JACC: HEART FAILURE VOL. 12, NO. 5, 2024

PUBLISHED BY ELSEVIER

MECHANICAL CIRCULATORY SUPPORT/CARDIAC TRANSPLANT

Incidence, Outcomes, and Opportunity for Left Ventricular Assist Device Weaning for Myocardial Recovery

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ABSTRACT

BACKGROUND Myocardial recovery occurs in patients with advanced heart failure on left ventricular assist device (LVAD) support, but there is the premise that it is rare with uncertain results.

OBJECTIVES The goal of this study was to investigate the incidence and consequence of LVAD explant after myocardial recovery.

METHODS Using the United Network for Organ Sharing registry, LVAD implants in the United States between 2005 and 2020 were tracked until death, transplantation, or explant for myocardial recovery. The cohort undergoing explant was followed up for heart failure relapse (defined as relisting followed by delisting due to death, being too ill, or transplantation; or second durable LVAD implant).

RESULTS Of 15,728 LVAD implants, 126 patients underwent explant for recovery, which only occurred in 55 (38%) of 145 implanting centers. The crude cumulative incidence was 0.7% at 2 years, whereas the incidence reached 4.7% among designated centers in the selected young nonischemic cohort. Of 126 explanted patients, 76 (60%) were subsequently delisted for sustained recovery. Heart failure relapsing had a relatively higher hazard in the early phase, with a 30-day incidence of 6% (7 of 126) but tapered following with the freedom rate of 72.5% at 4 years.

CONCLUSIONS In the United States, LVAD explant for myocardial recovery was underutilized, leading to a very low incidence at the national level despite a realistic rate being achieved in designated centers for selected patients. With follow-up extending up to 4 years after explant, more than one-half were successfully removed and stayed off the waitlist, and approximately 70% were free from heart failure relapse events. (J Am Coll Cardiol HF 2024;12:893-901)

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Stavros Drakos, MD, served as Guest Associate Editor for this paper. Barry Greenberg, MD, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 22, 2023; revised manuscript received November 2, 2023, accepted December 7, 2023.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2023.12.006

ABBREVIATIONS AND ACRONYMS

ICD = implantable cardioverter-defibrillator

LVAD = left ventricular assist device

UNOS = United Network of Organ Sharing

Implantation of a durable left ventricular assist device (LVAD) has become a standard therapy for patients with end-stage heart failure.[1] Its principal intention is to replace the function of the left ventricle, which is typically believed to have failed to an irreversible level until the indication of implantation is met, either heart transplantation or for life. LVAD support provides a favorable hemodynamic environment for the left ventricle as it offers rest and off-loading of pressure. Under these conditions, structural reverse remodeling and subsequent functional recovery occur in some left ventricles to the point where the LVAD becomes unnecessary and can be explanted.

The concept of bridge to recovery is not new and has been observed and explored since the era of the first-generation LVADs.[2] However, the reported incidence of LVAD explant varies widely, ranging from 1% to >50%.[2-11] This large variation may come from the difference in the era, patient population/selection, or the center commitment and experience. Not all centers actively look for myocardial recovery as a practical endpoint or apply strategies to favor the recovery process. Therefore, the real-world incidence reported by registry studies may not necessarily represent the true incidence of myocardial recovery in the current era of modern continuous-flow LVADs. Furthermore, most reports have focused on the rate of explant but not on the consequences of explant. The outcomes after LVAD explant seem ill defined, either because a sample size is too small given the overall low incidence of explant or a small study size despite achieving a high explant rate, or because the follow-up data are too short or not available.

We therefore conducted a nationwide retrospective cohort study using the national database of the United States to investigate the incidence and consequences of LVAD explant after myocardial recovery.

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METHODS

DATA SOURCE. The United Network of Organ Sharing (UNOS) registry, a national transplant-specific database in the United States, was queried. This registry has prospectively collected patient-level data on the entire transplant population in the United States, including information on the donors, candidates, and recipients involved in every organ transplantation, since 1987. The data set used in this study was released on July 1, 2021.

