat AF after continuous-flow LVAD implantation is needed.

Keywords: Heart-assist devices; atrial fibrillation; stroke; heart failure

Introduction

Durable mechanical circulatory support with continuous-flow left ventricular assist devices (LVADs) has become an increasingly valuable therapeutic strategy for providing hemodynamic support for patients with end-stage heart failure. Continuous-flow LVADs have replaced the previous generation of pulsatile LVADs in clinical practice because of their associated prolonged survival rate and lower burden of adverse events.[1,2]

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Indications for continuous-flow LVAD support include bridge to orthotopic heart transplant for transplantation candidates and destination therapy for patients who do not qualify for transplantation. Following the 2018 US donor heart allocation score change[3] and given the scarcity of donor hearts for transplantation, destination therapy has become the most popular indication for continuous-flow LVAD implantation. Before the score change in October 2018, approximately 49% of continuous-flow LVAD recipients had an indication for bridge to transplant (BTT) and 50% had an indication for destination therapy. Following the guideline change, a minority of patients were implanted with the procedure indicated as BTT, while 70% were implanted with the procedure indicated as destination therapy.[3,4] Differences in clinical context and baseline characteristics between patients selected for the BTT and destination therapy pathways inform their respective implantation indications, leading to distinct clinical courses and subsequently variable outcomes.[5-8] Although much of the literature on continuous-flow LVADs has evaluated patients with indications for BTT and destination therapy together, these baseline distinctions between cohorts confirm the need to evaluate them separately.

Despite the major therapeutic benefits of continuous-flow LVADs, the devices are not without complications associated with hemocompatibility, including stroke, thrombosis, and bleeding, as well as those not associated with hemocompatibility, such as arrhythmias, infection, and right ventricular failure.[9-12] Stroke remains one of the leading complications associated with continuous-flow LVAD implantation, with a reported incidence of up to 28.7%.[13-17] Clinical trials of continuous-flow LVADs, including destination therapy–only cohorts, report a stroke incidence rate up to 30% depending on the LVAD model, indication type, and patient age group.[18] The HeartMate 3 continuous-flow LVAD (Abbott) has been shown to be superior to the HeartMate II continuous-flow LVAD (Abbott) in terms of postoperative stroke incidence.[19] Risk factors for stroke after continuous-flow LVAD implantation in patients who undergo destination therapy have not, however, been well established. Further, the current literature on the evaluation of postoperative stroke in patients who undergo continuous-flow LVAD with a destination therapy indication has not been thoroughly delineated, especially with respect to other postoperative complications, such as postoperative arrhythmia.

Key Points

- Incidence of developing stroke remains high in continuous-flow LVAD recipients, with a rate of 27% noted at 5 years following implantation.
- The risk of stroke following continuous-flow LVAD implantation for destination therapy remains high in patients who develop POAF.
- The HeartMate 3 device (Abbott Laboratories) and use of amiodarone at discharge are associated with decreased stroke risk.

Abbreviations

BTT, bridge to transplant
CIF, cumulative incidence function
GI, gastrointestinal
HVAD, HeartWare Ventricular Assist Device
LVAD, left ventricular assist device
POAF, postoperative atrial fibrillation

Supplementary Materials

For supplemental materials, please see the online version of this paper

In addition to the stroke risk associated with continuous-flow LVAD, implantation is associated with the development of postoperative atrial tachyarrhythmias. Postoperative atrial fibrillation (POAF) is the most common arrhythmia following cardiac surgery,[20-22] occurring in approximately 35% of patients.[23] Postoperative AF has been well established as an independent predictor of late adverse events, including stroke and transient ischemic attack.[24,25] The association between POAF and stroke has been well documented, yet further investigation is warranted in continuous-flow LVAD cohorts. This study aimed to evaluate the outcomes and competing risk factors for postoperative stroke in patients who underwent continuous-flow LVAD with a destination therapy indication at a single center.

Patients and Methods

This study was approved by the Washington University School of Medicine and Barnes-Jewish Hospital institutional review board. Informed consent and permission for release of information were obtained from all patients. The Interagency Registry for Mechanically Assisted Circulatory Support and the institution's Society of Thoracic Surgeons database were used for

preoperative demographic data, perioperative results, and follow-up for longitudinal complications. Missing data, survival, and additional outcomes were ascertained through chart review.

Patient Population

All patients who had undergone LVAD implantation at the reporting institution between January 2010 and June 2020 were retrospectively evaluated (N = 820). Exclusion criteria were as follows: patients who underwent LVAD implantation for a BTT indication; patients who underwent dual LVAD and right ventricular assist device procedures; patients with multiple LVAD implantation events, with only the most recent surgery maintained; and recipients of isolated right ventricular assist device, HeartMate XVE (Thoratec/St Jude), total artificial heart, or biventricular assist devices. Patients were further classified by the type of LVAD device placed: HeartMate II (Abbott), HeartMate 3 (Abbott), and HeartWare Ventricular Assist Device (HVAD; Medtronic). The approach to LVAD insertion was left to the discretion of the attending physician. The analyzed cohort included 311 patients (Fig. 1).

Management of Perioperative AF: Institutional Protocols

It is not the reporting institution's protocol to treat POAF prophylactically in the preoperative setting. For patients with preoperative AF, β-blocker therapy is reinitiated after the patient has been weaned off inotropic support and remains hemodynamically stable. Home-based amiodarone therapy is initiated at the onset of POAF. With respect to anticoagulation, the institution's written and multidisciplinary approved protocols begin with the administration of aspirin 325 mg on postoperative day 0. Aspirin is continued for life. On postoperative day 1, intravenous heparin is initiated at a flat rate of 750 units per hour. This therapy transitions to administration using an intravenous heparin nomogram begun on postoperative day 2 with concomitant initiation of warfarin 1 mg. The target partial thromboplastin time range while on heparin is 60 to 90 seconds. The patient's warfarin dose is sequentially increased until a target international normalized ratio of 2.0 to 3.0 is reached. Heparin is discontinued once the target international normalized ratio has been reached. Patients with preoperative AF who required oral anticoagulation are converted to intravenous heparin preoperatively.

