Stroke Complications in Patients Requiring Durable Mechanical Circulatory Support Systems After Extracorporeal Life Support

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Stroke is one of the leading complications following durable mechanical circulatory support (MCS) implantation. The aim of this multicenter study was to investigate stroke complications in patients requiring durable MCS following extracorporeal life support (ECLS). Data of 11 high volume MCS centers were collected and evaluated to identify patients who underwent durable MCS implantation after ECLS support between January 2010 and August 2018. The primary outcome was stroke following durable MCS implantation. Univariate and multivariate logistic regression analyses were performed to determine predictors of stroke. Overall, 531 patients met the inclusion criteria. Only patients who were supported with continuous flow pumps were included in this study accounting for 495 patients (median age 54 years old [interquartile range 47–60]). A total of 136 patients (27%) developed postoperative stroke on device during the follow-up (48% ischemic and 52% hemorrhagic) after a median durable MCS support of 320 [32–1,000] days, accounting for 0.17 events per patient-year. Of 133 patients with known date of stroke, a total of 47 (10%) developed stroke during the first 30 days (64% ischemic and 36% hemorrhagic), and 86 patients developed stroke after 30 days (38% ischemic and 62% hemorrhagic) of durable MCS support (late stroke). Survival rate was significantly lower in patients with hemorrhagic stroke ($p = 0.00091$). Stroke appears to be a common complication in patients transitioned to durable MCS support after ECLS. Hemorrhagic stroke is a more common type of late stroke and is associated with inferior outcomes. *ASAIO Journal* 2023; 69;145–150

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Stroke is a major shortcoming of left ventricular assist device (LVAD) therapy; it may confer significant long-term disability and is associated with high mortality. The reported incidence of stroke among patients who receive continuous-flow LVADs is noted to vary 0.08–0.29 events per patient-year (EPPY), and is dependent on the type of device implanted.[1–4] Further, a 3.3 times lower stroke incidence rate with HeartMate III compared with HeartMate II has been recently reported in the newest analysis of the Momentum 3 study.[5] Notably, almost all of the reported studies have focused on primary LVAD implants, which is a different risk constellation compared with LVAD candidates with prior extracorporeal life support (ECLS).

It has been repeatedly shown that neurologic complications are one of the common complications in patients on ECLS.[6,7] Further, when a durable mechanical circulatory support system (MCS) is necessary, the MCS implantation adds the potential risk of durable assist device related neurologic injuries. That being said, we hypothesize that durable MCS patients with prior ECLS support may represent a high risk group for neurologic injuries, due to risk conferred by both the ECLS and the durable MCS. To avoid ECLS related complications, timely decision to proceed with durable MCS is necessary. However, the decision to implant a durable MCS in a patient with ECLS, is very challenging and the implantation threshold may vary between the institutions.[8] Our group recently published the largest series on durable MCS patients bridged with ECLS.[9] We have shown that the survival rate of 53% in this cohort of patients is significantly lower than with the traditional VAD candidates. Further, we were able to identify several survival predictors, and an app "Durable MCS after ECLS calculator" was introduced, which helps in future patient selection and avoids unnecessary resource utilization. Due to lack of studies with specific focus on stroke rate in LVAD patients with prior

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ECLS support, the main objective of this study was to investigate the incidence, type, and risk factors of stroke in patients who underwent durable MCS implantation after ECLS support, by analyzing data of Durable MCS after ECLS registry.

Materials and Methods

Study Design, Definitions, and Data Collection

The Durable MCS after ECLS registry is a multicenter retrospective study, that gathered data on consecutive patients who underwent durable MCS implantation directly after ECLS between January 2010 and August 2018, in eleven high volume European centers. Patients who did not meet the ECLS weaning criteria were considered for durable MCS after adequate neurologic evaluation. The decision to proceed with durable MCS was only made after excluding neurologic deficits using CT scans and neurologic examinations. Notably, the majority of the patients were sedated, and on ventilator before durable MCS implantation. For this study, all patients who underwent the implantation of total artificial heart, pulsatile pumps, or earlier generation pumps after ECLS were excluded from the analysis. The remaining patients who were supported with HeartWare HVAD (Medtronic, Minneapolis, MN), HeartMate II (Abbott, Abbott Park, IL), or HeartMate III (Abbott, Abbott Park, IL) we included in the analysis.

