Dynamic Forecasts of Survival for Patients Living With Destination Left Ventricular Assist Devices: Insights From INTERMACS

Katherine C. Michelis, MD; Lin Zhong, MPH; Matthias Peltz, MD; Ambarish Pandey, MD, MSCS; W. H. Wilson Tang, MD; Anand Rohatgi, MD; James B. Young, MD; Mark H. Drazner, MD, MSc; Justin L. Grodin, MD, MPH

BACKGROUND: Left ventricular assist devices (LVADs) improve outcomes in patients with end-stage heart failure and are increasingly implanted for destination therapy. We describe dynamic estimates of event-free survival with conditional survival probabilities in a destination therapy LVAD population.

METHODS AND RESULTS: We studied 8245 adult patients in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) implanted with a continuous-flow destination therapy LVAD. The composite primary end point was death, device exchange or removal, or heart transplantation. Conditional survival probabilities were calculated and stratified by implantation characteristics and nonfatal adverse events experienced within the first year after implant. Probabilities of surviving an additional 1 to 3 years were numerically higher after longer prior event-free survival. INTERMACS profile 1, extracorporeal membrane oxygenation support, prior or concomitant surgery, and dialysis within 48 hours of implantation were associated with significantly lower event-free survival in the first year but did not impact event-free survival beyond then. For patients who experienced a nonfatal adverse event within the first year, subsequent 1-year conditional survival was lower than in the absence of that event for stroke (65% [95% CI, 57%–73%] versus 75% [95% CI, 73%–77%]; P<0.001), device-related infection (64% [95% CI 57%–71%] versus 76% [95% CI, 74%–78%]; P<0.001), and pump thrombosis or malfunction (64% [95% CI, 57%–70%] versus 76% [95% CI, 74%–78%]; P<0.001).

CONCLUSIONS: Conditional survival in patients with destination therapy LVADs improves over time, even for patients with unfavorable implantation characteristics. However, LVAD-related complications including stroke, device-related infection, and pump thrombosis or malfunction have an enduring negative influence on dynamic estimates of long-term prognosis.

Key Words: destination therapy ■ left ventricular assist device ■ mechanical circulatory support

Left ventricular assist devices (LVADs) improve survival, functional capacity, and quality of life in patients with end-stage heart failure who are not candidates for heart transplantation.1,2 Over the past decade, in parallel with the rising prevalence of end-stage heart failure, the proportion of LVADs implanted for destination therapy (DT) has increased.3,4 Because DT LVADs are implanted with the intention of being a lifelong therapy, the process of deciding whether and when to implant a DT LVAD can be challenging for clinicians, patients, and caregivers.5,6

While baseline risk factors for adverse events at the time of implant are informative, they fail to show the dynamic nature of prognosis as it evolves over time. This is particularly relevant for patients implanted with DT LVADs who are expected to live with their LVAD longer than those implanted as a bridge to cardiac transplantation. In contrast to standard cumulative survival
Michelis et al Conditional Survival of Patients With DT LVADs

CLINICAL PERSPECTIVE

What Is New?
- This study provides dynamic estimates of survival for patients who are living with destination therapy left ventricular assist devices, taking into account time already survived since implantation, implantation characteristics, and device-related adverse events.
- Patients with a destination therapy left ventricular assist device generally have a better prognosis after surviving ≥1 years, even if they had unfavorable characteristics at the time of implantation.

What Are the Clinical Implications?
- Certain adverse events including nonfatal stroke, pump thrombosis or malfunction, and device-related infection have a persistently negative influence on long-term event-free survival.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition                        |
|--------------|-----------------------------------|
| CS           | conditional survival              |
| DT           | destination therapy               |
| INTERMACS    | Interagency Registry for Mechanically Assisted Circulatory Support |
| LVAD         | left ventricular assist device     |

probabilities from implantation, conditional survival probabilities are related to prior survival and are well-suited to elucidate the long-term prognosis after device implantation becomes more remote.7

INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) has reported conditional survival 3 months after implantation and the influence of interim adverse events on additional survival.8 However, that and other conditional survival analyses were limited in scope and did not necessarily focus on a thorough appraisal of long-term conditional survival in patients with DT LVADs.3,10

Therefore, using data from INTERMACS, we aim to provide dynamic estimates of survival for patients with DT LVADs, focusing on how baseline characteristics and nonfatal LVAD-related adverse events that occurred within the first year impact long-term conditional survival.