The data set comprises several organ-specific files and supplemental files for additional information. The thoracic main file contains information on heart transplantation, including one record per each waitlist registration and delisting with its reason if it happened. There is a supplemental file separate from the thoracic main file, the mechanical circulatory support device file, which contains information on the mechanical circulatory device type, brand, implantation date, explant date, and reason for explant for patients listed for heart transplantation. These data were maintained so that all patients with mechanical support devices intended as a bridge to transplantation at any point could be captured, even if the initial strategy was destination therapy or a bridge to candidacy. As the device implantation date was only available from March 7, 2005, this date was chosen as the starting point for study enrollment. Both the thoracic main file and mechanical circulatory support device file contained unique patient and waiting list identifiers, which allowed the data to be merged and longitudinally analyzed for patients who had multiple listings.

STUDY DESIGN AND PARTICIPANTS. This study was a national registry retrospective cohort analysis investigating the incidence and outcomes of LVAD explant after myocardial recovery in patients who underwent durable LVAD implantation as a bridge to transplantation in the United States between March 7, 2005, and July 1, 2020. LVAD implantation in this study was limited to the contemporary axial or centrifugal continuous-flow durable LVADs alone, namely HeartMate II (Abbott Cardiovascular), HeartWare (Medtronic), and HeartMate 3 (Abbott Cardiovascular). Information on all LVAD implants intended at some point as a bridge to transplantation was extracted from the mechanical circulatory support file and merged with the thoracic main file. The mechanical circulatory support file includes LVAD explant dates and reasons for explant, including myocardial recovery.

As a secondary analysis, in a subgroup cohort of patients who underwent LVAD explant for myocardial recovery, we tracked follow-up outcomes extending to 5 years after explant and investigated the following: 1) the rate of successful delisting from the heart transplant waitlist; 2) the rate of relisting; and 3) the rate of "heart failure relapse events," which we defined as the composite hard endpoints of heart transplantation, second LVAD implantation, and delisting due to death or being too sick for transplant. All patients who underwent LVAD explant were confirmed to stay on the waitlist after LVAD

explant; some remained on the list, some became delisted and stayed off the list, and some became delisted but relisted later. Successful delisting was defined only when the reason for delisting was myocardial recovery and not relisted during the follow-up. The study period began in 2005, when the use of modern continuous ventricular assist devices began with available implantation dates, and ended 1 year before the data release date, based on the UNOS recommendations for data use.

This study was approved by the Program for Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai. The approval included a waiver of informed consent.

STUDY ENDPOINTS. In the primary analysis (all LVAD implants as a bridge to transplantation), the outcomes of interest were death, heart transplant, and LVAD explant secondary to myocardial recovery on LVAD support. Deaths recorded in the UNOS data set were ascertained through the Organ Procurement and Transplant Network. In the secondary analysis (all LVAD explants after myocardial recovery), the outcomes of interest were successful delisting, relisting, and heart failure relapse events.

STATISTICAL ANALYSIS. Symmetrically distributed continuous variables are reported as mean ± SD and were compared by using the Student's *t*-test. Skewed distributed continuous variables are reported as median with IQRs and were compared by using the Wilcoxon rank sum test. Categorical variables are expressed as proportions and were compared by using the Pearson chi-square test.

In the primary analysis, the cumulative incidences of myocardial recovery, mortality, heart transplantation, and waiting on the list were constructed by using competing risk analysis, with each event being mutually exclusive. To obtain risk-adjusted HRs for the outcome of myocardial recovery, the cause-specific multivariable Cox regression model was fit adjusted for the following patient variables: age, sex, race, etiology of heart failure, body mass index, prior cerebrovascular disease, diabetes mellitus, functional status, education status, pulmonary vascular resistance, implantable cardioverter-defibrillator (ICD) implantation, LVAD type, and LVAD implantation year. In the secondary analysis, time-to-event analysis for freedom from heart failure relapse events was constructed by using the Kaplan-Meier method. Cox proportional hazards models were fit entering the aforementioned variables used to calculate HRs. The proportional hazards assumption was examined by using Schoenfeld residuals and found valid in all Cox models.