The Interagency Registry for Mechanically Assisted Circulatory Support definitions were used for postoperative complications except for right ventricular failure, which was considered only if mechanical support of the right ventricle was necessary. Stroke was defined as ischemic or hemorrhagic stroke based on the CT finding. Further, stroke was categorized as disabling stroke (modified Rankin Scale score ≥3) *versus.* nondisabling stroke. The study protocol was approved by the individual Health Research Ethics Boards.

Study Outcome

The primary outcome of the study was any kind of stroke during the follow-up after durable MCS implantation. Stroke was defined as early (within the first 30 days after durable MCS implantation) or late stroke (after 30 days of durable MCS implantation). Secondary outcomes postdurable MCS implantation included all-cause mortality and mortality caused by stroke.

Surgical Approach

The ECLS implantation at each institution was performed on emergency basis in cardiogenic shock patients for various reasons. The ECLS cannulation was performed using either central or peripheral ECLS approach. The durable MCS was implanted either in a standard fashion through a median sternotomy or less invasive technique. The outflow graft was connected to the ascending aorta in all cases. Some of the patients were operated on ECLS without using cardiopulmonary bypass. However, cardiopulmonary bypass was used at the time of durable MCS implantation for the other patients; either because of the necessity of concomitant procedures or surgeon preference. The impact of surgical techniques (with or without CPB as well as sternotomy *vs.* less invasive technique) on the stroke events was also investigated.

Anticoagulation Protocol

Once the patient was supported with ECLS, heparin was given for anticoagulation with target ACT of (180–200 sec) or activated partial prothrombin time of (40–60 sec). The anticoagulation was withheld in case of bleeding complications on ECLS. The anticoagulation protocol following durable MCS was similar between the centers and based on manufacturer recommendations. Heparin was initiated 24 hours after surgery, if no bleeding was seen. The target PTT was 40–50 sec in the first 24–48 hours after heparin initiation followed by target PTT value of 50–60 sec. Some minor variation between the centers was the timing of Aspirin therapy. Some centers started acetyl salicylic acid (ASS) (100 mg) from the first postoperative day, other centers later after removal of chest tubes. Warfarin was given later with target INR of 2–3. Platelet function test was performed in some centers and ASS was replaced with Clopidogrel when ASS resistance was detected. In cases of stroke events, the anticoagulation was adjusted based on the type of stroke and recommendation from neurologist.

Statistical Analysis

Continuous study variables were evaluated for both normal distribution and outlier activity. Data were reported as mean with standard deviation if normally distributed, or as median with the interquartile range (IQR) otherwise. For categorical data, the frequencies are given. Statistical tests were performed according to type, normality, and scedasticity of data with Welch two-sample t-test, Wilcoxon signed-rank test, or χ^2 test. Kaplan-Meier estimates were calculated to describe survival, with the date of MCS implantation as the starting point. Comparison of survival curves was performed using the log-rank test. Competing risk analysis *via* cox proportional hazards regression model was performed for baseline parameters with a p value <0.10 in the descriptive analysis for early and late stroke. Because of variability in the use of pump types between the centers, we included center names in the statistical modeling as a covariate to determine if there are differences in the outcome based upon center.

Results

Study Population

Overall, 531 patients met the inclusion criteria. Patients who were supported with pulsatile pumps, CardioWest total artificial heart, or earlier generation pumps were excluded from the analysis. The remaining 495 patients (median age 54 years old [IQR 47–60], 81% male, median ECLS support duration 5 [2–8] days and median STS score of 5.0% [3.5–7.2] and model of end stage liver disease [MELD] score of 18 [11–25]) were supported with either HeartWare HVAD in 370 patients (75%), HeartMate II in 81 patients (16%) or HeartMate III in 44 patients (9%). Up to 156 patients (32%) of the total cohort had a history of cardiopulmonary resuscitation before ECLS support. A total of 206 patients (42%) were operated on ECLS without using a cardiopulmonary bypass machine, and 94 patients (19%) underwent concomitant procedures at the time of durable MCS implantation. Minimal invasive MCS implantation technique was used in 42 patients (8%). Following durable MCS implantation, bleeding requiring reexploration was