METHODS

Study Population
Data from INTERMACS were acquired through the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute. INTERMACS includes all adults (≥19 years) who received a US Food and Drug Administration–approved mechanical circulatory support device between March 1, 2006, and December 31, 2017, at 170 active centers throughout the United States and Canada.11 Anonymized data and materials have been made publicly available at the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute and can be accessed at https://biolincc.nhlbi.nih.gov/studies/intermacs/. Data collection for INTERMACS has been previously described.12 In short, data for each patient were entered into INTERMACS by clinical personnel at participating INTERMACS centers at the time of LVAD implantation and during periodic follow-up. Collected information included clinical, surgical, and demographic characteristics; device-related information; adverse events; and clinical outcomes. For this analysis, patients were included who had a durable, continuous-flow LVAD implanted as DT (Figure S1). Patients implanted with LVADs as bridge-to-transplant or bridge-to-recovery, who had a prior LVAD, or who required temporary or long-term biventricular support were excluded. The institutional review board at the University of Texas Southwestern Medical Center determined that this study was exempt from review.

Adverse Events
The following adverse events were defined by INTERMACS and evaluated as an exposure for this analysis if they were both nonfatal and occurred within the first year after implantation: gastrointestinal bleeding, stroke, device-related infection, device complication, or renal dysfunction.12 Gastrointestinal bleeding was classified by source: upper, lower, or unknown but with guaiac-positive stools. Stroke was classified as ischemic/embolic, hemorrhagic, or other. Device-related infection was classified by location: driveline, exit cannula, pump interior, or pump pocket. Device complication referred to suspected or confirmed device thrombosis or device malfunction. Renal dysfunction referred to either acute or chronic renal dysfunction. Variable codes for these adverse events are displayed in Table S1. Acute renal dysfunction was defined as abnormal renal dysfunction necessitating initiation of dialysis or a rise in serum creatinine ≥3 times the baseline or ≥5 mg/dL that was sustained for at least 48 hours. Chronic renal dysfunction was defined as a rise in serum creatinine ≥2 mg/dL above baseline or a need for hemodialysis that was sustained for at least 90 days.
End Points
The composite primary end point for this study was defined to reflect failure of the originally implanted device and included death, device exchange or removal, or heart transplantation. Heart transplantation was included in the composite end point as the development of adverse events after DT LVAD implantation may influence the decision for transplantation in patients previously thought to not be candidates. Follow-up was censored at LVAD removal for cardiac recovery.

Statistical Analysis
Categorical variables are presented as number (percentage) and continuous variables are presented as median values with interquartile range.

Conditional survival (CS) probabilities were calculated using Kaplan–Meier estimates of survival for an additional 1, 2, 3, 4, and 5 years conditioned on a prior survival of 0, 1, 2, or 3 years after device implantation. CS is the probability of surviving an additional t years given that a patient has already survived s years after an event and is illustrated by the following formula:\(^7\):

\[ \text{Var}[\text{CS}(t|s)] = \text{CS}(t|s)^2 \times \sum_{s+1}^{t} \frac{d_k}{r_k(r_k-d_k)} \]

To determine the influence of clinical characteristics at implantation on the evolution of prognosis, CS probabilities were calculated for 1 additional year of survival conditioned on having survived 1, 2, or 3 years after device implantation across strata of baseline characteristics.

The hazard plot in Figure S2 highlights the early risk of the composite end point within the first year after DT LVAD implantation. Because we wanted to explore how nonfatal events during this “high-risk” period influenced prognosis over time, a separate CS analysis was performed 1 year from implantation. CS probabilities were calculated using the Kaplan–Meier method for 1 additional year of survival conditioned on having previously survived 1, 2, or 3 years from the 1-year landmark (2, 3, or 4 years from implantation). We further calculated standard errors of conditional survival probabilities using a variation of the Greenwood formula.

\[ \text{Var}[\text{CS}(t|s)] = \text{CS}(t|s)^2 \times \sum_{s+1}^{t} \frac{d_k}{r_k(r_k-d_k)} \]

Given n intervals between time s and time t, \(d_k\) is the number of events during interval k and \(r_k\) is the number at risk at the beginning of interval k.\(^\text{13}\)

These analyses were stratified by type or subtype of adverse event and number of adverse events. Comparisons in survival estimates were compared via the log-rank test. Two-sided \(P<0.05\) values were considered statistically significant. All statistical analyses were performed with R version 3.6.0 (The R Foundation).

