Incidence and Predictors of Cognitive Decline in Patients with Left Ventricular Assist Devices

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Background—After left ventricular assist device (LVAD) placement for advanced heart failure, increased cerebral perfusion should result in improved cognitive function. However, stroke (a well-known LVAD complication) and subclinical cerebral ischemia may result in transient or permanent cognitive decline. We sought to describe the incidence and predictors of cognitive decline after LVAD using a valid, sensitive assessment tool.

Methods and Results—Among 4419 patients in the Interagency Registry for Mechanically Assisted Circulatory Support who underwent LVAD implantation between May 2012 and December 2013, cognitive function was assessed in 1173 patients with the Trail Making B Test before LVAD and at 3, 6, and 12 months. The test detects several forms of cognitive impairment, including subclinical stroke. Cognitive decline was defined as a clinically important increase during follow-up using a moderate Cohen’s effect size of 0.5×baseline SD (32 s). The cumulative incidence of cognitive decline in the year after LVAD implantation, treating death and transplantation as competing risks, was 29.2%. In adjusted analysis, older age (≥70 versus <50 years; hazard ratio, 2.24; 95% confidence interval 1.46–3.44; \( P_{\text{trend}}<0.001 \)) and destination therapy (hazard ratio, 1.42; 95% confidence interval 1.05–1.92) were significantly associated with greater risk of cognitive decline.

Conclusions—Cognitive decline occurs commonly in patients in the year after LVAD and is associated with older age and destination therapy. These results could have important implications for patient selection and improved communication of risks before LVAD implantation. Additional studies are needed to explore the association between cognitive decline and subsequent stroke, health status, and mortality in patients after LVAD. (Circ Cardiovasc Qual Outcomes. 2015;8:285-291. DOI: 10.1161/CIRCOUTCOMES.115.001856.)

Key Words: brain ischemia ■ heart-assist devices ■ mild cognitive impairment

Patients with advanced heart failure (HF) who receive left ventricular assist devices (LVAD) typically experience marked improvements in health-related quality of life1 and survival,2 when compared with those treated only with optimal medical management. Because neurocognitive dysfunction caused by hypotension occurs in ≈25% to 50% of patients with advanced HF,3-4 another potential benefit of LVAD implantation is improved cognitive function resulting from restoration of adequate cerebral perfusion. Unfortunately, this potential benefit can be offset by the high risk of adverse neurological events that accompanies LVAD therapy. Although stroke is a well-described and readily diagnosed complication of LVAD,6 other factors associated with LVAD implantation (eg, cardiopulmonary bypass postperfusion syndrome, silent microthromboembolic events, and device-related changes in cerebral perfusion) may also adversely affect cognitive function but be less obvious to clinicians.5-11 Few studies have addressed cognitive changes in patients after LVAD implantation, and these studies not only yielded conflicting results but were also limited by small sample sizes, missing baseline assessment of cognitive function, minimal adjustment for confounders, and lack of real-world applicability.12-17 As such, the burden of cognitive decline among patients receiving LVADs is largely unknown. Therefore, we leveraged the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)—a multicenter, observational registry of patients receiving mechanical circulatory support in the United States—to identify the real-world incidence and predictors of cognitive decline after LVAD. Given improving survival trends among patients with LVADs,7 the
WHAT IS KNOWN

• In patients with advanced heart failure, left ventricular assist device (LVAD) therapy should not only improve cognitive function by restoring adequate cerebral perfusion, but may also increase risk of cerebral thrombotic events (ie, subclinical or clinical stroke), which may offset this improvement in cognition.
• Small studies have yielded mixed results about the incidence and direction of change in cognition after LVAD implantation.