documented in 172 patients (35%), and mechanical right ventricular support for right ventricular failure was necessary for 212 (43%) of the patients. The median follow-up time of the entire cohort independent of the stroke events was 520 days [35–1,349]. During the follow-up, 102 patients (21%) underwent heart transplantation and in 25 patients (5%) the device was explanted after recovery of the left ventricular function. Postoperative driveline infection was reported in 118 (24%) of the patients and postoperative gastrointestinal bleeding complication was documented in 89 (18%) of the patients during the follow-up. The 30 days and 1 year survival for the total cohort were 76.8% and 54.5%, respectively.

Primary and Secondary Outcomes

A total of 136 patients (27%) developed postoperative stroke on the device during the follow-up (48% ischemic and 52% hemorrhagic) after a median VAD support of 320 [32–1,000] days, accounting for 0.17 events per patient-year. Figure 1 shows freedom from a stroke during the follow-up in the study cohort. A total of 47 (10%) and 102 (21%) developed stroke during the first 30 days and 1 year, respectively. Forty-seven patients (10%) developed disabling stroke (modified Rankin Score ≥3). Forty-nine patients (10%) died caused by stroke. The survival rate was significantly lower in patients who developed hemorrhagic stroke during the follow-up compared with ischemic stroke (p = 0.00091) (Figure 2). The incidence of stroke in different kinds of pumps was as follows: HeartMate II (23%), HeartMate III (18%), and HeartWare (29%). This was corresponding to 0.176 EPPY, 0.091 EPPY, and 0.184 EPPY for HeartMate II, HeartMate III, and HeartWare HVAD, respectively (p = 0.16). Figure 3 illustrates freedom from stroke based on the durable MCS type.

Early Versus Late Stroke

To better characterize the risk factors for stroke, we further categorized patients into those who developed stroke in the early 30 days (early stroke) and those who developed stroke after 30 days (late stroke). A total of 47 patients (10%) developed stroke during the first 30 days. The type of stroke during the first 30 days was ischemic stroke in 64% *versus* hemorrhagic in 36% of the cases. Twelve of those 47 patients with early stroke (26%) died caused by stroke. Figure 4 illustrates the correlation between stroke events and survival. Notably, in 12 of 136 patients with stroke, the type of stroke was unknown. The majority of early mortalities were caused by multiple organ failure so early stroke had no impact on the survival following durable MCS implantation. Perioperative characteristics of patients with or without early *versus* late stroke is shown in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A809). The only risk preoperative risk factor for early stroke was Base excess <2 mmole/L (p = 0.02). Further, early stroke was associated with higher postoperative rates of respiratory failure, liver failure, and gastrointestinal bleeding (p = 0.008, 0.039, and 0.025, respectively).

Of the 380 patients from the total cohort who survived the first 30 days, 6 dropped out based on durable MCS explanation. Of the 374 remaining patients, a total of 86 patients developed stroke after 30 days of durable MCS support (late stroke). The type of stroke after 30 days was ischemic stroke in 38% *versus* hemorrhagic in 62% of the cases. Unlike early stroke, late stroke was associated with inferior survival following durable MCS implantation (Figure 4). The perioperative characteristics of patients with or without late stroke are shown in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A809). A higher rate of epinephrine use on ECLS was observed in patients who developed late stroke (p = 0.04). Further, late stroke was associated with higher transfusion rates of fresh frozen plasma (FFP) during the first 24 hours (p = 0.02), as well as higher rates of pump thrombosis events (p = 0.0027). Moreover, those with late stroke had a higher rate of HeartWare HVAD pumps (85% *vs*. 71%, p = 0.01). The median VAD support duration was 497 days [195–1193] in patients with late stroke and 584 days [204–1188] in those without late stroke (p = 0.56).