Table 1. Baseline Characteristics

| Characteristic                        | N=8244 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 | N=8235 |
|--------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Age, y (N=8244)                      | 64 (55–71) | 6591 (80.0) | 5693 (69.0) | 1268 (19.1) | 1097 (13.3) | 6734 (82.2) | 318 (3.9) | 451 (6.8) | 114 (1.4) | 3422 (41.5) | 3126 (37.9) | 6655 (84.4) |
| Year of implant, No. (%)             | 2006–2010 | 570 (6.9) | 2011–2014 | 4094 (49.7) | 2015–2017 | 3581 (43.4) | LVEDD, cm (N=6160) | 6.7 (6.1–7.4) | Pulmonary capillary wedge pressure, mm Hg (N=5288) | 24 (18–30) | Sodium, mmol/L (N=8230) | 136 (133–138) | BUN, mg/dL (N=8194) | 26 (19–38) | Creatinine, mg/dL (N=8225) | 1.3 (1.0–1.7) | NT-proBNP, pg/mL (N=1847) | 4557 (2197–8942) | Total bilirubin, mg/dL (N=7715) | 1 (0.6–1.5) | Albumin, g/dL (N=7661) | 3.4 (3.0–3.8) | Hemoglobin, g/dL (N=8204) | 11.2 (9.8–12.8) | Glycated hemoglobin, % (N=856) | 6.2 (5.7–7) |

Values are presented as median (interquartile range) unless otherwise indicated for categorical variables. Because of missing data, N is listed for those variables where the cohort with available data was <8245. BMI indicates body mass index; BUN, serum urea nitrogen; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanical Circulatory Support Devices; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

\(\text{*Concomitant surgery included atrial septal defect, ventricular septal defect, or patent foramen ovale closure; valvular repair or replacement; coronary artery bypass grafting; congenital cardiac surgery; extracorporeal membrane oxygenation decannulation; intra-aortic balloon pump removal; or right ventricular assist device explant.}\)

\(\text{\textsuperscript{1}Previous cardiac surgery included valvular repair or replacement; coronary artery bypass grafting; congenital cardiac surgery; previous extracorporeal membrane oxygenation or right ventricular assist device; or Dor aneurysmectomy.}\)
RESULTS

Patient Characteristics
There were 8245 patients in INTERMACS who received a durable, continuous-flow LVAD for DT between March 1, 2006, and December 31, 2017. The baseline characteristics of the study cohort are shown in Table 1. The median age was 64 years (interquartile range, 55–71 years); the majority were men (80.0%), white (69.0%), and had New York Heart Association class IV symptoms (84.4%) at the time of DT LVAD implantation. Only 3.9% of patients received a centrifugal device, with 93.1% undergoing implantation between 2011 and 2017. There were 13.3% implanted as INTERMACS profile 1 (cardiogenic shock).

CS of the Study Cohort
Conditional probabilities of additional event-free survival according to prior survival for the study cohort are plotted in Figure 1. The conditional probabilities for an additional 1 to 5 years of survival were estimated for patients who had survived 0 to 3 years after the time of implantation. The probability of surviving an additional 1 to 3 years numerically increased given a longer time of prior survival. However, while probabilities of surviving an additional 4 or 5 years appeared relatively stable for patients with up to 2 years of prior survival, these estimates were numerically lower for patients with ≥3 years of prior survival.

Implantation Characteristics and CS
The probabilities of an additional 1-year of survival conditioned on prior survival time across strata of characteristics at DT LVAD implantation are shown in Figure 2. Consistent with the analysis in Figure 1, the additional 1-year event-free survival tended to numerically increase over time since implantation. Year of implantation, body mass index, and support with an intra-aortic balloon pump did not appear to influence differences in additional 1-year event-free survival for each year already survived from implantation. Interestingly, the additional 1-year event-free survival estimates after 1 or 2 years of prior survival were higher for patients aged 69 to 88 years at implantation compared with patients in the younger age groups (P<0.001). Women, white patients, and those with a centrifugal flow device, dialysis within 48 hours of implantation, INTERMACS profile 1, prior or concomitant surgery, and extracorporeal membrane oxygenation support who had not yet survived 1 year after implantation had lower estimates of additional 1-year event-free survival than patients without these characteristics (P<0.05 for all comparisons). However, the influence of these characteristics on CS did not persist for patients after a

Figure 1. Additional 1-year event-free survival conditional on time already survived.
longer time of prior survival. For example, after 3 years of prior survival with their device, patients with INTERMACS profile 1 at implantation had a similar likelihood of surviving the next year compared with patients who had a lower-risk INTERMACS profile (1-year CS probability after 3 years of prior survival was 77% [95% CI, 68%–85%] for patients with INTERMACS profile 1 versus 76% [95% CI, 73%–78%] for patients with other INTERMACS profiles, $P=0.5$). Of the 121 patients who had dialysis within 48 hours of implantation, 17% required dialysis within the first year after implantation, with a mean duration of 18±15 days.

**Figure 2.** Additional 1-year event-free survival conditional on time already survived and stratified by characteristics at implantation.