WHAT THE STUDY ADDS

• In a large multicenter registry, cognitive decline occurred in >1 in 4 patients in the year after LVAD implantation, whereas older age and a device strategy of destination therapy were associated with a greater likelihood of cognitive decline.
• Cognition often improved among those patients without cognitive decline, supporting the notion that LVADs do improve cerebral perfusion, unless a patient experiences an ischemic event; unfortunately, this occurs commonly.
• Although further research is needed to better understand the effects of cognitive decline events on quality of life and risk of stroke or death, these results could provide important implications for preparing patients prior to LVAD placement through better communication about the potential risks of the therapy.

Methods

Study Design and Population

INTERMACS is a prospective national registry of patients with advanced HF receiving durable mechanical circulatory support. Established in 2005, INTERMACS is administered through a National Heart, Lung, and Blood Institute–funded contract to the University of Alabama at Birmingham and is focused on quality improvement and scientific research. All consecutive, noninfarcted patients who are ≥19 years and receive Food and Drug Administration–approved devices are screened for enrollment in the registry, regardless of length of device implantation. Data are collected through medical chart abstraction and patient interviews by trained personnel at each participating site. Comorbidities and clinical conditions before device implantation that might be considered risks for poor outcomes are abstracted from the chart by trained data personnel (eg, severe diabetes mellitus, severe depression, malnutrition, and frailty), although explicit definitions of these conditions are not provided by INTERMACS for standardization. Follow-up is attempted on all surviving patients at 1 week, 1 month, 3 months, 6 months, and every 6 months thereafter for the life of the device (ie, patients are censored at the time of transplant, death, or explant for either myocardial recovery, or are followed up for up to 1 year after explant for device complication). The Institutional Review Board at the University of Alabama at Birmingham granted a waiver of individual patient informed consent in INTERMACS because it is considered primarily a quality improvement registry. All participating sites obtained Institutional Review Board protocol approval, as well.

Definition of Cognitive Decline

Cognitive decline was defined based on serial Trail Making Test, part B (TMT-B) scores. These were collected before LVAD placement and at each follow-up beginning with 3 months. The TMT-B was developed originally in 1944 as a part of the Army Individual Test Battery, was later incorporated into the Halstead-Reitan Neuropsychological Test Battery, and has become one of the most well-validated and widely used measures of cognitive dysfunction. The test is specific for executive dysfunction, attention/concentration, working memory, problem-solving and frontal lobe injury, but has been shown to measure many components within the broad construct of cognitive function. In the test, the subject connects 25 dots labeled with alternating, consecutive numbers and letters (1, A, 2, B, etc.) as quickly as possible and must correct errors (with prompting if needed) before connecting the next dot. A longer time to complete the test indicates a worse score/poorer cognition. The TMT-B is sensitive to several neurologic impairments and processes, including subclinical cerebral ischemia and cognitive decline, as described in conditions such as atrial fibrillation, carotid stenosis, silent stroke, and hypertension. Within INTERMACS, the test was administered in person, either inpatient or outpatient, at each follow-up. Data collection personnel were given detailed instructions on test administration and a script to standardize test delivery.

Given a lack of normative TMT-B data in the LVAD population (who are notably sicker and with higher rates of cognitive dysfunction than a healthy adult population), we defined a meaningful change in cognition based on Cohen’s d effect size, which quantifies the magnitude of effect in terms of baseline variation of the specific study population. Meaningful cognitive decline was defined as an increase of 32 seconds or longer (0.5×baseline TMT-B score SD of 64 s, corresponding to a moderate effect size), either from one time point to the next (eg, 100 s at baseline to 132 s at 3 months) or additively over consecutive time points (eg, 100 s at baseline to 120 s at 3 months to 132 s at 6 months). Among patients without baseline decline, we defined cognitive improvement as a ≥32-s decrease (shorter time) in TMT-B score between baseline and last follow-up scores.

Statistical Analysis

Baseline characteristics were compared between patients with cognitive decline versus no cognitive decline using χ² tests for categorical variables and t tests for continuous variables. Next, to account for differential follow-up, we examined the incidence of cognitive decline over the year after LVAD with cumulative incidence curves. As attrition from mortality or transplantation could introduce bias, we treated these as competing events. Given that ≈20% of patients had missing interval TMT-B data between baseline and last follow-up scores, we performed a sensitivity analysis censoring such patients at the assessment just before their first missing assessment.