Post hoc analyses were further added. First, the whole LVAD patient cohort was divided into 2 groups according to whether LVAD implantation was performed in a center which had experience of LVAD explant for myocardial recovery. The patients' characteristics were then compared. Second, the incidence of explant for myocardial recovery was recalculated only among centers with LVAD explant experience and additionally in a subgroup of patients with favorable factors for recovery, which were selected by clinical intuition and subdistribution Cox models run as noted earlier.

All tests were 2-tailed: an alpha level of 0.05 was considered statistically significant. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc) and the R programming language version 3.6.2 (R Foundation for Statistical Computing).

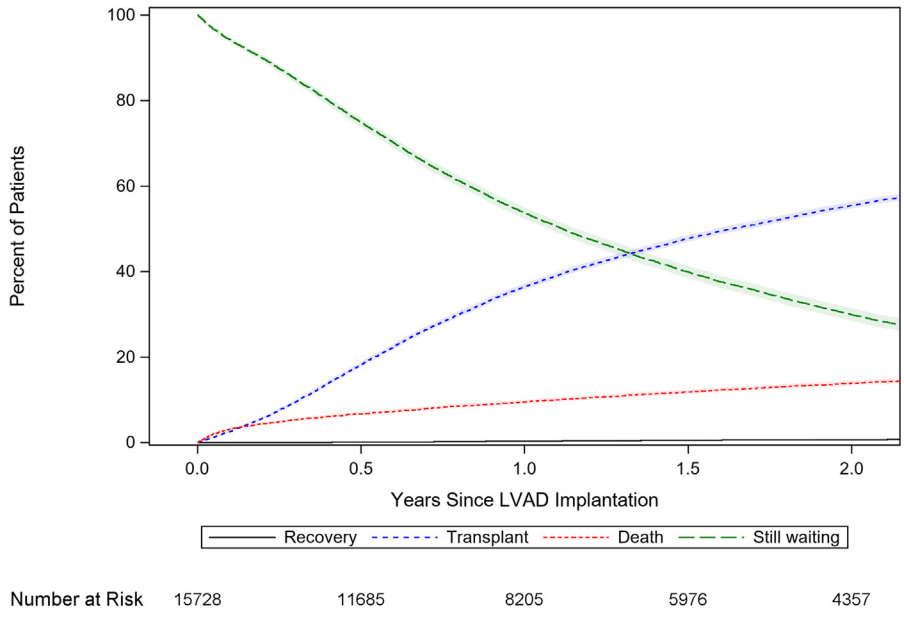
RESULTS

NATIONAL TRENDS AND CENTER VARIATION IN LVAD EXPLANT PRACTICE. Between March 7, 2005, and July 1, 2020, a total of 15,728 continuous-flow LVADs were implanted as a bridge to transplantation, of which 126 LVADs were explanted because of myocardial recovery. During the study period, there were 145 hospitals that had implanted LVADs, but only 55 (38%) hospitals explanted at least one LVAD for myocardial recovery. Of the study cohort of 15,728 LVADs, 8,882 (56%) were implanted by 55 centers with explant experience, and 6,904 (44%) were implanted by 90 centers without explant experience; the patient baseline characteristics and hemodynamics at LVAD implantation were comparable between the groups (Supplemental Table 1). The annual number of LVAD explants is shown in Supplemental Figure 1.