ECMO indicates extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; and INTERMACS, Interagency Registry for Mechanical Circulatory Support Devices. *$P<0.05$, **$P<0.001$. 
Nonfatal Adverse Events Within the First Year After DT LVAD Implantation and Their Influence on Conditional Event-Free Survival

Figure S3 shows the number and distribution of adverse events that occurred in the first year after DT LVAD implantation for patients with prior survival ≥1 year. Gastrointestinal bleeding occurred most often (2861 events), and device-related infection was the next most common adverse event (853 events). Strokes and renal dysfunction happened least frequently (420 events and 427 events, respectively).

Figure 3 displays the additional 1-year event-free survival probabilities conditioned on having survived 1 to 3 years after DT LVAD implantation and stratified by the occurrence of each adverse event within the first year after implantation. Patients who survived 1 year after implantation and experienced a stroke, device-related infection, or device complication in that first year had a lower likelihood of surviving the next year in comparison to those without that event in the first year. The conditional 1-year event-free survival estimates were 65% (95% CI, 59%–72%; P<0.001), 64% (95% CI, 58%–70%; P<0.001), and 64% (95% CI, 58%–70%; P<0.001) for stroke, device-related infection, and device complication, respectively, versus at least 75% in the absence of each adverse event. Importantly, however, the probability of additional 1-year event-free survival numerically increased with increasing time already survived for patients who experienced these events. Of note, for patients who had already survived 2 or 3 years with a DT LVAD, device-related infection was the only adverse event associated with a significantly lower likelihood of additional 1-year event-free survival than in the absence of that event (P<0.001 and P=0.027 for 2 and 3 years of prior survival, respectively). There were no significant differences in the probabilities of an additional 1-year of event-free survival conditioned on time already survived for patients who experienced gastrointestinal bleeding or renal dysfunction in comparison to those who did not experience these events in the
first year ($P=0.19$ and $P=0.96$ for 1 year of prior survival for gastrointestinal bleeding and renal dysfunction, respectively).

To further explore the effect of each type of adverse event on prognosis, we stratified CS by the subtypes of adverse events that occurred within the first year (Figure S4). Among patients who had a device-related infection, the additional 1-year event-free survival probabilities were numerically lowest for patients who survived an infection not limited to the driveline (ie, of the exit cannula, interior, or pocket). None of these patients had event-free survival to 4 years from DT LVAD implantation (ie, 1 year of additional event-free survival after having survived 3 years from DT LVAD implantation). The additional 1-year event-free survival estimates for each year already survived were comparable for subtypes of gastrointestinal bleeding, stroke, or device complication.

**Number of Adverse Events After DT LVAD Implantation Impacts CS**

Overall, additional 1-year event-free survival numerically decreased with an increasing number of types of adverse events for each year already survived since DT LVAD implantation (Figure 4). The probabilities of additional 1-year event-free survival for patients who experienced 0, 1, 2, or 3 different types of adverse events within 1 year of DT LVAD implantation and had already survived 1 year were 78% (95% CI, 76%–80%), 73% (95% CI, 70%–76%), 65% (95% CI, 60%–70%), and 66% (95% CI, 53%–80%), respectively ($P<0.001$).

The probabilities of additional 1-year event-free survival conditioned on having survived 1, 2, or 3 years and stratified by the number (0, 1, or $\geq 2$) of the same type of adverse event during the first year after LVAD implantation are presented in Figure S5. The conditional 1-year event-free survival of patients who survived $\geq 2$ strokes within the first year after implantation was <50% ($P<0.001$ in comparison to patients with 0 or 1 stroke). For patients who had $\geq 2$ device-related infections within the first year, probabilities of conditional 1-year event-free survival declined over time and relative to patients with 0 or 1 device-related infection. CS probabilities for additional 1-year event-free survival were no different whether patients had 0, 1, or $\geq 2$ reported episodes of gastrointestinal bleeding or renal dysfunction within the first year after DT LVAD implantation.

