

Appendix 1: Methods

Study variables and definitions

The primary diagnosis of RHF after LVAD implantation was made by the presence of at least two of the clinical evidences (i.e., ascites, peripheral edema, elevated estimated or measured CVP) or at least one of the manifestations (i.e., renal failure, liver injury, cardiac index <2.2 L/min/m², mixed venous oxygen saturation $<50\%$, reduction in pump flow $>30\%$ from the previous baseline, or elevated lactate >3.0 mmol/L), consistent with INTERMACS definition. Other post-LVAD complications were also defined according to standard INTERMACS definitions.

Statistical analysis

Categorical variables were compared using chi-square or Fisher's exact tests; continuous variables were compared using two-sample *t*-tests or Wilcoxon rank-sum tests. All statistical testing was two-sided with an alpha level of 0.05.

A Fine and Gray competing risk model was used to calculate the cumulative incidence rate of stroke with a relative 95% standard error, considering death and heart transplantation as competing events. The cumulative incidence rate of death was calculated in a similar manner, considering heart transplantation as a competing event.

A Cox proportional hazard regression analysis was performed to identify predictors of early stroke at 6 months after implantation. Variables that were significant on univariable analyses or that were clinically relevant were included in the multivariable analyses. Preoperative frailty, stroke history, cardiac surgery history, preoperative CVP, device type, concomitant valve surgery, postoperative RHF, antiplatelet use, atrial fibrillation, mean MAP within 3 days of implantation, mean CPP within 3 days of implantation and at POD 0 and 1 were included in multivariable analysis. The backward elimination method was used for model selection in the multivariable analysis. Multivariable analyses for RHF and CPP were conducted separately, due to multicollinearity. Results are reported as HRs with 95% CIs.

ROC curve analysis for early stroke was performed, and the AUC was calculated. An AUC of 0.5 was considered no better than chance, whereas an AUC of 1 indicated a perfect accuracy. The optimal cutoff for predicting early stroke by CPP was determined using the maximum value of the Youden index, the sum of sensitivity, and a specificity of minus one.

Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and R Statistical software version 4.0.2 (R Project for Statistical Computing, Vienna, Austria).

Table S1 Previous cardiac surgery history

Variables	No stroke group (n=56)	Stroke group (n=14)	P value
Valve surgery	3 (5.4)	3 (21.4)	0.090
Aortic valve surgery	1 (1.8)	1 (7.1)	
Mitral valve surgery	1 (1.8)	1 (7.1)	
Aortic valve and mitral valve surgery	0 (0.0)	1 (7.1)	
Mitral valve and tricuspid valve surgery	1 (1.8)	0 (0.0)	
Coronary artery bypass graft surgery	3 (5.4)	6 (42.9)	0.001
Totally thoracoscopic ablation	1 (1.8)	0 (0.0)	>0.99

Data are expressed as number (%).

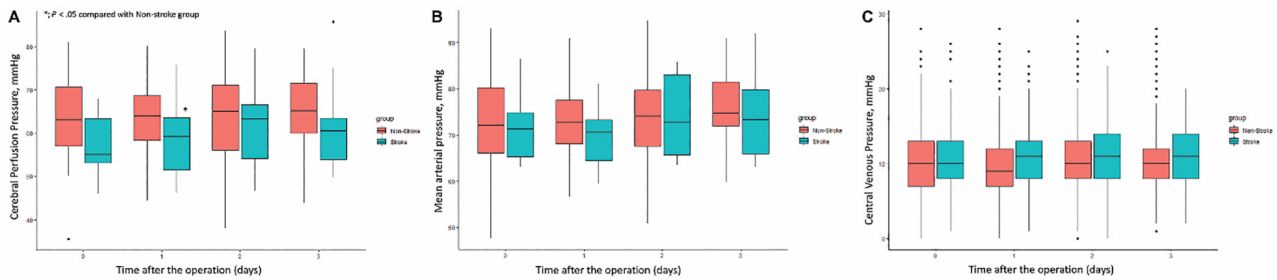


Figure S1 Serial changes in (A) CPP, (B) MAP, and (C) CVP according to stroke. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the top and bottom ends of the line mark the 90th and 10th percentiles. CPP, cerebral perfusion pressure; MAP, mean arterial pressure; CVP, central venous pressure.