INCIDENCE AND FACTORS ASSOCIATED WITH LVAD EXPLANT FOR MYOCARDIAL RECOVERY. The cumulative incidence of LVAD explant for myocardial recovery was 0.7% (95% CI: 0.6%-0.8%) at 2 years after LVAD implanted as a bridge to transplantation (**Figure 1**). The median duration from LVAD implantation to explant was 1.3 years (Q1-Q3: 0.32-2.0 years) (range: 0.1-8.3 years), and the majority of explants (75.2%) occurred within 2 years after implantation. Among centers alone that had experience with LVAD explant, the cumulative incidence of LVAD explant for myocardial recovery was 1.2% (95% CI: 0.9%-1.4%) at 2 years after LVAD implantation.

Favorable factors associated with LVAD explant for myocardial recovery were younger age, lower body mass index, nonischemic etiology, lower pulmonary

FIGURE 1 Competing Events After Contemporary Continuous-Flow LVAD Implantation



The cumulative incidence of mutually exclusive events (mortality, heart transplantation, left ventricular assist device [LVAD] explant for myocardial recovery, and waiting on the transplantation list) is plotted against time from LVAD implantation. Shaded areas represent 95% CIs.

vascular resistance, axial-flow LVAD, and no history of ICD implantation (adjusted HRs from the multivariable cause-specific Cox model provided in Supplemental Table 2). Lower creatinine levels and no history of stroke also showed near-significant associations.

The post hoc analyses of the selected cohorts with favorable factors for myocardial recovery are presented in Supplemental Table 3. In the patient cohort with age <40 years, nonischemic etiology, no history of ICD implantation, and HeartMate II LVAD, the cumulative incidence of myocardial recovery reached 8.7% (95% CI: 5.5%-12.8%) at 2 years after LVAD implantation. With the more selected cohort further limited to nonobese female patients only, the cumulative incidence was 10.7% at 2 years.

CONSEQUENCE OF LVAD EXPLANT. The baseline characteristics of the 126 patients who underwent LVAD explant for myocardial recovery are presented in **Table 1**. The mean age was 41 years, 65% of the patients were male, and 60% were white. The majority of the patients (87%) had dilated cardiomyopathy as the etiology of heart failure. A flowchart of follow-up outcomes after LVAD explant is shown in **Figure 2**. After LVAD explant, 76 (60%) of 126 patients were subsequently delisted for myocardial recovery and remained off the list, and 50 (40%) of 126 patients remained listed or were relisted. Of these 50 patients who remained on or were back on the list, 20 (40%) underwent transplantation, 6 (12%) had a second durable LVAD, 11 (22%) were delisted for death or being too ill, and the remaining 13 (26%) were still waiting or delisted for other reasons.

During follow-up, 37 patients eventually had a heart failure relapse event (whichever of the following 3 events happened first: second durable LVAD implant, heart transplantation, or being delisted due to death or being too ill). The freedom from heart failure relapse events after LVAD explant was 82.9% (95% CI: 75.1%-88.5%) at 1 year and 72.5% (95% CI: 63.2%-79.7%) at 4 years (**Central Illustration**). The median time from LVAD explant to relapse events was 0.72 (Q1-Q3, 0.002-2.60) years, but 7 patients (5.6% of all explanted patients, and 13.5% of all relapse events) experienced a relapse event within 30 days after LVAD explant. The baseline characteristics of patients who experienced relapse events and those who did not are presented in **Table 1**. The patient characteristics were generally comparable, except that the patients with relapse events had a higher rate of ICD implantation than those without (57% vs 29%; $P = 0.042$). In multivariable analysis, no

factors were found that were associated with a relapse event (Supplemental Table 4).

DISCUSSION

In this nationwide investigation capturing all continuous LVADs implanted as a bridge to transplantation in the United States, LVAD explant for myocardial recovery was a practice only selected centers performed, and the majority of centers did not perform it at all over the 15-year study period. About one-half of LVADs were implanted by centers with no experience regarding LVAD explant. As a result, the overall incidence of LVAD explant appeared be low at <1%, whereas the incidence reached 5% to nearly 10% by designated centers for selected patients such as those who were younger and had a nonischemic etiology of shorter duration.