**DISCUSSION**

Dynamic forecasts of survival are not available for patients already living with DT LVADs. We describe the evolution of long-term event-free survival as a function of time already survived in patients with advanced heart failure implanted with DT LVADs and note several key observations. First, the additional 1-year event-free survival probabilities were numerically higher for patients with DT LVAD given a longer time already survived from implantation. This observation highlights a long-term survivor bias for patients who have already survived the higher-risk first year after implantation. Second, some patient characteristics at implantation influence long-term conditional event-free survival. Older age at implantation was associated with a paradoxically higher probability of an additional year of event-free survival given more time already survived in comparison to younger age at implantation. While certain characteristics, including female sex, white race, early dialysis after implantation, INTERMACS profile 1, prior or concomitant cardiac surgery, and extracorporeal membrane oxygenation support confer a higher upfront risk, the influence of these factors on event-free survival diminishes as DT LVAD implantation becomes a more remote event. Third, complications as a consequence of the LVAD, specifically incident stroke, device-related infection, and device complication (pump thrombosis or malfunction), that were nonfatal and occurred within the first year from DT LVAD implantation, were associated with a significant decrement in long-term CS. Finally, more types of adverse events within the first year were associated with increasingly reduced event-free survival over time.
These results serve as a reference for clinicians when patients with DT LVAD, either before or after implantation, inquire about their prognosis with an LVAD. Patients and their families may use this information to manage their expectations or make decisions about goals of care. For example, a patient who has already survived for 3 years after DT LVAD implantation may be reassured that the probability of surviving the next year with the same device is 76%, which is a substantial improvement from the 49% 4-year survival estimated at the time of implantation. Furthermore, our observations concerning the influence of nonfatal adverse events on CS may inform cardiac transplantation listing strategies for patients who may become eligible for cardiac transplantation by 12 months after device implantation or extrapolated to individuals with LVADs placed as bridge-to-transplantation.

Much has already been published to guide clinicians in the process of appropriately selecting candidates for DT LVAD, mostly by highlighting prognostically unfavorable patient characteristics at the time of implantation. For example, the HeartMate II Risk Score stratifies the risk of morality and mortality based on preoperative characteristics. Similarly, the current INTERMACS annual report emphasizes the prognostic impact of clinical factors at LVAD implantation. While these analyses inform long-term risk from implantation onward, they yield little insight into how a patient’s risk might evolve over time. For instance, characteristics such as older age and INTERMACS profile 1 at implantation are associated with an early mortality risk.

A recent analysis of patients with durable LVAD (<50% DT) from INTERMACS demonstrated that there was a stepwise rise in the risk of mortality with increasing age and that patients ≥75 years had the highest risk of death. For patients who had not yet survived 1 year after implant, we did not observe a difference in additional 1-year event-free survival, although our oldest tertile included relatively younger patients (≥69 years), and we restricted our analysis to a DT population without a concomitant right ventricular assist device, which was a predictor of adverse outcomes in the aforementioned study. Over time, we observed that older age is associated with a relatively higher likelihood of event-free survival. Potential explanations for this finding include a survivor bias for patients who are lower risk but receive DT LVADs because of age or possible attrition of younger patients through cardiac transplantation.

In addition, our observation that patients implanted as INTERMACS profile 1 improve their survival outlook over time emphasizes the crucial role for an intensive multidisciplinary strategy in managing patients who receive DT LVADs in critical cardiogenic shock. Further, these data provide support offering DT LVAD to such patients, recognizing that while they experience a higher upfront risk early following implantation, among those who survive, their prognosis is comparable to those less acutely ill at time of implantation.

Similarly, dialysis within 48 hours of implantation was associated with an initial lower likelihood of event-free survival that did not persist after more years of prior survival. Only a minority of these patients (17%) had an ongoing need for dialysis within the first year, and the duration of dialysis was short. This observation suggests that when temporary, dialysis around the time of LVAD implantation may not have a marked impact on long-term survival.

Prior studies have highlighted the increased risk of death after device-related infection. Our analysis demonstrates how a device-related infection and, in particular, infections of the pump itself or the pocket in the first year after implantation, translate to relatively low probabilities of subsequent long-term event-free survival with the primary LVAD device. These findings likely reflect the difficulty in definitively treating these infections as well as attempts to achieve source control through device exchange or transplant. Even driveline infections, which were common in this cohort as well as in other contemporary cohorts, were indicators of a poor prognosis over the long term. Not surprisingly, patients who survived a stroke or device complication in the first year after DT LVAD implantation also had relatively low conditional probabilities of further event-free survival. Compared with the 2-year survival probability conditional on having survived a stroke within the 3 months after implantation of a bridge-to-transplant or DT continuous-flow device reported previously by INTERMACS, we observed a slightly lower likelihood of 2-year survival with the primary DT LVAD when we conditioned our analysis on having survived a stroke at any point during the first year in a DT population.