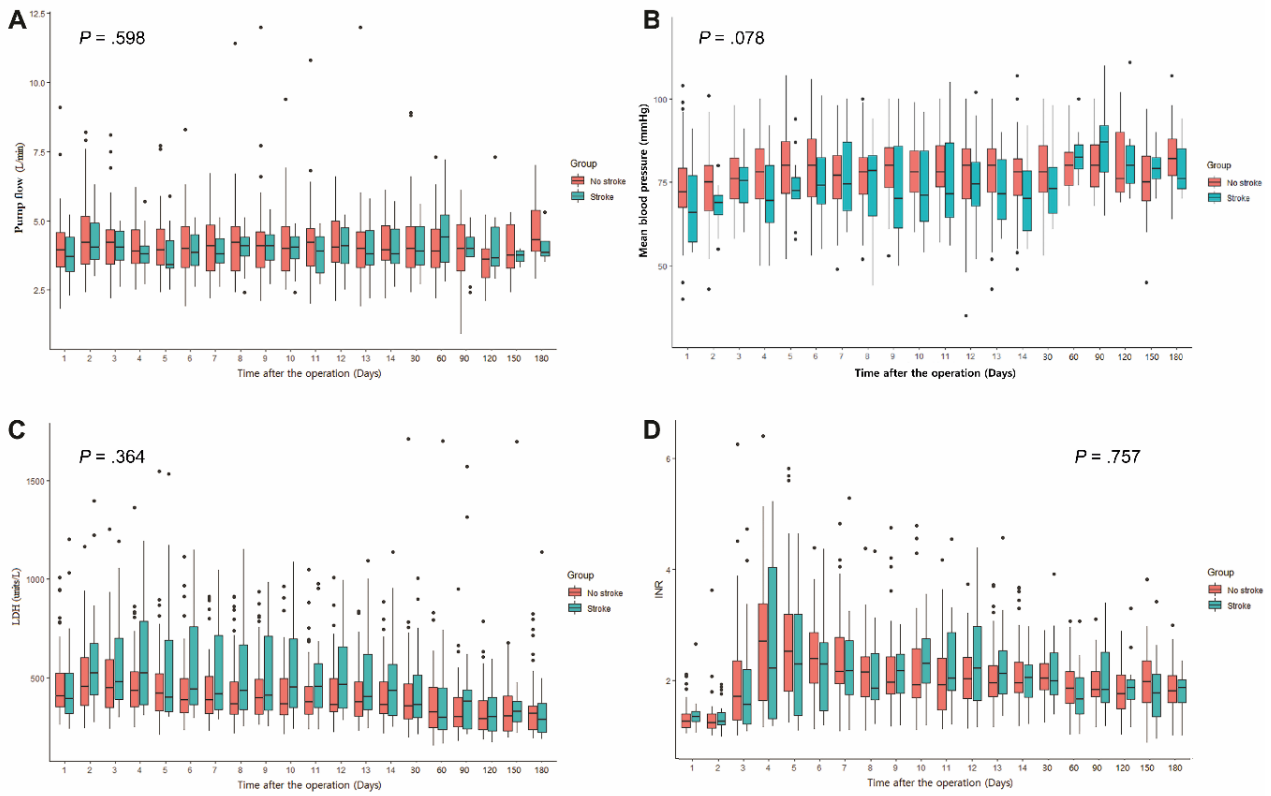


Figure S2 Serial changes in (A) pump flow, (B) pump flow index, (C) LDH, and (D) INR. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the top and bottom ends of the line mark the 90th and 10th percentiles. LDH, lactate dehydrogenase; INR, international normalized ratio.

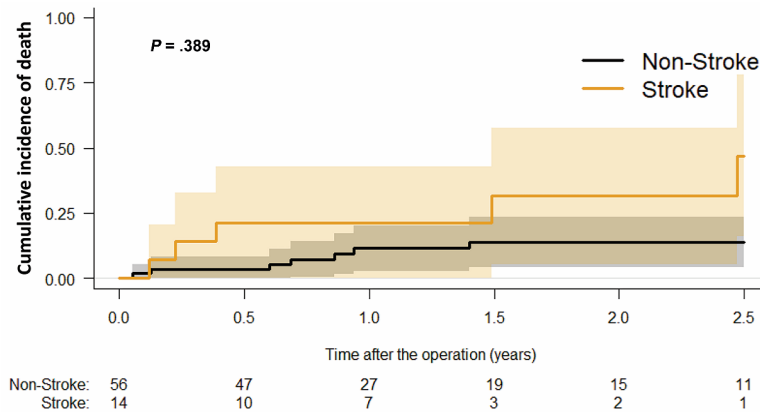


Figure S3 Time to event curves for death according to stroke. Cumulative incidence function was used. The colored shaded areas in both curves represent the 95% CI. CI, confidence interval.