After LVAD explant with a mean follow-up time of 4 years, 60% of patients who underwent explant were removed from the heart transplant waiting list and were never relisted, most likely indicating sustained myocardial recovery. The other 40% of patients remained on the list or were relisted for transplant, one-half of whom then underwent transplantation or a second LVAD implant, and one-quarter of whom were delisted due to death or being too ill for transplant. The 4-year freedom from heart failure relapse was 73%, with a relatively high 6% risk in the very early phase after explant.

In contemporary practice, LVAD support has been established as the standard therapy for patients with end-stage heart failure, which is considered to be irreversible. The major indications for this therapy were therefore intended as a bridge to transplantation or as destination therapy, but there have been intriguing observations of patients who exhibited substantial recovery of the native heart, even to a sufficient level that allows for LVAD explant.[2] This phenomenon sparked interest in using LVADs as a platform for myocardial recovery. A seminal report by Birks et al[3,4] from a dedicated group in England accomplished a 60% rate of LVAD explant, albeit in a selected group of patients, by applying protocol-based systematic LVAD management and an aggressive pharmacologic regimen. This high rate was not initially replicated in the United States even among experienced centers, although in this study such aggressive protocols were not applied.[8] However, recently, there was a multicenter collaboration from 6 institutions in which HeartMate II LVADs were placed prospectively in 40 patients in a study of targeted cardiac recovery. The key inclusion criteria for this study were age 18 to 59 years, left ventricular ejection fraction <25%, nonischemic cardiomyopathy, and duration of heart failure ≤5 years. They were able to achieve the primary endpoint of being alive without a mechanical support device or transplant 1 year later in 40% of all enrolled study patients.[5] In contrast, the registry studies consistently showed low incidence of LVAD explant in real-world practice.[9-11]

The crude incidence of LVAD explant in our study, calculated by all LVADs implanted by all centers, was low and seems in line with the most recent Interagency Registry for Mechanically Assisted Circulatory Support report that found an overall low rate of device explant <2% at 2 years, regardless of indications as either a bridge to transplantation or destination therapy.[1] Notably, our data showed that LVAD explant for myocardial recovery was a practice that was never performed over 15 years in two-thirds of the centers that implanted nearly one-half of LVADs during the study period.

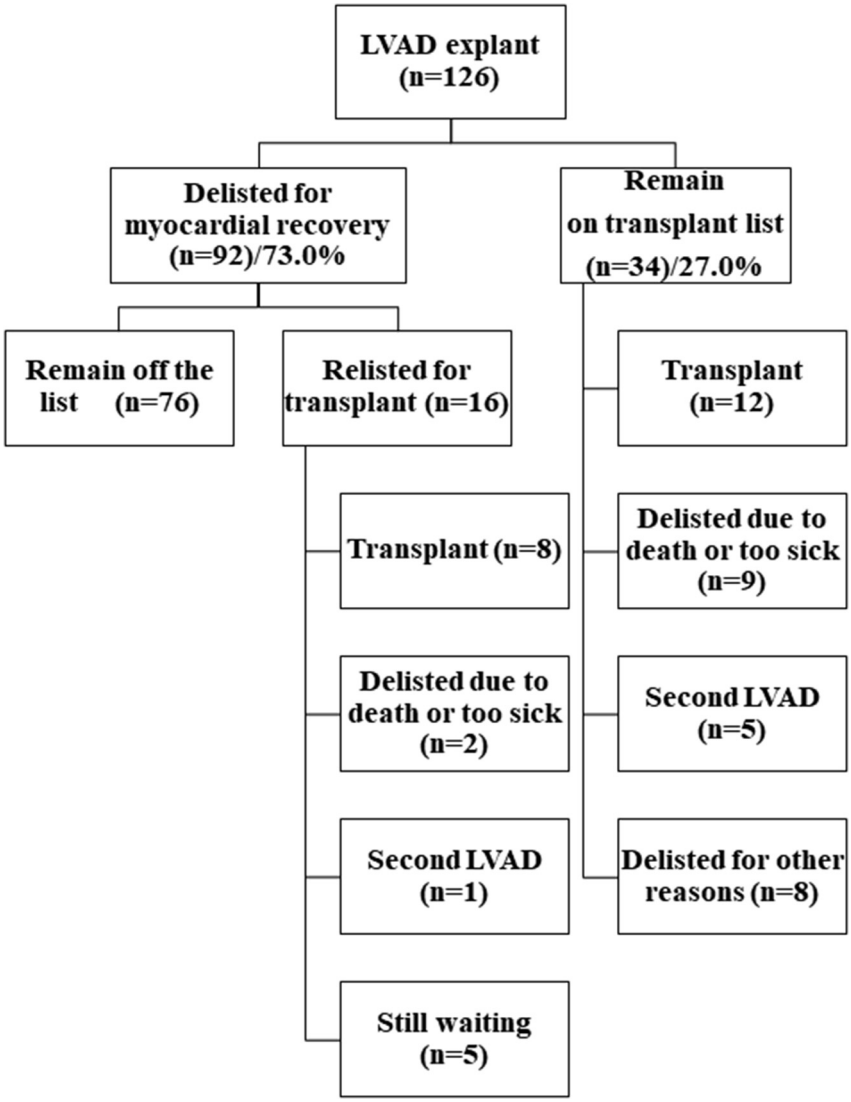
No clinically relevant differences were observed between patients who underwent LVAD implant at centers with or without explant experience. This could suggest that there are potentially recovered patients who are not given access to LVAD explant in many centers. Despite the real-world incidence being apparently "extremely rare," we found that, in a highly selected patient group among designated