We then constructed a multivariable competing risks regression model based on the Fine and Gray proportional subhazards model to identify predictors of cognitive decline, accounting for the competing risks of death and transplantation. Factors included in the model were selected a priori based on literature review and clinical judgment and included age, body mass index, sex, device strategy (bridge to transplant [including bridge to decision/transplant likely or moderately likely] versus destination therapy [including bridge to decision/transplant unlikely]), INTERMACS profile (an assessment of clinical severity of HF; 1–2 [multiorgan failure and declining clinical status despite inotropes] versus 3–7 [more stable disease]), baseline TMT-B score, current smoking, frailty, chronic renal disease, pulmonary disease, atrial arrhythmia, severe diabetes mellitus, malnutrition, history of major stroke, peripheral vascular disease, history of malignancy, history of alcohol or illicit drug abuse, and severe depression. Because of potential practice effects on test–retest score...
improvement with the TMT-B, we conducted a sensitivity analysis in which the number of follow-up tests taken by the patient (1, 2, or 3) was included in the multivariable model. In a final sensitivity analysis, we excluded any patients who experienced a stroke between device implantation and 12 months, to assure that the results were not driven entirely by clinical strokes. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC), and statistical significance was determined by a 2-sided $P$ value of <0.05.

Missing Data
Patients were included if they had a baseline and at least 1 follow-up TMT-B. The baseline characteristics of patients in the analytic cohort were compared with those who survived at least 3 months (and thus had the opportunity for follow-up) but were missing baseline TMT-B data or missing all follow-up TMT-B data. To minimize the effect of selection bias because of loss to follow-up, we constructed a multivariable logistic regression model to determine the probability of having missing data. We then weighted each of the patients in the analytic cohort by the inverse probability of the likelihood of having missing data. Results of this analysis were consistent with the primary analysis, and thus only the unweighted analyses are presented. Baseline data were generally complete, with 96% of patients not missing any baseline covariate data and an average of 0.04 items missing per patient. Missing data were imputed using sequential regression imputation conditioning on all covariates and outcomes (IVWare; Institute for Social Research, Ann Arbor, MI).

Results
Study Population
There were 4419 patients with advanced HF who were ≥19 years and received durable LVADs from May 2012 (when the TMT-B was first systematically collected in INTERMACS) to December 2013—patients who received total artificial hearts and right and biventricular assist devices were not considered for this analysis. We excluded patients who received pulsatile-flow LVADs (n=4) and those who received LVADs with device strategies including bridge to recovery (n=11), rescue therapy (n=8), and others (n=14). There were 369 patients who died before the 3-month follow-up and thus had no opportunity to complete any follow-up TMT-B assessments. Of the remaining 4013 eligible patients, 2840 were excluded because of missing TMT-B data (2138 missing baseline and 702 missing all follow-up). Our final cohort, therefore, included 1173 patients (Figure 1), among whom 60 to 69 was the most common age group (34%), 20% were women, and 40% were INTERMACS profile 1 to 2 at implant.

Compared with those in the analytic cohort, patients with missing baseline data were younger ($P_{age}<0.001$), more likely designated for bridge to transplant ($P<0.001$), and had more severe HF (INTERMACS profile 1–2; $P<0.001$) and higher rates of interventions before device implantation (intra-aortic balloon pump, dialysis, ventilator, feeding tube, and extracorporeal membrane oxygenation; $P<0.001$ for all). Patients missing follow-up data were similar to those in the analytic cohort (Table I in the Data Supplement).

Cognition and Incidence of Cognitive Decline
Among the subset of patients with 12-month follow-up TMT-B (n=349), unadjusted mean (±SD) scores improved from of 126±61 s at baseline to 103±53 s at 1 year. In unadjusted analysis of the 1173 patients with available follow-up data through 1 year, 21.0% experienced meaningful cognitive decline, whereas 34.5% had improved cognitive function and the remaining 44.5% had no significant change in cognition.