Table S2 Univariable analysis for postoperative early stroke

Variables	Univariable analysis		
	HR	95% CI	P value
Age (years)	0.990	0.955–1.027	0.598
Male sex	1.634	0.512–5.213	0.407
Body mass index (kg/m ²)	1.011	0.852–1.201	0.899
Preoperative comorbidity			
Frailty	7.994	1.045–61.135	0.045
DM	1.303	0.437–3.888	0.635
HTN	1.460	0.506–4.211	0.484
Chronic renal failure	1.242	0.431–3.580	0.689
Previous stroke history	2.190	0.733–6.540	0.160
Smoking history	1.258	0.436–3.626	0.671
Solid organ cancer	0.449	0.060–3.488	0.449
Atrial fibrillation	1.019	0.353–2.936	0.973
Cardiac surgery history	5.409	1.873–15.621	0.002
CPR history	0.819	0.274–2.785	0.819
ECMO status before LVAD implantation	1.588	0.551–4.580	0.392
Liver dysfunction	0.750	0.603–2.641	0.750
Ischemic etiology of heart failure	2.029	0.680–6.060	0.205
Preoperative ECHO			
LVEF			0.363
30–39%	1		
20–29%	1.572	0.393–6.291	
<20%	0.572	0.174–1.873	
TR			0.756
None	1		
Mild	1.245	0.129–11.971	
Moderate	0.787	0.209–2.971	
Severe	0.417	0.070–2.499	
Mean PAP (mmHg)	1.017	0.964–1.073	0.535
CVP (mmHg)	1.066	0.970–1.170	0.183
Operative			
Device type			0.157
HMII	1		
HVAD	7.373	0.964–56.391	
HM3	<0.001		
Concomitant valve surgery	0.247	0.032–1.886	0.178
Intracardiac thrombus removal	0.578	0.076–4.419	0.597
Postoperative			
RHF	5.050	1.686–15.129	0.004
Infection	0.516	0.115–2.306	0.386
Antiplatelet use	0.393	0.132–1.174	0.094
Heparin bridging	3.166	0.414–24.209	0.267
Atrial fibrillation	2.418	0.810–7.220	0.114
TTR using the Rosendaal method	0.593	0.208–1.691	0.328
Pump flow within 7 days of implantation	0.853	0.466–1.561	0.606
Mean MAP within 3 days of implantation	0.934	0.862–1.011	0.092
Mean CVP within 3 days of implantation	1.132	0.915–1.401	0.254
Mean CPP within 3 days of implantation	0.944	0.880–1.012	0.103
Mean CPP at POD 0	0.945	0.892–1.002	0.057
Mean CPP at POD 1	0.920	0.858–0.985	0.017
Mean CPP at POD 2	0.985	0.925–1.048	0.629
Mean CPP at POD 3	0.953	0.889–1.022	0.181

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; ECHO, echocardiography; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; PAP, pulmonary arterial pressure; CVP, central venous pressure; HMII, HeartMate II Left Ventricular Assist System; HVAD, HeartWare Ventricular Assist System; HM3, HeartMate 3 Left Ventricular Assist System; TTR, time in therapeutic range; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; POD, postoperative day; RHF, right heart failure.

Table S3 Multivariable analysis for postoperative early stroke

Variables	Multivariable analysis		
	HR	95% CI	P value
Preoperative			
Cardiac surgery history	3.916	1.323–11.594	0.014
Postoperative			
Antiplatelet use	0.286	0.093–0.881	0.029
CPP at POD 1	0.923	0.858–0.992	0.030

HR, hazard ratio; CI, confidence interval; CPP, cerebral perfusion pressure; POD, postoperative day.