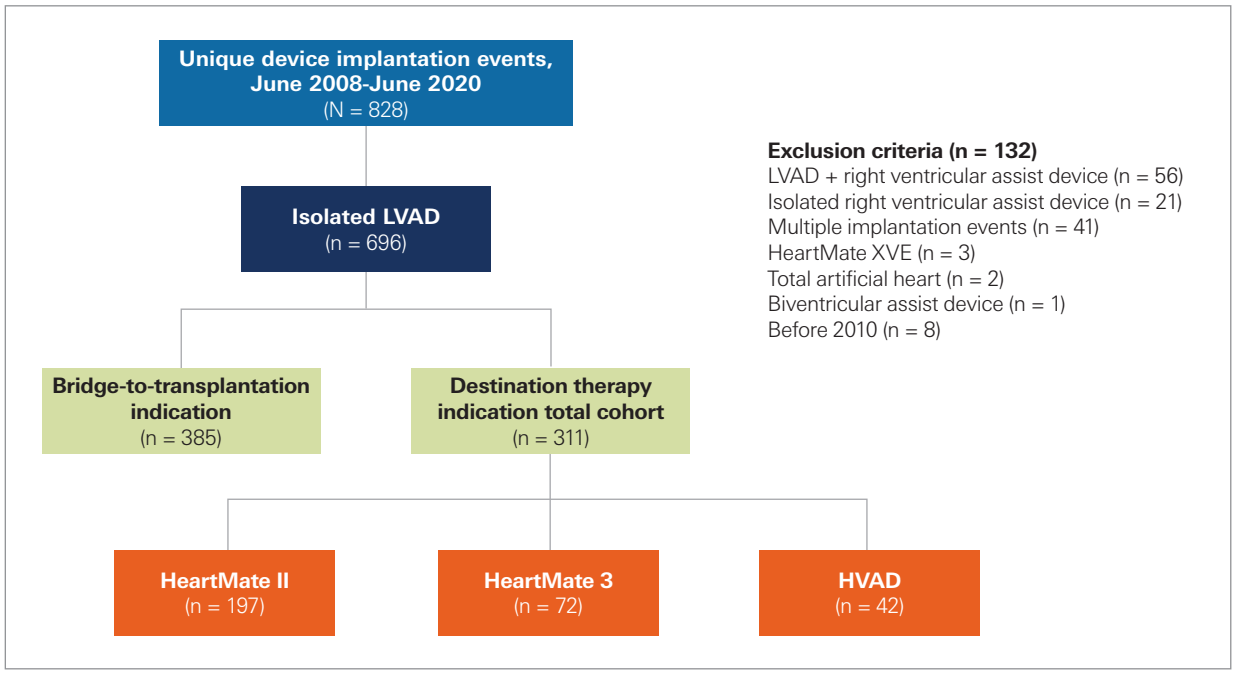

Fig. 1 Consolidated Standards of Reporting Trials diagram demonstrates population selection, exclusion criteria, and classification by LVAD type. Values represented as n = number of patients.
HVAD, HeartWare Ventricular Assist Device; LVAD, left ventricular assist device.

The 2014 American Association for Thoracic Surgery guidelines for management of new-onset POAF suggest the use of intravenous β-blockers, nondihydropyridine calcium channel blockers, digoxin, or amiodarone; nonpharmacologic management includes cardioversion with or without pretreatment with antiarrhythmic drugs.[23,26] Patient charts were reviewed for techniques to manage POAF, including the use of antiarrhythmic drugs and cardioversion. Patients requiring postoperative amiodarone on discharge were evaluated at 1-month and 3-month follow-up. If they were found to be in normal sinus rhythm at these visits, amiodarone was discontinued. If patients remained in AF at their 3-month follow-up, amiodarone was continued for life.

Diagnosis and Treatment of Stroke

Stroke was defined as any new-onset focal or global neurologic deficit determined by standard neurologic evaluation, with deficits lasting beyond 24 hours to distinguish stroke from transient ischemic attack. These findings were confirmed by neurology consult and verified using computed tomography diagnostic imaging. To determine the subtype of the stroke, anatomic and radiologic findings from computed tomographic images and neurology consults were evaluated. Chart review of electronic health records for radiographic imaging, neurology consult service, and follow-up notes were conducted to identify patients who may not have been captured by the national databases used in this study. Treatment of stroke was guided by stroke type: embolic or hemorrhagic. Embolic stroke management modalities included intra-arterial embolectomy and antithrombotic medication. Reversal of coagulopathy has been indicated as treatment for hemorrhagic strokes, with antithrombotic medications resuming within 2 weeks of stroke treatment.[17] Antithrombotic regimens included antiplatelet medication, anticoagulant medication, combination therapies, or more aggressive regimens as indicated.

Statistical Analysis

Continuous variables were expressed as median (IQR) values. The Mann-Whitney *U* test was used to evaluate differences between the 2 groups. Kruskal-Wallis testing was used to evaluate differences among multiple groups, and post hoc Dwass-Steel-Critchlow-Fligner testing was used to adjust statistically significant results for multiple comparisons. Categorical variables were expressed as frequencies and percentages and compared using the χ^2 test. $P < .05$ was considered statistically significant.

The risk of stroke was evaluated using a competing-risks methodology, such that the proportion of patients who developed a stroke during longitudinal follow-up was represented visually by the cumulative incidence function (CIF). Patients were categorized into 1 of 3 mutually exclusive states at each time point. If a patient developed a stroke at any point during the follow-up period, then this was the terminal state, and the patient was classified as part of the stroke cohort. In patients who never developed a stroke during follow-up, the other terminal state was death during follow-up; otherwise, patients were considered to be alive and censored at their last follow-up date. Cumulative incidence functions were generated for the competing risks of death and stroke during the follow-up period. Because the 3 states are mutually exclusive, the probability of remaining alive and free from stroke was equivalent to the probability of not experiencing any of the competing risks and was therefore depicted as a composite Kaplan-Meier estimate. This composite end point was presented alongside the CIFs for each competing risk.

Predictors of stroke were identified using Fine-Gray subdistribution hazards regression. Potential predictors that were deemed clinically relevant based on the judgment of senior authors as well as on prior work indicating their association with the development of postoperative stroke,[14-16,27-30] which had sufficient events per variable, were selected for inclusion in the univariable model to increase the accuracy of the regression coefficients. Forward selection of univariable predictors with $P < .20$ was used to create the final multivariable model. Analysis was performed using SPSS Statistics, version 25 (IBM Corp), and R, version 3.6.3, statistical software using the *cmprsk* package (R Foundation for Statistical Computing) for the competing-risk analysis and graphical output of CIF. SAS OnDemand for Academics (SAS Institute Inc) was used to generate baseline comparisons.