As many patients expired early after durable MCS implantation, caused by multiple organ failure, competing for risk analyses *via* cox proportional hazards regression model for

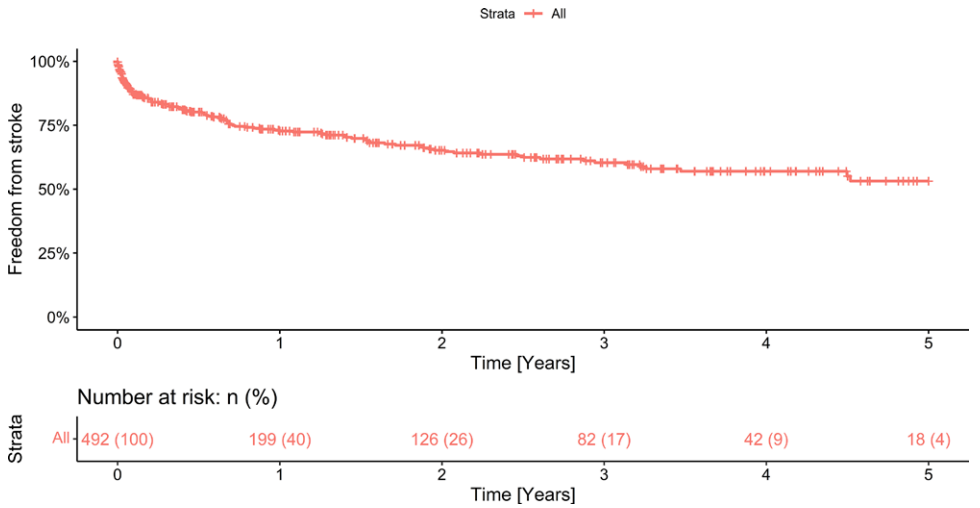

Figure 1. Freedom from stroke during the entire follow-up after durable MCS implantation. At 1 year of follow-up, only 75% of the patients were free of any kind of stroke. Note that three patients have been excluded based on the missing date of stroke. MCS, mechanical circulatory support. full color online

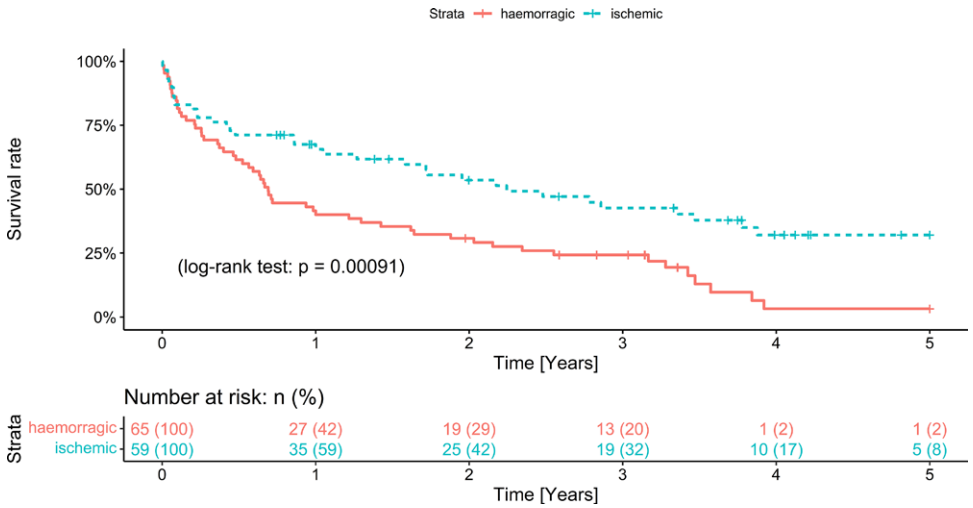

Figure 2. Survival based on type of stroke. Patients with hemorrhagic stroke on durable MCS showed significantly lower survival than those with ischemic stroke complications (p = 0.00091). Note that for 12 of 136 patients with stroke the type of stroke was unknown. MCS, mechanical circulatory support. full color online