After accounting for differential follow-up and competing risks of death and transplantation, the cumulative incidence of cognitive decline in the year after LVAD implantation was 29.2% (Figure 2). In the sensitivity analysis where patients were censored before missing interval TMT-B assessments, the results were similar, with a cumulative incidence of cognitive decline over the first year after LVAD of 24.6%.

Predictors of Cognitive Decline
The baseline characteristics of those with versus without cognitive decline are shown in the Table. Patients with cognitive decline tended to be older ($P_{age}<0.001$) and more likely designated for destination therapy ($P<0.001$), to be in INTERMACS profiles 3 to 7 (more stable HF; $P=0.005$) and have shorter baseline TMT-B times (better cognition; $P=0.035$) before implant. In a multivariable, proportional subhazards model with death and transplantation as competing risks, significant predictors of cognitive decline included increasing age ($≥70$ versus $<50$ years; hazard ratio [HR], 2.24; 95% confidence interval [CI], 1.46–3.44; $P_{age}<0.001$) and destination therapy strategy (HR, 1.42; 95% CI, 1.05–1.92; $P=0.023$), with nonsignificant trends for history of major stroke (HR, 1.64; 95% CI, 0.92–2.94; $P=0.094$) and malignancy (HR, 1.38; 95% CI, 0.96–1.98; $P=0.081$; Figure 3). The sensitivity analysis including a variable for the number of times a patient had completed the TMT-B showed that frequency of repeat testing was not associated with cognitive decline (HR, 0.98 per each additional test; 95% CI, 0.74–1.31; $P=0.902$). Finally, the results of the sensitivity analysis excluding 74 patients with documented clinical stroke in the first year after LVAD were also consistent with the primary analysis, with a 1-year cumulative incidence of cognitive decline of 28.5%. Factors associated with cognitive decline also remained similar in this analysis (Table II in the Data Supplement).
In a large national registry of patients with advanced HF who received LVAD support, a substantial proportion of patients exhibited the expected trend of cognitive improvement, likely representing restoration of cerebral perfusion. However, after accounting for the competing risks of death and transplantation, cognitive decline occurred in over one quarter of the patients based on available follow-up data in the year after device implantation. Older age and destination therapy were found to be predictors of cognitive decline. These results were not meaningfully different when censoring patients at the time of missing interval follow-up, accounting for practice effects of the test, or excluding patients with stroke after LVAD implantation. Furthermore, the rate of cognitive decline observed after LVAD was dramatically higher than would be expected because of normal aging, which is estimated to be 0.02 to 0.05 SD per year in healthy subjects ≥ 60 years. Although other factors, such as multiple comorbidities, may account for some of this decline, we think that LVADs are independently associated with cognitive decline, as well, because of their accompanying high risk for neurological events because of cerebral ischemia of various causes. We think that these results could have important implications for preparing patients before LVAD placement through better communication about the potential risks of the procedure, as well as potentially contributing to patient selection, given the high level of self-care required by LVAD recipients.

Previous studies of the effects of LVADs on cognition have primarily been single-center registries or substudies of larger trials. Early studies focused on patients who subsequently had heart transplant and generally found worse cognition post-transplant among patients who received LVADs before transplant when compared with those who did not. In one of these studies, the cognitive decline observed in patients who had pretransplant LVAD support was linked to the presence of thrombus on the device at the time of explant. In contrast, in a small, single-center prepost study of patients who received LVADs without subsequent transplant, cognitive function was reported as improved at 12 weeks. Importantly, however, this cohort did not achieve normalization of cognitive function by the end of the study when compared with matched healthy subjects. More recent studies have demonstrated evidence of sustained cognitive improvement or, at least, stability with LVAD therapy. In 3 studies of patients after LVAD, mean scores on a number of neurocognitive tests, including the TMT-B, either remained stable or improved for ≤ 24 months although baseline measures were only obtained for comparison in 1 study.