Results

Baseline Characteristics

Over the study period, the majority of recipients were male (n = 246 [79%]) and White (n = 246 [79%]), with a mean (SD) age of 60 (12) years. Patients implanted with a continuous-flow LVAD (n = 311) were classified by the type of device implanted: HeartMate II (n = 97 [63%]), HeartMate 3 (n = 72 [23%]), and HVAD

(n = 42 [14%]). The most common Interagency Registry for Mechanically Assisted Circulatory Support profile for recipients was type 2: progressive decline (n = 196 [63%]). Dilated cardiomyopathy as a result of ischemia (n = 149 [48%]) or idiopathic causes (n = 146 [47%]) were the most common heart failure etiologies. The median (IQR) follow-up time was 1.9 (0.6-3.4) years. In the cohort, 42 patients had clinically significant improvement in functional status, crossed over to a BTT indication, and were subsequently transplanted. Detailed baseline characteristics can be found in Table I and Supplemental Table I.

Perioperative Results

Median (IQR) cardiopulmonary bypass time was 68 (56-89) minutes. The most common postoperative complications were the development of AF (n = 110 [35%]) and gastrointestinal (GI) events, including upper or lower GI bleeding, gastroenteritis, and unspecified GI disorders requiring hospitalization (n = 85 [27%]). The median (IQR) postoperative hospital length of stay was 22 (16-35) days. Thirty-three patients (11%) died within 30 days of their procedure. Comprehensive perioperative outcomes can be found in Table I and Supplemental Table I.

Rhythm Outcomes

A total of 35% (n = 110) of patients developed POAF. Among these patients, 67% (n = 74) developed POAF within the first 2 postoperative days (Fig. 2). New-onset AF, defined as POAF identified in patients who had not been known to have preoperative atrial arrhythmia, was discovered in 21% (n = 64) of patients. The median (IQR) day of POAF onset was postoperative day 2 (1-3). Incidence of POAF did not differ based on LVAD type (P = .61). Of the patients who developed POAF, 85% (n = 94) received amiodarone as treatment, and 20% (n = 22) underwent attempted cardioversion to restore normal sinus rhythm (Table II). One patient had an atrioventricular node ablation with an upgrade to a biventricular implantable cardioverter-defibrillator at an external institution that did not deem the patient a suitable candidate for catheter ablation because of failed amiodarone loading and cardioversion. Other treatment outliers included 6 patients who received lidocaine and 2 patients who received digoxin for medical management of their POAF in addition to amiodarone. Patients who

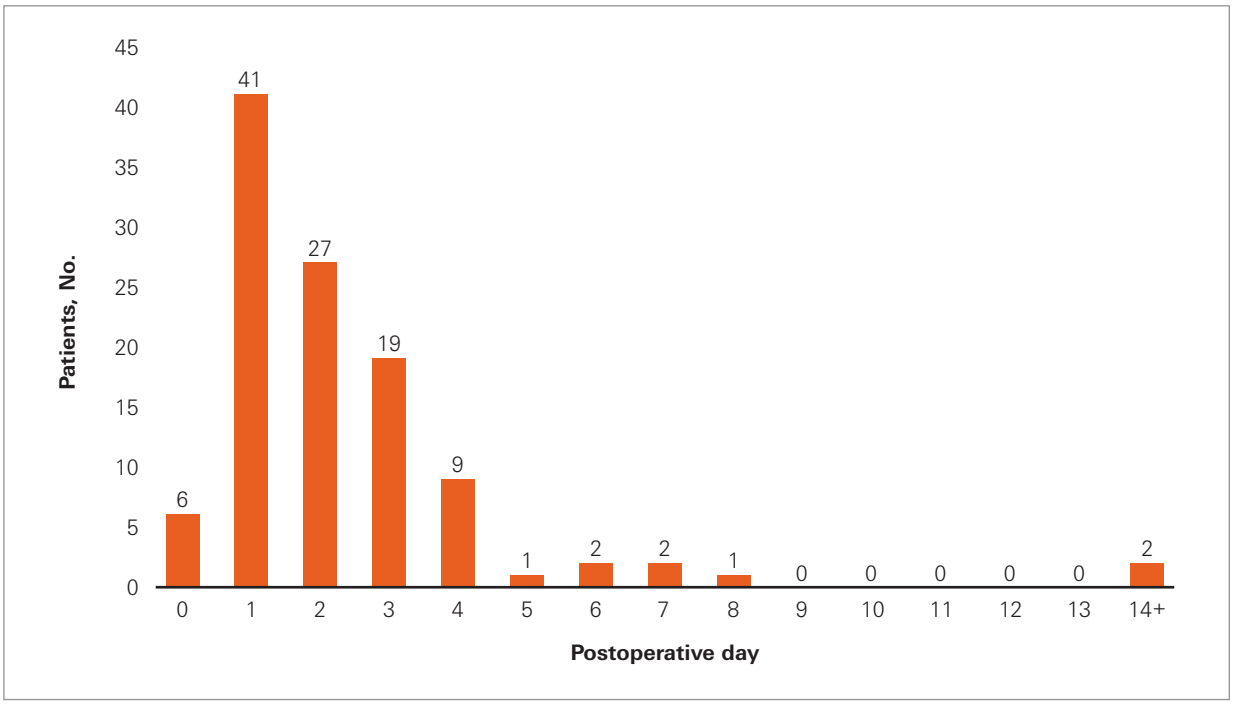

Fig. 2 Postoperative day on which POAF was diagnosed is shown, expressed as the number of patients developing POAF on a given day; 67% of patients developed POAF within the first 2 postoperative days. Corresponding median (IQR) values can be found in Table II.
POAF, postoperative atrial fibrillation.