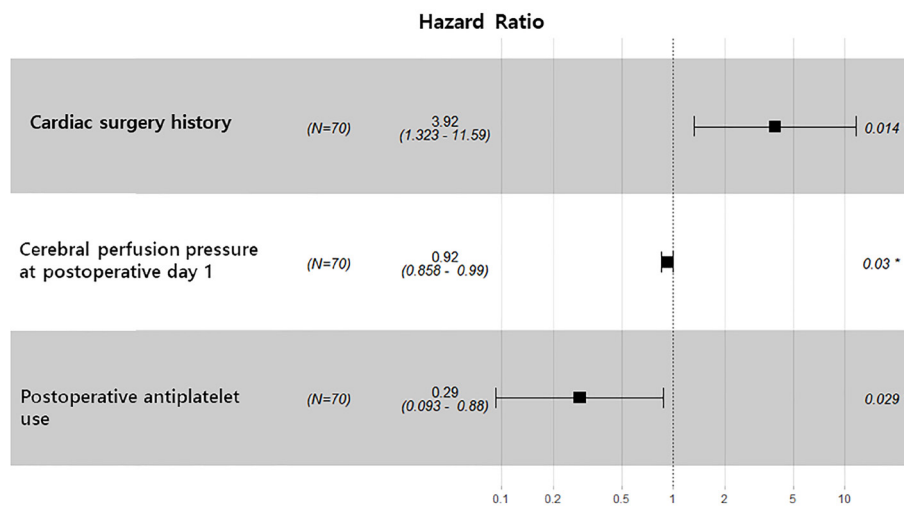


Figure S4 Forest plot based on the results of multivariate analysis of the factors associated with early stroke. Note: The factors that were found to be significant ($P < 0.1$) in univariate analysis and clinically relevant were entered into a multivariate Cox regression model.

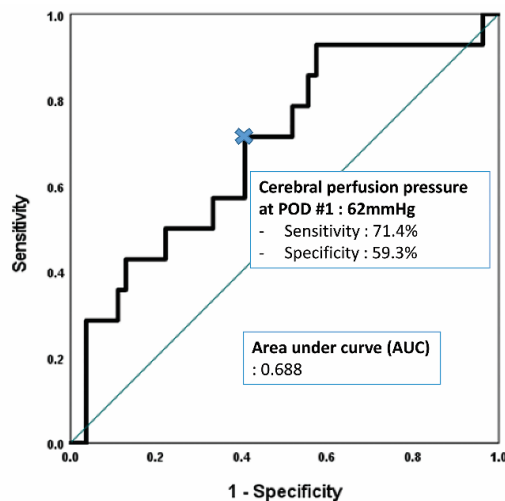


Figure S5 ROC curve for prediction of stroke by CPP at POD 1. Optimal cutoff values using the Youden index were 62 mmHg. POD, postoperative day; AUC, area under the curve; ROC, receiver operating characteristic; CPP, cerebral perfusion pressure.

Table S4 Clinical characteristics and echocardiographic characteristics 6 months after implantation

Variables	No RHF group (n=48)	RHF group (n=22)	P value
Age (years)	65.94±12.04	56.68±15.71	0.009
Male sex	40 (83.3)	15 (68.2)	0.263
Body mass index (kg/m ²)	23.48±3.04	22.80±3.06	0.394
Preoperative comorbidity			
Frailty	30 (62.5)	15 (68.2)	0.848
DM	30 (62.5)	11 (50.0)	0.469
HTN	26 (54.2)	8 (36.4)	0.260
Dialysis	18 (37.5)	9 (40.9)	0.994
Previous stroke history	11 (22.9)	4 (18.2)	0.893
Smoking history	24 (50.0)	11 (50.0)	>0.99
Solid organ cancer	6 (12.5)	3 (13.6)	>0.99
Liver dysfunction	13 (27.1)	9 (40.9)	0.379
Atrial fibrillation	28 (58.3)	12 (54.5)	0.970
Cardiac surgery history	12 (25.0)	7 (31.8)	0.760
CPR history	15 (31.3)	7 (31.8)	>0.99
ECMO status before LVAD implantation	16 (33.3)	8 (36.4)	>0.99
Ischemic etiology of heart failure	26 (54.2)	9 (40.9)	0.440
Medical support status			0.022
Bridge to transplantation	23 (47.9)	15 (68.2)	
Bridge to candidacy	1 (2.1)	3 (13.6)	
Destination therapy	24 (50.0)	4 (18.2)	
Preoperative ECHO			
LVEF			0.621
30–39%	5 (10.4)	4 (18.2)	
20–29%	24 (50.0)	11 (50.0)	
<20%	19 (39.6)	7 (31.8)	
TR			0.306
Mild	31 (64.6)	9 (40.9)	
Moderate	9 (18.8)	7 (31.8)	
Severe	6 (12.5)	5 (22.7)	
Mean PAP (mmHg)	35.05±10.10	37.59±12.30	0.422
CVP (mmHg)	11.38±5.88	13.35±7.47	0.289

Data are expressed as number (%) or mean ± standard deviation. RHF, right heart failure; DM, diabetes mellitus; HTN, hypertension; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; ECHO, echocardiography; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; PAP, pulmonary arterial pressure; CVP, central venous pressure.