Our study adds significantly to this body of literature on cognitive function in patients after LVAD implantation in many ways. Our analytic cohort was substantially larger (∼10x larger than the largest previous study) and comes from an observational registry with few exclusion criteria, rendering our results more generalizable. In addition, baseline measurements of cognitive function were available for comparison, and we defined a meaningful change in neurocognitive function using accepted statistical techniques. Although previous studies have yielded conflicting results about the directionality of changes in neurocognitive function after LVAD, ours is the first to highlight the heterogeneity of LVAD treatment on cognition, where some patients clearly improve and others decline.

Patients with advanced HF who receive LVADs are likely to experience improved survival. However, this device also exposes patients to new risks, such as cognitive decline. Previous research has shown that only 30% of patients remain free from major adverse events (infection, bleeding, device malfunction, stroke, or death) at 1 year after LVAD. Cognitive decline has been less well studied than these adverse events, in part, because serial testing is needed to recognize its often-subtle presentation. We think that the high incidence of cognitive decline reported herein is a particularly
important finding given the assumption that long-term neurocognitive function should improve when cerebral perfusion is restored because of LVAD therapy, just as function of other end organs has been shown to do.42 Notably, we found that among those without cognitive decline (ie, those who did not have subclinical cerebral ischemic events), cognitive function frequently does improve. These results support the notion that LVADs do improve cerebral perfusion and, consequently, cognition, unless the patient experiences an ischemic event. Unfortunately, such events are common. Our results could have potential implications for prospective risk modeling to better communicate these risks to prospective LVAD patients. Future expansion of our preliminary work on predictors of cognitive decline could ultimately support such goals.

Our results should be interpreted in the context of several potential limitations. First and most importantly, the majority of LVAD implants in INTERMACS had to be excluded from this analysis because of missing TMT-B scores (particularly at baseline). Patients with missing baseline data may have been too ill to complete the test, which requires both concentration and the physical capability to hold a pen and draw lines. This illness could have either precluded patients from taking the test at all (ie, patients who were ventilated and sedated) or precluded them from having enough cognitive function to complete the test (ie, altered mental status because of cardiogenic shock and cerebral hypoperfusion). Although we were able to illustrate that those with missing baseline data were much more ill than those who were able to complete the TMT-B at baseline, we are only able to hypothesize about what specific deficit precluded their taking the test. As such, the findings here only reflect and can be applied to a portion of the LVAD-eligible population. We did attempt to minimize these limitations of sample selection bias because of illness severity through inverse propensity weighting and the use of a cumulative incidence model with competing risks analysis. Nevertheless, how to best capture cognitive decline in patients either too sick to complete testing or in those with severe cognitive impairment at baseline remains unclear.

Furthermore, the TMT-B has not been validated in this population, and is likely subject to floor effects, wherein patients with poor cognition before LVAD implantation might not have been able to exhibit further decline on the test. As such, the findings here only reflect and can be applied to a portion of the LVAD-eligible population. We did attempt to minimize these limitations of sample selection bias because of illness severity through inverse propensity weighting and the use of a cumulative incidence model with competing risks analysis. Nevertheless, how to best capture cognitive decline in patients either too sick to complete testing or in those with severe cognitive impairment at baseline remains unclear.