TABLE I. Baseline Demographics and Perioperative Characteristics[a]

Characteristic	Overall (N = 311)	HeartMate II (n = 197)	HeartMate 3 (n = 72)	HVAD (n = 42)	*P* value
INTERMACS profile, No. (%)					.01[b]
1: Critical cardiogenic shock	84 (27)	50 (25)	19 (26)	15 (36)	
2: Progressive decline	196 (63)	131 (67)	41 (57)	24 (57)	
3: Stable but inotrope dependent	23 (7)	9 (5)	12 (17)	2 (5)	
4: Resting symptoms	8 (3)	7 (4)	0 (0)	1 (3)	
Age, median (IQR), y	63 (55-69)	63 (56-69)	67 (59-71)	59 (47-64)	.003[b]
Black race, No. (%)	65 (21)	37 (19)	19 (26)	9 (21)	.40
Male, No. (%)	246 (79)	149 (76)	65 (90)	32 (76)	.03[b]
Body mass index, median (IQR)	27.4 (24.4-31.7)	27.5 (24.6-31.7)	26.0 (24.1-30.4)	30.2 (24.7-35.7)	.04[b]
Blood type, No. (%)					.29
O	132 (42)	86 (44)	29 (40)	17 (40)	
A	121 (39)	79 (40)	23 (32)	19 (45)	
B	48 (15)	25 (13)	18 (25)	5 (12)	
AB	10 (3)	7 (4)	2 (3)	1 (2)	
Type of cardiomyopathy, No. (%)					.21
Dilated: idiopathic	146 (47)	92 (47)	31 (43)	23 (55)	
Dilated: ischemic	149 (48)	91 (46)	39 (54)	19 (45)	
Dilated: other	11 (4)	10 (5)	1 (1)	0 (0)	
Restrictive	4 (1)	4 (2)	0 (0)	0 (0)	
Hypertrophic	1 (<1)	0 (0)	1 (1)	0 (0)	
Inotrope dependence, No. (%)	267 (86)	170 (86)	61 (85)	36 (86)	.74
Diabetes, No. (%)	159 (51)	107 (54)	34 (47)	18 (43)	.30
Dyslipidemia, No. (%)	241 (77)	151 (77)	59 (82)	31 (74)	.54
Hypertension, No. (%)	251 (81)	162 (82)	58 (81)	31 (74)	.45
Smoking history, No. (%)	181 (58)	109 (55)	49 (68)	23 (55)	.15
Current implantable cardioverter defibrillator, No. (%)	251 (81)	163 (83)	57 (79)	31 (74)	.38

Continued

TABLE I. Baseline Demographics and Perioperative Characteristics,[a] *Continued*

Characteristic	Overall (N = 311)	HeartMate II (n = 197)	HeartMate 3 (n = 72)	HVAD (n = 42)	*P* value
Pulmonary hypertension, No. (%)	152 (49)	134 (68)	6 (8)	12 (29)	<.001[b]
Frailty, No. (%)	36 (12)	16 (8)	12 (17)	8 (19)	.04[b]
Dialysis, No. (%)	16 (5)	10 (5)	1 (1)	5 (12)	.04[b]
Chronic lung disease, No. (%)	144 (46)	93 (47)	31 (43)	20 (48)	.82
Peripheral vascular disease, No. (%)	48 (15)	33 (17)	10 (14)	5 (12)	.67
Prior stroke, No. (%)	33 (11)	21 (11)	11 (15)	1 (2)	.10
Atrial fibrillation, No. (%)	140 (45)	80 (41)	36 (50)	25 (57)	.09
CHA_2DS_2-VASc score, median (IQR)	3 (3-4)	3 (3-4)	3 (3-4)	3 (2-3)	.01[b]
Preoperative labs					
Creatinine, median (IQR), mg/dL	1.34 (1.05-1.89)	1.36 (1.04-1.94)	1.36 (1.10-1.81)	1.34 (1.02-1.86)	.91
Total bilirubin, median (IQR), mg/dL	1.0 (0.6-1.5)	1.0 (0.6-1.6)	1.0 (0.6-1.2)	0.9 (0.6-1.2)	.59
Serum urea nitrogen, median (IQR), mg/dL	28 (20-41)	30 (20-43)	26 (19-38)	24 (19-38)	.06
Aspartate aminotransferase, median (IQR), IU/L	36 (26-59)	39 (27-66)	33 (25-47)	37 (25-59)	.16
Alanine aminotransferase, median (IQR), IU/L	38 (22-90)	42 (23-110)	33 (24-56)	31 (21-59)	.09
Albumin, median (IQR), g/dL	2.5 (3.2-3.9)	3.5 (3.2-3.9)	3.5 (3.1-3.8)	3.5 (3.1-3.9)	.76
International normalized ratio, median (IQR)	1.3 (1.1-1.4)	1.3 (1.1-1.4)	1.3 (1.2-1.4)	1.2 (1.1-1.4)	.19
Hemoglobin, median (IQR), g/dL	10.6 (9.4-12.2)	10.6 (9.6-12.2)	10.7 (9.1-12.2)	10.3 (9.2-11.4)	.36
White blood cells, median (IQR), $\times 10^9$/L	8.1 (6.3-10.6)	8.1 (6.3-11.1)	7.7 (6.1-10.1)	8.7 (6.4-10.5)	.36
Hemodynamic parameters					
Ejection fraction, median (IQR), %	18 (15-24)	18 (15-24)	19 (15-22)	18 (14-25)	.94
Left ventricular end-diastolic diameter, median (IQR), mm	6.7 (6.0-7.1)	6.7 (6.2-7.2)	6.6 (6.0-7.0)	6.7 (5.8-7.1)	.21
Moderate to severe right ventricular failure, No. (%)	113 (36)	68 (35)	30 (42)	15 (36)	.56
LVAD implantation variables					
Prior cardiac surgery, No. (%)	186 (60)	112 (57)	53 (74)	21 (50)	.02[b]
Prior LVAD implantation, No. (%)	48 (15)	35 (18)	5 (7)	8 (19)	.07
Upgraded from extracorporeal membrane oxygenation, No. (%)	12 (4)	8 (4)	1 (1)	3 (7)	.30