the baseline parameters with a p value <0.10 in the descriptive analysis was performed for early and late stroke following durable MCS implantation (Table 1). Based on this analysis only preoperative BE ≤ 0 mmol/l (OR 1.57; 95% CI, 1.1–2.24; p = 0.01) was a risk factor for early stroke. Because of some variability in the use of pump types between the centers, center type was included in the statistical analysis. Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A809) shows the results after including center as a covariable. Except for BE (OR 1.6; 95% CI, 1.07–2.41; p = 0.023) for early stroke, none of the other parameters or center were predictive for early or late stroke. Further, variations in the type of implanted pumps between the centers are shown in Supplementary Table 3 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A809). The majority of the centers predominately used HeartWare HVAD pump. Finally, no statistically significant differences were found between the specific type of concomitant procedures (aortic valve procedure *versus* tricuspid valve procedure *versus* CABG procedures *versus* other procedures) and stroke rates (p = 0.87 *vs*. 1.0 *vs*. 0.46 *vs*. 0.43, respectively).

Discussion

In this multicenter trial, we were able to characterize for the first time the incidence, types, and risk factors for stroke in patients who were supported with durable MCS after ECLS. We can summarize our main findings as follows:

1. With stroke incidence of 27% of the total patient population, stroke appears to be a common complication in this patient population.

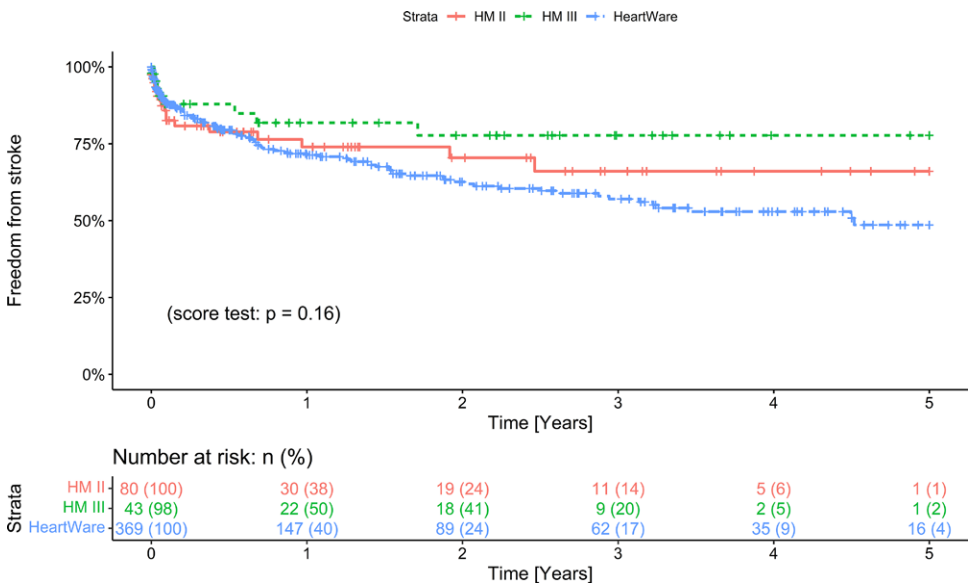

Figure 3. Freedom from stroke based on type of durable MCS used after ECLS. No significant differences were observed (p = 0.16). A trend toward lower stroke events in patients supported with HeartMate III was observed. ECLS, extracorporeal life support; MCS, mechanical circulatory support. full color online