Although gastrointestinal bleeding was the most common adverse event observed in our cohort, as well as in other cohorts of patients with LVADs, and is a cause of considerable morbidity, we did not observe any association with reduced event-free CS. Moreover, rates of gastrointestinal bleeding among patients with LVADs will likely decline in the future as newer-generation LVADs with improved hemocompatibility, such as the HeartMate 3 (Abbott), are implanted. With respect to renal dysfunction after LVAD implantation, we did not observe the same relationship with poor outcomes that has been reported in other studies. This may be because the definition of renal dysfunction used in our study included milder cases or was not sustained for long in the case of acute renal dysfunction.
LIMITATIONS
This study has limitations inherent to its design. Our analysis depends on the accuracy of the data entered into INTERMACS as adverse events were not independently adjudicated. The study cohort was mostly composed of patients implanted with axial flow devices, thus limiting the generalizability of these findings to more contemporary centrifugal-flow devices.\(^\text{17,18}\)

Given the demonstrated superiority of the HeartMate 3 centrifugal-flow pump relative to the HeartMate II device with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device, our results may underestimate long-term CS for individuals implanted with a newer-generation device in similarly selected populations. However, rates of mortality, driveline infection, and renal dysfunction were observed to be similar between the newer-generation pumps (the Heartmate 3 and the HeartWare LVAD [Medtronic]) and the HeartMate II device.\(^\text{3,17,18,30}\)

Additionally, there have been not significant differences between the HeartWare and the Heartmate II devices with respect to the rates of ischemic or hemorrhagic stroke assuming adequate blood pressure control.\(^\text{30}\) Also of note, the clinical characteristics of patients in the present study are comparable to those implanted with the Heartmate 3 or the HeartWare devices in clinical trials.\(^\text{17,18}\) Our findings are immediately relevant to the many patients still living with an axial-flow device. Finally, although the development of right-sided heart failure after LVAD implantation is an important adverse event associated with morbidity and mortality,\(^\text{31}\) we were unable to evaluate the relationship between severe right-sided heart failure and CS because of the small sample size (n=114 with 0 years of prior survival) and substantial dropoff thereafter of patients who were reported to have experienced this adverse event (n=44 and n=24 for 1 and 2 years of prior survival, respectively).

CONCLUSIONS
This study provides important prognostic information for patients living with a DT LVAD. We describe in detail the long-term event-free survival, highlighting how even patients with certain unfavorable baseline characteristics have a better prognosis with more time already survived. However, experiencing certain LVAD-related complications, including nonfatal stroke, pump thrombosis or malfunction, and especially device-related infection within the first year after implantation has a persistently unfavorable impact on long-term outcomes.

ARTICLE INFORMATION
Received March 4, 2020; accepted May 28, 2020.

Affiliations
From the Division of Cardiology, Department of Internal Medicine (K.C.M., A.P., A.R., M.H.D., J.L.G.), Division of Bioinformatics, Department of Clinical Sciences (L.Z.) and Department of Cardiovascular and Thoracic Surgery (M.P.), University of Texas Southwestern Medical Center, Dallas, TX; and Department of Cardiovascular MedicineDepartment of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH (W.H.T., J.B.Y.).

Sources of Funding
None.

Disclosures
Dr Peltz has been the site principal investigator for the Medtronic HeartWare ENDURANCE (A Clinical Trial to Evaluate the HeartWare Ventricular Assist System), the ENDURANCE supplemental trial, DT PAS (HeartWare Destination Therapy Post Approval Study), and APOGEE (A HeartWare HVAD Destination Product Surveillance Registry Platform). Dr Young was the National Institutes of Health study chair for INTERMACS. Dr Grodin is a consultant for Alnylam, Eidos, and Pfizer. The remaining authors have no disclosures to report.

Supplementary Materials
Table S1
Figures S1–S5

REFERENCES
1. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Aschheim DD, Tierney AR, Levitan RG, et al. Long-term use of a left ventricular assist device for end-stage heart failure. \textit{N Engl J Med}. 2001;345:1435–1443.
2. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooglu AJ, Delgado RM, Long JW, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. \textit{N Engl J Med}. 2009;361:2241–2251.
3. Kormos RL, Cowger J, Pagani F, Teuteberg JJ, Goldstein DJ, Jacobs JP, Higgins RS, Stevenson LW, Stehlik J, Atluri P, et al. The Society of Thoracic Surgeons INTERMACS database annual report: evolving indications, outcomes, and scientific partnerships. \textit{J Heart Lung Transplant}. 2019;38:114–126.
4. Han JJ, Acker MA, Atluri P. Left ventricular assist devices. \textit{Circulation}. 2018;138:2841–2861.
5. Pinney SP, Anjaneyulu AC, Lala A, Teuteberg JJ, Uriel N, Mehra MR. Left ventricular assist devices for lifelong support. \textit{J Am Coll Cardiol}. 2017;69:2845–2861.
6. Allen LA, Mcllvannan CK, Thompson JS, Dunlay SM, Rue SJL, Lewis EF, Patel CB, Blue L, Fairclough DL, Leister EC, et al. Effectiveness of an intervention supporting shared decision making for destination therapy left ventricular assist device: the DECIDE-LVAD randomized clinical trial. \textit{JAMA Intern Med}. 2018;178:520–529.
7. Hieke S, Kleber M, König C, Engelhardt M, Schumacher M. Conditional survival: a useful concept to provide information on how prognosis evolves over time. \textit{Clin Cancer Res}. 2015;21:1530–1536.
8. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB, Naftel DC. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. \textit{J Heart Lung Transplant}. 2017;36:1080–1086.
9. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G, Jaski B, Farrar DJ, Slaughter MS. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. \textit{J Am Coll Cardiol}. 2013;61:315–321.
10. Gosev I, Kiernan MS, Eckman P, Soleiman B, Klici A, Uriel N, Rich JD, Katz JN, Cowger J, Lima B, et al. Long-term survival in patients receiving a continuous-flow left ventricular assist device. \textit{Ann Thorac Surg}. 2018;105:696–701.
11. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Available at: https://biolinc.nhlbi.nih.gov/studies/intermacs; Accessed December 16, 2018.
12. Kirklin JK, Naftel DC, Stevenson LW, Kormos RL, Pagani FD, Miller MA, Ullsney K, Young JB. INTERMACS database for durable devices for circulatory support: first annual report. \textit{J Heart Lung Transplant}. 2008;27:1065–1072.
13. Davis F, McCarthy B, Freels S, Kupelian V, Bondy M. The conditional probability of survival of patients with primary malignant brain tumors: surveillance, epidemiology, and end results (SEER) data. Cancer. 1999;85:485–491.