Continued

TABLE I. Baseline Demographics and Perioperative Characteristics,[a] *Continued*

Characteristic	Overall (N = 311)	HeartMate II (n = 197)	HeartMate 3 (n = 72)	HVAD (n = 42)	*P* value
Upgraded from intra-aortic balloon pump, No. (%)	41 (13)	35 (18)	3 (4)	3 (7)	.01[b]
Time since LVAD placement, median (IQR), y	1.9 (0.6-3.4)	2.6 (0.6-4.2)	1.2 (0.5-2.0)	1.9 (1-2.5)	<.001[b]
Perioperative characteristics					
Cardiopulmonary bypass time, median (IQR), min	68 (56-89)	72 (57-93)	68 (54-83)	64 (44-74)	.04[b]
Intraoperative red blood cells, median (IQR), units	3 (1-5)	3 (1-6)	2 (1-4)	2 (1-6)	.01[b]
Intraoperative fresh frozen plasma, median (IQR), units	2 (0-4)	3 (1-5)	1 (0-2)	1 (0-3)	<.001[b]
Intraoperative platelets, median (IQR), units	2 (1-2)	2 (1-2)	2 (1-2)	1 (0-2)	.30

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category; HVAD, HeartWare Ventricular Assist Device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.
[a] Categorical variables are classified as yes/no for the presence or absence of the variable. Multiple comparisons for statistically significant variables are included in Supplemental Table I.
[b] $P < .05$ was considered statistically significant.
SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4. To convert total bilirubin to μmol/L, multiply by 17.104. To convert serum urea nitrogen to μmol/L, multiply by 0.357. To convert IU/L to μkat/L, multiply by 0.0167. To convert g/dL to g/L, multiply by 10.

TABLE II. Postoperative Outcomes[a]

Outcome	Overall (N = 311)	HeartMate II (n = 197)	HeartMate 3 (n = 72)	HVAD (n = 42)	*P* value
Reoperation for bleeding, No. (%)	34 (11)	20 (10)	8 (11)	6 (14)	.74
Sepsis, No. (%)	40 (13)	17 (8)	16 (22)	7 (17)	.01[b]
In-hospital stroke, No. (%)	16 (5)	10 (5)	3 (4)	3 (7)	.78
Kidney failure, No. (%)	51 (16)	25 (13)	17 (24)	9 (21)	.07
Dialysis, No. (%)	42 (15)	19 (11)	15 (23)	8 (21)	.03[b]
Gastrointestinal event, No. (%)	85 (27)	52 (26)	24 (33)	9 (21)	.35
Hospital length of stay, median (IQR), d	22 (16-35)	21 (15-33)	25 (19-36)	27 (17-48)	.03[b]
Intensive care unit length of stay, median (IQR), h	120.5 (72.6-242.5)	121.0 (74.3-208.3)	119.3 (72.2-325.6)	100.5 (50.8-429.2)	.98
30-d mortality rate, No. (%)	33 (11)	17 (9)	12 (17)	4 (10)	.16
Operative mortality rate, No. (%)	45 (14)	27 (14)	13 (18)	5 (12)	.59
Stroke and rhythm outcomes					
Stroke, No. (%)	71 (23)	58 (29)	7 (10)	6 (14)	.001[b]

Continued

TABLE II. Postoperative Outcomes,[a] *Continued*

Outcome	Overall (N = 311)	HeartMate II (n = 197)	HeartMate 3 (n = 72)	HVAD (n = 42)	*P* value
Stroke type, No. (%)					.97
Embolic	32 (45)	26 (46)	3 (43)	3 (50)	
Hemorrhagic	39 (55)	32 (55)	4 (57)	3 (50)	
POAF, No. (%)	110 (35)	67 (34)	29 (40)	14 (33)	.61
New-onset POAF, No. (%)	64 (21)	44 (22)	13 (18)	7 (17)	.59
Time of postoperative POAF onset, median (IQR), d	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	.58
Management strategies for patients with POAF, No. (%)					
Hospital management: amiodarone	94 (85)	56 (84)	26 (90)	12 (86)	.74
Hospital management: cardioversion attempt	22 (20)	13 (19)	8 (28)	1 (7)	.29
Hospital management: cardioversion success	19 (17)	13 (19)	5 (17)	1 (7)	.54
Amiodarone at discharge	118 (38)	66 (34)	32 (44)	20 (48)	.10
β-blocker at discharge	125 (40)	74 (38)	31 (43)	20 (48)	.41
Resolution within 90 d	100 (91)	60 (90)	27 (93)	13 (93)	.83

HVAD, HeartWare Ventricular Assist Device; POAF, postoperative atrial fibrillation.
[a] Multiple comparisons for statistically significant variables are included in Supplemental Table II. Categorical variables are classified as yes/no for the presence or absence of the variable.
[b] $P < .05$ was considered statistically significant.

developed POAF had a higher incidence than patients who did not of developing sepsis. There were no statistically significant differences in any other perioperative complications, including reoperation for bleeding, in-hospital stroke, GI events, and multisystem organ failure, between these patient groups (Table III).

The resolution of POAF to sinus rhythm occurred in 91% (100/110) of patients within 90 days. Of the patients who recovered within 90 days, 85% (85/100) were treated with amiodarone, and 15% (15/100) were treated with successful cardioversion while hospitalized. Three patients who did not recover sinus rhythm in 90 days experienced stroke. Slightly more than half of patients (55% [55/100]) who recovered within 90 days were discharged on amiodarone. Of the 10 patients whose POAF did not resolve in 90 days, 50% (n = 5) had preoperative AF. Beyond 90 days, 7 out of 9 patients' POAF never resolved because the patients experienced a complicated hospital course after LVAD implantation and died. The other 2 patients' POAF resolved after heart transplantation or after explantation and subsequent implantation of a new LVAD. Rhythm management and outcomes are further delineated in Table II, Supplemental Table II, and Figure 3.

Stroke Development

Incidence of stroke events was 23% (n = 71) among all LVAD recipients (Table II). Stroke was identified more frequently in patients who had received HeartMate II devices (n = 59 [29%]) than in

TABLE III. Perioperative Outcomes in Patients Who Developed Postoperative AF

	POAF (n = 110)	No POAF (n = 201)	*P* value
Reoperation for bleeding, No. (%)	16 (15)	18 (9)	.13
Pneumonia, No. (%)	23 (21)	34 (17)	.38
Gastrointestinal event, No. (%)	29 (26)	56 (28)	.78
Kidney failure, No. (%)	22 (20)	29 (14)	.21
Dialysis, No. (%)	17 (16)	25 (14)	.78
Sepsis, No. (%)	20 (18)	20 (10)	.04[a]
Multisystem organ failure, No. (%)	9 (8)	18 (9)	.82
In-hospital stroke, No. (%)	5 (5)	11 (5)	.72
Intensive care unit length of stay, median (IQR), h	140.7 (72.8-286.4)	117.3 (72.5-224.5)	.33
Hospital length of stay, median (IQR), d	24 (17-40)	22 (16-54)	.10
30-d mortality, No. (%)	15 (14)	18 (9)	.20

AF, atrial fibrillation; POAF, postoperative atrial fibrillation.
[a] *P* < .05 wa s considered statistically significant.