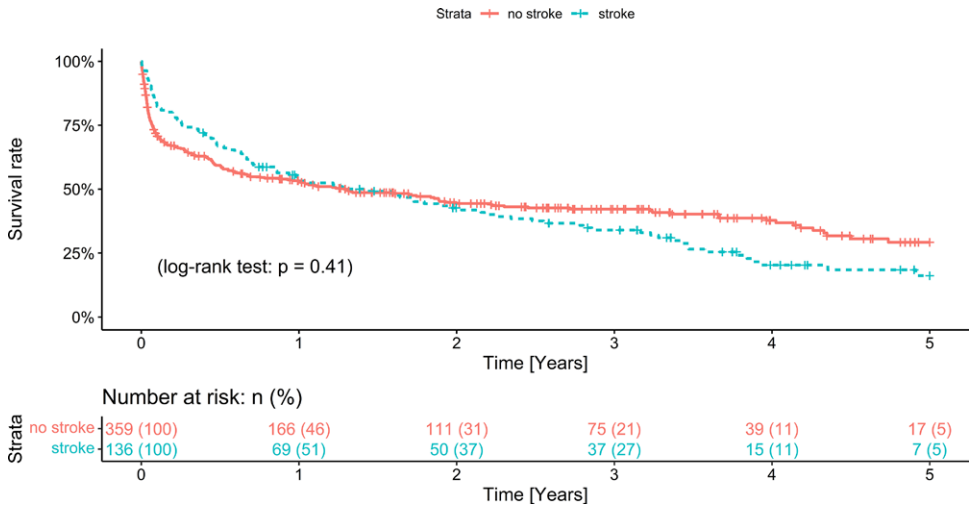

Figure 4. Kaplan–Meier survival in patients with or without stroke complications. Early stroke had no impact on the survival as the majority of the patients expired during the first 30 days caused by multiple organ failures. However, late stroke was associated with inferior outcomes. full color online

2. Ischemic stroke dominates early types of stroke and hemorrhagic stroke is a more common form of late stroke.
3. The survival rate after hemorrhagic stroke is significantly lower than ischemic stroke.
4. Early stroke has no negative impact on the outcome. However, the survival rate is limited in patients who develop stroke after 30 days of durable MCS support.

Stroke is one of the common complications following durable MCS support. The incidence of stroke among patients who receive continuous-flow LVADs is noted to vary 0.08–0.29 EPPY.[1–4] In the recent analysis of the Momentum Trial, a 3.3 times lower stroke incidence rate with HeartMate III has been reported compared with HeartMate II.[5] In our study, only patients who were supported with HeartWare HVAD, HeartMate II, and HeartMate III were included. The majority of the patients were supported with HeartWare HVAD (370 patients, 75%), followed by HeartMate II in 81 patients (16%), and HeartMate III in 44 patients (9%). This study was not designed to illustrate stroke differences between different kinds of pumps. The incidence of stroke in HeartMate II, HeartMate III, and HeartWare HVAD was 0.176 EPPY, 0.091 EPPY, and 0.184 EPPY, respectively ($p = 0.16$) (Figure 3).

Table 1. Competing Risk Analysis *via* Cox Proportional Hazards Regression Model Including Baseline Parameters for Early and Late Stroke Following Durable MCS Implantation After ECLS

Parameter	OR	95% CI	*p*
Early stroke			
Hb value (mg/dL)	1.07	0.98–1.18	0.15
BE ≤ 0 mmol/l	1.57	1.1–2.24	0.01
Less Invasive VAD Implantation	0.93	0.5–1.73	0.81
Late stroke			
Age (years)	1	0.97–1.03	0.81
Epinephrine use	1.3	0.63–2.66	0.48
Total Surgery Time (min)	1	0.99–1	0.53
CPB Time (min)	1	0.99–1	0.31
VAD Type: HM III	0.16	0.02–1.36	0.09
VAD Type: HeartWare HVAD	1.35	0.53–3.39	0.53

BE, base excess; CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; Hb, hemoglobin; HMIII, HeartMate III; MCS, mechanical circulatory support; VAD, ventricular assist device.

The incidence of stroke in our study is higher than the known reported rate of stroke after any kind of these pumps. We hypothesize that patients who require durable MCS after ECLS, will be objected to two hits, first from ECLS, which is already known for stroke complications, and second from the durable MCS implantation. Up to 10% of the stroke events were reported in the first 30 days, which may be procedure related. This rate is comparable with early stroke rates previously reported.[5] Notably, the rate of bleeding complications in this patient population (35%) is much higher than the bleeding rates after "conventional" VAD implantation. The reason beyond this observation is the fact that these patients have massive derangement of the coagulation cascades, which may be caused by cardiogenic shock status and inflammatory processes before ECLS implantation as well as the well described ECLS related bleeding tendencies. Further, we found a statistically significant association between no. of FFPs being administrated and incidence of late stroke ($p = 0.02$), Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A809).