14. Teuteberg JJ, Stewart GC, Jessup M, Kormos RL, Sun B, Frazier OH, Nafel DC, Stevenson LW. Implant strategies change over time and impact outcomes: insights from the INTERMACS (Intergroup Registry for Mechanically Assisted Circulatory Support). JACC Heart Fail. 2013;1:369–378.

15. Adamo L, Nassif M, Tibrewala A, Novak E, Vater J, Silvestry S, Itoh A, Ewald GA, Mann DL, LaRue SJ. The Heartmate Risk Score predicts morbidity and mortality in unmatched left ventricular assist device recipients and risk stratifies INTERMACS class 1 patients. JACC Heart Fail. 2015;3:283–290.

16. Caraballo C, DeFilippis EM, Nakagawa S, Ravindra NG, Miller EE, Mezzacappa C, McCullough M, Gruen J, Levin A, Reinhardt S, et al. Clinical outcomes after left ventricular assist device implantation in older adults: an INTERMACS analysis. JACC Heart Fail. 2019;7:1069–1078.

17. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Bryce SW, Najjar SS, Jeevanandam V, Anderson AS, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med. 2017;376:451–480.

18. Mehra MR, Uriel N, Naka Y, Cleveland JC, Yuzefpolkaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, et al. A fully magnetically levitated left ventricular assist device—final report. N Engl J Med. 2019;380:1618–1627.

19. Levy DT, Guo Y, Simkins J, Puisys VA, Muggia VA, Goldstein DJ, D’Alessandro DA, Minamato GY. Left ventricular assist device exchange for persistent infection: a case series and review of the literature. Transp Infect Dis. 2014;16:453–460.

20. Koval CE, Thuitt L, Moazami N, Blackstone E. Evolution and impact of drive-line infection in a large cohort of continuous-flow ventricular assist device recipients. J Heart Lung Transplant. 2014;33:1164–1172.

21. Lerman DT, Hamilton KW, Byrne D, Lee DF, Zeitzer K, Claridge T, Gray J, Minamato GY. The impact of infection among left ventricular assist device recipients on post-transplantation outcomes: a retrospective review. Transp Infect Dis. 2018;20:e12995.

22. Meyer AL, Malehsa D, Buddle U, Bara C, Haverich A, Stuebe M. Acquired von Willebrand syndrome in patients with a centrifugal or axial continuous flow left ventricular assist device. JACC Heart Fail. 2014;2:141–145.

23. Goda M, Jacobs S, Rega F, Peerlinck K, Jacquemin M, Droogne W, Vanhaecke J, Vanhaecke J, Van Cleemput J, Van den Bossche K, et al. Time course of acquired von Willebrand disease associated with two types of continuous-flow left ventricular assist devices: HeartMate II and CircuLite Synergy Pocket Micro-pump. J Heart Lung Transplant. 2013;32:539–545.

24. Demiroz ZT, Radovanovic V, Hochman LF, Gregoric ID, Letsou GV, Kar B, Bogaev RC, Frazier OH. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2011;30:849–853.

25. Akhter SA, Badami M, Murray K, Kohimoto T, Lozonschi L, Osaki S, Lushaj EB. Hospital readmissions after continuous-flow left ventricular assist device implantation: incidence, causes, and cost analysis. Ann Thorac Surg. 2015;100:884–889.