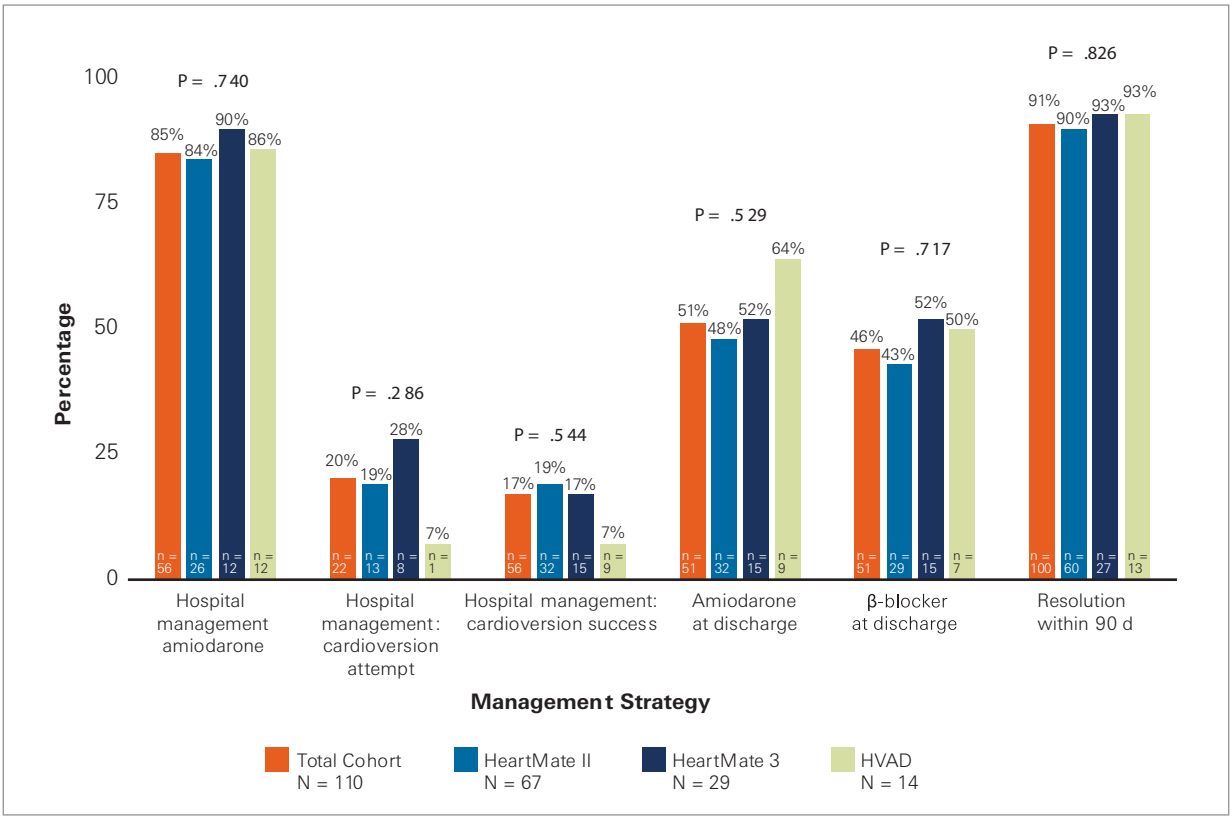

Fig. 3 Management strategies for patients who developed POAF are expressed as percentages by continuous-flow LVAD type. There were no statistically significant differences in management type among LVAD device groups. Corresponding frequencies and P values can be found in Table II. *P* < .05 was considered statistically significant.
HVAD, HeartWare Ventricular Assist Device; LVAD, left ventricular assist device; POAF, postoperative atrial fibrillation.

recipients of newer-generation centrifugal flow devices (P = .001). Among patients who developed stroke, 45% (n = 32) of the cases were embolic and 55% (n = 39) were hemorrhagic. The type of stroke did not vary based on LVAD type (P = .97). The composite probability of remaining alive and free of stroke was estimated to be 68% at 1 year, 43% at 3 years, and 27% at 5 years in recipients of continuous-flow LVADs (Fig. 4). The incidence of stroke at the same time points was 15%, 24%, and 26%. Composite end point estimates and CIFs from competing risks analysis can be found in Table IV.

Competing-Risks Analysis

Fine-Gray regression models of the subdistribution hazard function were used to evaluate potential predictors of stroke (Table V). Amiodarone continued at discharge (subdistribution hazard ratio, 0.55 [95% CI, 0.33-0.94]; P = .03) and HeartMate 3 implantation (hazard ratio, 0.41 [95% CI, 0.19-0.90]; P = .03) were associated with decreased stroke risk on multivariable analysis. Postoperative AF was associated with increased stroke development (0.55 [95% CI, 0.33-0.94]; P = .04). Preoperative AF (P = .08) and a history of stroke (P = .36) were not found to be statistically significant predictors of stroke.

Discussion

This study reports a single-center experience of stroke development with deficits lasting beyond 24 hours following implantation of continuous-flow LVADs for destination therapy in relation to clinical course and POAF. Prior studies have shown promising outcomes in BTT cohorts of patients who receive continuous-flow LVADs.[31,32] The work presented in this report offers a novel analysis of a cohort exclusively composed of patients whose treatment had a destination therapy indication. On robust competing-risks analysis, both HeartMate 3 use and amiodarone at discharge were associated with decreased stroke risk, while POAF was associated with an increased risk of stroke. Preoperative AF had no statistically significant relationship with stroke development following continuous-flow LVAD implantation.