Regarding types of stroke, in a systemic review by Sung *et al*. of stroke rates in patients supported with HeartWare HVAD and HeartMate II LVAD, it has been reported that overall, stroke occurred in 9.8% (or 0.08 EPPY) and roughly a third of patients died after ischemic stroke and nearly two-thirds died after a hemorrhagic stroke, making stroke one of the leading causes of death after LVAD placement.[10] In our study, up to 64% of early strokes were ischemic and merely 38% of the strokes were ischemic in late strokes. Similar to previous studies, survival rate was significantly lower in patients who developed hemorrhagic stroke ($p = 0.00091$) (Figure 2).

To better identify risk factors for stroke events, we performed a competing risk analysis *via* the cox proportional hazards regression model. With this model, we were able to differentiate risk factors of mortality from stroke risk factors, which was the main focus of our study. In previous studies, risk factors for stroke have included the durable MCS type, female sex, atrial fibrillation,

a history of stroke, hypertension, infection, pump thrombosis, gastrointestinal bleeding, and insufficient (for ischemic strokes) or excessive (for hemorrhagic) antithrombotic therapy.[5,11,12] In this study, preoperative BE < 0 (OR 1.57; 95% CI, 1.1–2.2; $p = 0.01$) was the only predictor for early strokes in the competing risk analyses. It appears that patients with metabolic acidosis and ECLS may develop more stroke complications, possibly indirectly related to the association of metabolic derangements and inflammatory response and consequent stroke complications. Considering late stroke events, patients who developed late stroke had a higher rate of epinephrine use preoperatively ($p = 0.04$). Many centers use Epinephrine to promote ejection and reduce the risk of left ventricular distention on ECLS. This intermittent ejection seems to correlate with late stroke events. Further, a strong association was found between late stroke events and the number of FFP units during the first 24 hours ($p = 0.02$) as well as pump thrombosis events ($p = 0.0027$). This finding is not surprising as the association between pump thrombosis and stroke has been previously reported.[13]

Considering outcome after stroke, we found that early stroke has no impact on survival early after durable MCS implantation (Figure 4). Twelve of those 47 patients with early stroke (26%) died caused by stroke. The majority of patients in the initial face expire caused by multiple organ failure. However, late stroke events after durable MCS implantation was associated with inferior outcome (Figure 4). Similar to other studies on stroke after durable MCS, stroke remains one of the complications that negatively impact the outcome of durable MCS therapy.

This study had many limitations; it is a retrospective data analysis. However, many centers collected data in their database prospectively. Nevertheless, type and date of stroke were not available for few patients. Further, minor differences between the centers existed considering starting date of ASS therapy. We cannot, therefore, comment on the impact of these differences on the outcome. However, the majority of centers used protocols recommended by the manufacturer. Notably, the exact number of patients who returned to normal neurologic status before the surgery is unknown but limited to less than 3% of the entire cohort based on personal communication with the participating centers. Therefore, almost all patients underwent a CT scan to rule out acute events before durable MCS implantation. Based on this observation, we assume that neurologic hits in these patients may occur perioperatively. Moreover, data exist only on the first event of stroke. No data on patients who developed more than one stroke event were collected. We also did not collect data on the management strategies of stroke events (surgical *vs*. conservative). Another limitation includes missing data on blood pressure values, which is reported as stroke predictor in previous studies. Further, no data on the INR values at the time of stroke events were collected. Therefore, we cannot comment on the impact of INR value on stroke events. Finally, we did not collect data on septicemia events after durable MCS therapy, which is also known as risk factor for stroke. However, collected data on driveline infection rates showed no association with early or late stroke events.

In conclusion, this study characterizes for the first time the largest series of stroke events in patients requiring durable MCS after ECLS support. Stroke appears to be a frequent complication in this sick patient population. Ischemic stroke dominates early 30 days and hemorrhagic stroke is more common after 30 days of support. Hemorrhagic stroke is associated with negative outcomes. Strong association between postoperative pump thrombosis and stroke events was observed.

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