Figure 3. Baseline factors associated with cognitive decline among patients with left ventricular assist devices. CI indicates confidence interval; TMT-B, Trailmaking Test, part B; BMI, body mass index; and INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

### Table. Baseline Characteristics of Patients With vs Without Cognitive Decline

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cognitive Decline (n=246)</th>
<th>No Decline (n=927)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>17.1</td>
<td>26.0</td>
</tr>
<tr>
<td>50–59</td>
<td>22.8</td>
<td>24.5</td>
</tr>
<tr>
<td>60–69</td>
<td>32.5</td>
<td>34.2</td>
</tr>
<tr>
<td>≥70</td>
<td>27.6</td>
<td>15.4</td>
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<tr>
<td>Female, %</td>
<td>16.7</td>
<td>20.3</td>
</tr>
<tr>
<td>Body mass index, mean±SD</td>
<td>28.5±6.2</td>
<td>28.8±6.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-existing conditions, %</th>
<th>Cognitive Decline</th>
<th>No Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>33.6</td>
<td>43.7</td>
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<tr>
<td>3–7</td>
<td>66.4</td>
<td>56.3</td>
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<tr>
<td>Frailty</td>
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<tr>
<td>Chronic renal disease</td>
<td>22.0</td>
<td>21.3</td>
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<tr>
<td>Pulmonary disease</td>
<td>32.1</td>
<td>30.6</td>
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<tr>
<td>Atrial arrhythmia</td>
<td>24.8</td>
<td>20.1</td>
</tr>
<tr>
<td>Severe diabetes mellitus</td>
<td>8.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Malnutrition/cachexia</td>
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<td>2.3</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>History of major stroke</td>
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<td>2.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4.5</td>
<td>5.9</td>
</tr>
<tr>
<td>History of malignancy</td>
<td>12.2</td>
<td>7.1</td>
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<tr>
<td>Current smoker</td>
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<td>3.2</td>
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<tr>
<td>History of alcohol/drug abuse</td>
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<td>6.4</td>
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<tr>
<td>Severe depression</td>
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<td>2.6</td>
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<tr>
<td>Device strategy, %</td>
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<tr>
<td>Bridge to transplant</td>
<td>40.7</td>
<td>53.7</td>
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<tr>
<td>Destination therapy</td>
<td>59.3</td>
<td>46.3</td>
</tr>
<tr>
<td>Baseline Trail Making Test, part B time, s, mean±SD</td>
<td>123.1±59.0</td>
<td>132.7±64.8</td>
</tr>
</tbody>
</table>

INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support.
the improvement in cerebral perfusion from the LVAD itself, contributes to an expected trajectory of improved scores over time in the population. As such, we think that episodes of significant worsening in scores do, in fact, represent real events of cognitive decline.

Third, the clinical significance of cognitive decline, per our definition, is not conclusively known. We defined a clinically meaningful change in the TMT-B based on a moderate effect size and found high rates of cognitive decline. However, whether these changes translate into meaningful effects on quality or quantity of life or other important outcomes is unknown, although subclinical cerebral ischemia and cognitive decline have been shown in non-LVAD studies to be associated with poor outcomes in older patients with HF and cerebrovascular disease.14,15 Similarly, although impermanent neurocognitive events, such as transient ischemic attack and delirium, are known to be associated with poor outcomes,16–17 whether transient cognitive decline carries the same prognostic importance as permanent decline in the setting of an LVAD is unknown. Unfortunately, in this analysis, we did not have adequate follow-up data to distinguish between transient and permanent decline. Finally, as is the case with observational studies, there remains the possibility of unmeasured confounding in our analysis of predictors of cognitive decline after LVAD placement, and these results should only be considered hypothesis generating.

Our findings reveal substantial heterogeneity in neurocognitive function after LVAD implantation, with a high incidence of cognitive decline among a contemporary population of patients with advanced HF receiving LVADs. Although patients receiving LVADs do experience improved end-organ perfusion, the risk of adverse neurological events, presumably at least in part because of subclinical cerebral ischemia, is substantial. These results should prompt further investigation into the mechanisms and predictors of cognitive decline after LVAD implantation, with goals of better prognosticating (or preventing) this outcome and engendering more transparent conversations with patients about the entirety of potential risks before implantation. Future work should also explore outcomes associated with transient and permanent patterns of decline, including their effect on health status and risk of subsequent stroke or death, to optimize quality of life among patients living with LVADs.

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Disclosures
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