Several studies have evaluated the incidence of stroke as a postoperative complication of continuous-flow LVAD implantation for all indications. Mixed results of stroke incidence in this literature can be attributed to differences in baseline cohort characteristics and demographics, in patient management by center, in definitions of stroke employed in the study, and in device models.[13-17] Results of the MOMENTUM 3 trial showed that patients who received the HeartMate 3 were 3.3 times less likely to develop late stroke

TABLE IV. Composite End Point Kaplan-Meier Estimates and Cumulative Incidence Functions for the Development of Stroke and Death Following Continuous-Flow LVAD Implantation

	Cumulative incidence function, %			
Year	Stroke	Death	Alive and free from stroke, %	No. at risk
1	15	17	68	187
2	21	26	53	125
3	24	33	43	79
4	26	40	34	46
5	27	46	27	24

LVAD, left ventricular assist device.

TABLE V. Predictions for the Development of Stroke in Continuous-Flow LVAD Recipients on a Univariable and Multivariable Subdistribution Hazards Regression Model[a]

	Univariable			Multivariable		
Variable	**Subdistribution hazard ratio**	**95% CI**	***P* value[b]**	**Subdistribution hazard ratio**	**95% CI**	***P* value[b]**
INTERMACS profile 1	1.07	0.63-1.81	.81			
HeartMate 3	0.42	0.19-0.914	.03[a]	0.41	0.19-0.90	.03[b]
Current implantable cardioverter-defibrillator	0.69	0.40-1.19	.18	0.66	0.38-1.14	.14
Age	1.01	0.99-1.03	.40			
Black race	1.50	0.89-2.53	.13	1.52	0.89-2.58	.12
Male sex	0.91	0.52-1.59	.73			
Body mass index	1.00	0.97-1.03	.95			
Ischemic heart failure	0.94	0.59-1.49	.78			
Diabetes	1.11	0.70-1.77	.65			
Hypertension	1.4	0.75-2.93	.26			
Preoperative AF	0.65	0.40-1.05	.08	0.71	0.44-1.15	.17
Prior stroke	1.40	0.69-2.83	.36			
POAF	1.41	0.88-2.24	.15	1.68	1.03-2.73	.04[b]
Amiodarone at discharge	0.61	0.36-1.01	.06	0.55	0.33-0.94	.03[b]
β-blockers at discharge	0.72	0.44-1.17	.19	0.77	0.46-1.28	.31

AF, atrial fibrillation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; POAF, postoperative atrial fibrillation.

[a] These variables were included for the final multivariable model. The remaining multivariable predictors reflect sequential addition to the most parsimonious model.

[b] $P < .05$ was considered statistically significant.

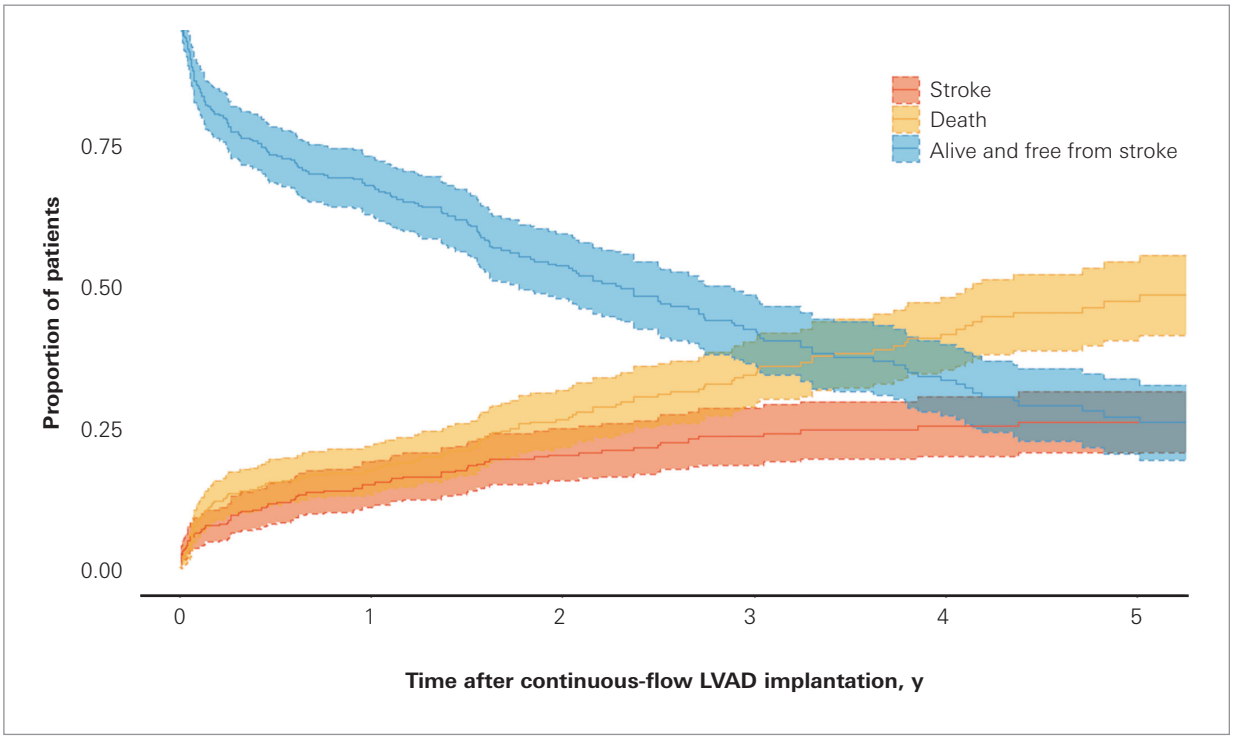

Fig. 4 Competing risks model for development of stroke and death after continuous-flow LVAD implantation is shown. Cumulative incidence functions for stroke development and death are presented with corresponding shaded CIs alongside the Kaplan-Meier composite end point for remaining alive and free of stroke. Corresponding estimates can be found in Table IV. LVAD, left ventricular assist device.

relative to those implanted with HeartMate II, with an incidence rate between 7.9% and 10.1% in 3 cohorts of HeartMate 3 patients.[33-36] In contrast, stroke was observed in 29.7% of patients who received HVADs and 12.1% of patients who received HeartMate II in the ENDURANCE trial.[37] A single-center retrospective study in 2018 evaluating stroke outcomes of patients who received the HeartMate II device, with both BTT and destination therapy indications, reported a late stroke incidence of 21%; they defined late stroke as including transient ischemic attack, ischemic stroke, and hemorrhagic stroke any time after LVAD implantation.[38]