Table S5 Surgical characteristics and postoperative characteristics at 6 months

Variables	No RHF group (n=48)	RHF group (n=22)	P value
Surgical characteristics			
Device type			0.029
HMII	20 (41.7)	3 (13.6)	
HM3	0 (0.0)	1 (4.5)	
HVAD	28 (58.3)	18 (81.8)	
Intracardiac thrombus removal	5 (10.4)	3 (13.6)	>0.99
Concomitant valve surgery	11 (22.9)	5 (22.7)	>0.99
Postoperative characteristics			
Time from LVAD implantation to RHF (days)	–	1 [0–6]	–
Postoperative early stroke	5 (10.4)	9 (40.9)	0.008
Time from LVAD implantation to stroke (days)	105 [1.29–180]	48 [12–180]	0.606
Time from RHF to stroke (days)	–	45 [11–147]	–
Antiplatelet use	40 (83.3)	16 (72.7)	0.479
Heparin bridging	39 (81.3)	18 (81.8)	>0.99
Postoperative atrial fibrillation	11 (22.9)	5 (22.7)	>0.99
Postoperative infection	15 (31.3)	2 (9.1)	0.088
Postoperative pump thrombosis	0 (0.0)	0 (0.0)	NA
Heparin induced thrombocytopenia	0 (0.0)	0 (0.0)	NA
TTR using Rosendaal method <40%	30 (62.5)	11 (50.0)	0.350
Pump flow within 7 days of implantation (L/min)	4.18±1.00	3.89±0.69	0.222
Mean MAP within 3 days of implantation (mmHg)	73.97±10.69	69.20±10.72	<0.001
Mean CVP within 3 days of implantation (mmHg)	9.85±3.70	11.82±4.39	<0.001
Mean CPP within 3 days of implantation (mmHg)	64.13±10.56	57.38±11.55	<0.001
Mean CPP at POD 0 (mmHg)	63.66±12.29	54.61±11.00	<0.001
Mean CPP at POD 1 (mmHg)	63.10±10.09	57.69±11.15	<0.001
Mean CPP at POD 2 (mmHg)	65.75±9.49	60.33±12.64	<0.001
Mean CPP at POD 3 (mmHg)	73.138±12.44	67.37±12.69	<0.001

Data are expressed as number (%), mean ± SD, or median [range]. RHF, right heart failure; HMII, HeartMate II Left Ventricular Assist System; HM3, HeartMate 3 Left Ventricular Assist System; HVAD, HeartWare Ventricular Assist Device System; LVAD, left ventricular assist device; NA, not available; TTR, time in therapeutic range; MAP, mean arterial pressure; CVP, central venous pressure; CPP, cerebral perfusion pressure; POD, postoperative day.

Table S6 Management of patients with postoperative RHF

Variables	Postoperative RHF (n=22)
In hospital	
Inotropes [†]	
Number (%)	22 (100.0)
Duration (days), median [range]	7 [2–44]
Inhaled NO	
Number (%)	9 (40.9)
Duration (days), median [range]	2 [1–7]
CRRT	
Number (%)	15 (68.2)
Duration (days), median [range]	7.5 [1–23]
RVAD implantation	
Number (%)	4 (18.2)
Duration (days), median [range]	8.5 [5–12]
At discharge, n (%)	
Sildenafil	15 (68.2)
Digoxin	8 (36.4)
High dose diuretics [‡]	4 (18.2)
6 months after LVAD implantation, n (%)	
Sildenafil	10 (45.5)
Digoxin	3 (13.6)
High dose diuretics [‡]	4 (18.2)
Duration between RHF onset and stroke, median [range]	45 [11–147]

[†], inotropes included intravenous medications such as dobutamine and milrinone; [‡], high dose diuretics were defined as furosemide at a daily oral dosage of 80 mg or more, or torasemide at a daily oral dosage of 20 mg or more. RHF, right heart failure; NO, nitric oxide; CRRT, continuous renal replacement therapy; RVAD, right ventricular assist device; LVAD, left ventricular assist device.