26. Bansal A, Uriel N, Colombo PC, Narisetty K, Long JW, Bhimaraj A, Cleveland JC, Goldstein DJ, Stulak JM, Najjar SS, et al. Effects of a fully magnetically levitated centrifugal-flow or axial-flow left ventricular assist device on von Willebrand factor: a prospective multicenter clinical trial. J Heart Lung Transplant. 2019;38:906–918.

27. Netuka I, Ivík P, Tučanová Z, Gregor S, Szárszoi O, Sood P, Crandall D, Rimsans J, Connors JM, Mehra MR. Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump: the MAGENTUM 1 study. J Heart Lung Transplant. 2018;37:579–586.

28. Doshi R, Taha M, Pisipati S, Patel K, Al-Khafaji J, Desai R, Shah J, Gullapalli N. Impact of chronic kidney disease on in-hospital outcomes following left ventricular assist device placement: a national perspective. Heart Lung. 2020;49:48–53.

29. Bansal N, Halipern S, Katz R, Hal YN, Tamura MK, Kreuter W, O’Hare AM. Outcomes associated with left ventricular assist devices among recipients with and without end-stage renal disease. JAMA Intern Med. 2018;178:204–209.

30. Milano CA, Rogers JG, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Mokadam NA, Mahr C, Miller JS, Markham DW, et al. HVAD: the ENDURANCE supplemental trial. JACC Heart Fail. 2018;6:792–802.

31. Dang NC, Topkara VK, Mercando M, Kay J, Kruger KH, Aboodi MS, Oz MC, Naka Y. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant. 2006;25:1–6.
SUPPLEMENTAL MATERIAL
| Adverse Event Variable                  | Code                                               |
|---------------------------------------|----------------------------------------------------|
| Gastrointestinal bleeding             |                                                   |
| Upper                                 | BLEEDING_SOURCE_UP_GASTRO                         |
| Lower                                 | BLEEDING_SOURCE_LOW_GASTRO                        |
| Unknown but with Guaiac positive stools | BLEEDING_SOURCE_GI_UNK_POS_STOOL                  |
| Stroke                                | AE_NEURO_CVA                                      |
| Device-related infection              |                                                   |
| Driveline                             | INFECT_LOC_PUMP_DRVLINE                           |
| Exit cannula                          | INFECT_LOC_PUMP_EXIT_CAN                          |
| Pump interior                         | INFECT_LOC_PUMP_INTERIOR                          |
| Pump pocket                           | INFECT_LOC_PUMP_POCKET                            |
| Device complication                   |                                                   |
| Thrombosis                            | AE_DEV_THR_EVNT                                   |
| Malfunction                           | AE_DEV_MALF_EVNT                                  |
| Renal dysfunction                     | RENAL_DYS                                         |
Figure S1. Flow Diagram of the Selection of the Study Cohort from the INTERMACS Database.

Data accessed from the INTERMACS Registry pertained to mechanical support devices implanted between March 1, 2006 and December 31, 2017. (L=left; R=right; VAD=ventricular assist device).
Figure S2. Hazard rate for the study cohort of the composite endpoint of death, device exchange, or heart transplant, censored at device removal for recovery.
Figure S3. Distribution of Adverse Events during the First Year after LVAD Implantation for Patients Who Survived ≥1 Year.

Of the 2861 gastrointestinal bleeding events, 1379 were upper gastrointestinal, 751 lower gastrointestinal, and 731 of unknown gastrointestinal source. Of the 420 strokes, 236 were ischemic or embolic, 162 hemorrhagic, and 22 unknown. Of the 853 device-related infections, 716 were driveline-related and 137 involved another pump site, which was either the exit cannula, interior, or pump pocket. Of the 643 device complications, 460 were malfunction and 183 thrombosis. There were 427 renal dysfunction events.
For patients with ≥1 year of survival after LVAD implantation, conditional survival probabilities for additional 1-year event-free survival are shown for those patients who experienced sub-types of the following adverse events within the first year after implantation: gastrointestinal bleeding (upper, lower, or unknown source), stroke (ischemic or embolic or hemorrhagic), device-related infection (driveline or involving another pump site), and device complication (malfunction or thrombosis).
Figure S5. Additional 1-Year Event-Free Survival Conditional on Time Already Survived and Stratified by Number of Adverse Events of the Same Type.

For patients with ≥1 year of survival after LVAD implantation, conditional survival probabilities for additional 1-year event-free survival are shown for those patients who experienced 0, 1, or 2 or more of the following adverse events within the first year after implantation: gastrointestinal bleeding, stroke, device-related infection, device complication, and renal dysfunction. **denotes P<0.001.