Of note, Medtronic had stopped the sale and distribution of the HVAD as of June 2021 as a result of an increased risk of adverse neurologic events and mortality.[39] This study's finding of decreased stroke risk with the HeartMate 3 device compared with the HVAD is consistent with this development as well as with previous works.[19,39]

Studies have historically focused on outcomes of mixed cohorts of continuous-flow LVAD recipients, including patients with indications for both BTT and destination therapy as well as BTT-only cohorts. With the increase in continuous-flow LVAD implantation as destination therapy, however, it is crucial to analyze postoperative outcomes in destination therapy–only cohorts. The literature has reported an incidence of stroke of 29.7% in patients who received HVADs, of 12.1% to 21% in patients who received HeartMate II devices, and of 7.9% to 10.1% in patients who received HeartMate 3 devices.[33-38] The current study, with a modern cohort of patients implanted with HVADs, HeartMate II devices, and HeartMate 3 devices for destination therapy only, reports an overall stroke incidence of 15% at 1 year postoperatively, 24% at 3 years, and 27% at 5 years. A similar proportion of patients who developed hemorrhagic stroke relative to embolic stroke is reported, which is consistent with prior literature.[40]

Preoperative AF has been shown to increase the risk of thromboembolic events following continuous-flow LVAD implantation.[29] The current study, however, demonstrates the minimal effect of preoperative AF on stroke—that is, there is no statistically significant

relationship. A prior retrospective study identified that increasing age, mitral valve surgery, aortic valve surgery, race, previous congestive heart failure, and hypertension were associated with POAF in patients who underwent cardiac surgery.[22] The incidence of POAF after cardiac surgery has been approximated at 35%,[23] which is consistent with the rates observed in the current study's cohort following continuous-flow LVAD implantation. Prior studies of POAF after continuous-flow LVAD implantation have found that POAF has no negative impact on mortality or thrombotic complications within the first 30 days but that it shows increased risk for future AF, ischemic stroke, and continuous-flow LVAD thrombosis.[41] The findings reported here, identifying POAF as a predictor for the development of stroke events following continuous-flow LVAD implantation, are consistent with those in the existing literature.[41]

Amiodarone has classically been used for rhythm control in AF as well as for prophylaxis of the development of POAF, as outlined by previous work on POAF management.[23] Therapeutic guidelines for the use of antiarrhythmic drugs state that β-blockers, nondihydropyridine calcium channel blockers, digoxin, and amiodarone should be considered for symptomatic patients with POAF as an attempt at chemical cardioversion to sinus rhythm.[26] In addition, anticoagulation is often used in combination with amiodarone after cardiac surgery and is required unless contraindicated in patients who undergo continuous-flow LVAD.[42,43] In the cohort presented here, 38% of patients were discharged after continuous-flow LVAD implantation on amiodarone; amiodarone at discharge was a negative predictor of stroke risk. This protective effect of amiodarone against stroke may be a result of the medication decreasing the burden of POAF after continuous-flow LVAD implantation in patients with a destination therapy indication, given POAF's association with an increased risk of the development of stroke in this study and in the literature.[41] Preoperative amiodarone has been used as effective prophylaxis against POAF, with a class IIa indication, although the 2014 American Association for Thoracic Surgery guidelines indicate that the decision to use amiodarone prophylactically should account for surgical procedure.[26] This cohort included 45% of patients with a history of AF before surgery, but history of preoperative AF was not found to be associated with increased stroke risk. Further investigation into the use of prophylactic amiodarone for the prevention of POAF in this cohort is warranted.

Study Limitations

Although this is one of the first single-center studies to report a consistent and comprehensive analysis with long-term follow-up in patients who undergo continuous-flow LVAD with a destination therapy indication, there are limitations. This study was retrospective and nonrandomized; therefore, it was subject to inherent selection bias. For null results in particular, the sample size may have contributed to the increased risk of type II error. The sample size was too small to allow for evaluation of predictors for each device type. Variables were chosen for inclusion in the Fine-Gray regression based on perceived clinical relevance and prior work, and the number of variables included was limited by the events per variable; results are therefore subject to this inherent selection bias. Further evaluation of stroke in this patient population is recommended, with similarly robust statistical methodology and granularity in patient follow-up among larger patient cohorts. Referral patterns, destination therapy patient selection, and local demographics may have altered the patient population. Adverse events that occurred at other centers may not have been reported to national databases or to the reporting institution, so estimates for late complication rates may be underestimated. All patients were closely monitored according to the reporting center's protocol, however, and follow-up data were obtained from both national databases and institutional records.

Conclusion

As destination therapy becomes an increasingly common indication for continuous-flow LVAD implantation, it will become crucial to better elucidate the profile of adverse events associated with this device indication. Stroke remains a critical complication of LVAD surgery, and although recent work has suggested that the newer generation of devices may be associated with decreased stroke risk, results regarding stroke incidence in the literature remain mixed. This report characterizes the postoperative stroke profile of a cohort of destination therapy–only patients who received modern devices. The study's robust competing risks analysis further evaluated risk factors for stroke, identifying that the development of POAF is associated with increased stroke risk while the use of the HeartMate 3 device

and amiodarone decrease the incidence of stroke. These results suggest that careful management of POAF with amiodarone may be protective against stroke development. Further work in a larger patient cohort using similarly robust statistical methodologies will be required to clarify these trends and explore avenues of arrhythmic prophylaxis and management to reduce POAF and improve outcomes associated with continuous-flow LVAD placement in the destination therapy setting.

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Conflict of Interest Disclosure: G. A. Ewald has relationships with Abbott Laboratories (speaker and consultant). A. Itoh has relationships with Abbott Laboratories (speaker), Medtronic (speaker), and Abiomed (speaker). M. R. Moon has relationships with Medtronic (consultant). R. J. Damiano, Jr, has relationships with AtriCure, Inc (speaker and research funding), LivaNova PLC (speaker), Medtronic (consultant), and Edwards Lifesciences (speaker). M. F. Masood has relationships with Abbott Laboratories (speaker). All other authors have no relationships to disclose.

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