TABLE 1 Baseline Characteristics at LVAD Implantation Among Patients Who Had Subsequent LVAD Explant for Myocardial Recovery Based on Whether a Heart Failure Relapse Event Happened

	Overall (N = 126)	Relapse (n = 37)	No Relapse (n = 89)	*P* Value
Age, y	41.0 ± 14.6	42.1 ± 15.0	40.5 ± 14.5	0.57
Male	82 (65.1)	28 (75.7)	54 (60.7)	0.10
Race				0.65
White	75 (59.5)	22 (59.5)	53 (59.6)	
Black	29 (23.0)	10 (27.0)	19 (21.4)	
Others	22 (17.5)	5 (13.5)	17 (19.1)	
Blood type O	69 (54.9)	18 (48.7)	51 (57.3)	0.37
Body mass index, kg/m^2	26.9 ± 5.4	27.0 ± 5.2	26.9 ± 5.5	0.86
Education: college or higher	66 (52.4)	17 (46.0)	49 (55.0)	0.35
Etiology of heart failure				0.61
Dilated	110 (87.3)	34 (91.9)	76 (85.4)	
Ischemic	11 (8.7)	2 (5.4)	9 (10.1)	
Cerebrovascular disease	4 (3.2)	3 (8.1)	1 (1.1)	0.075
Diabetes	21 (16.7)	6 (16.2)	15 (16.9)	0.93
Creatinine	1.1 ± 0.52	1.1 ± 0.57	1.1 ± 0.50	0.42
Dialysis	2 (1.6)	1 (2.7)	1 (1.2)	0.50
Functional status poor	41 (32.5)	12 (32.4)	29 (32.4)	0.98
Pulmonary vascular resistance, WU	2.1 ± 1.3	2.3 ± 1.6	2.0 ± 1.1	0.31
ICD implanted	54 (42.9)	21 (56.8)	33 (37.1)	0.042
LVAD implant year, median	2013	2011	2013	0.036
Duration from implant to explant, y	1.5 ± 1.1	1.4 ± 0.78	1.6 ± 1.2	0.40

Values are mean ± SD or n (%) unless otherwise indicated.
ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device.

FIGURE 2 Flowchart of Follow-Up Outcomes After LVAD Explant for Recovery

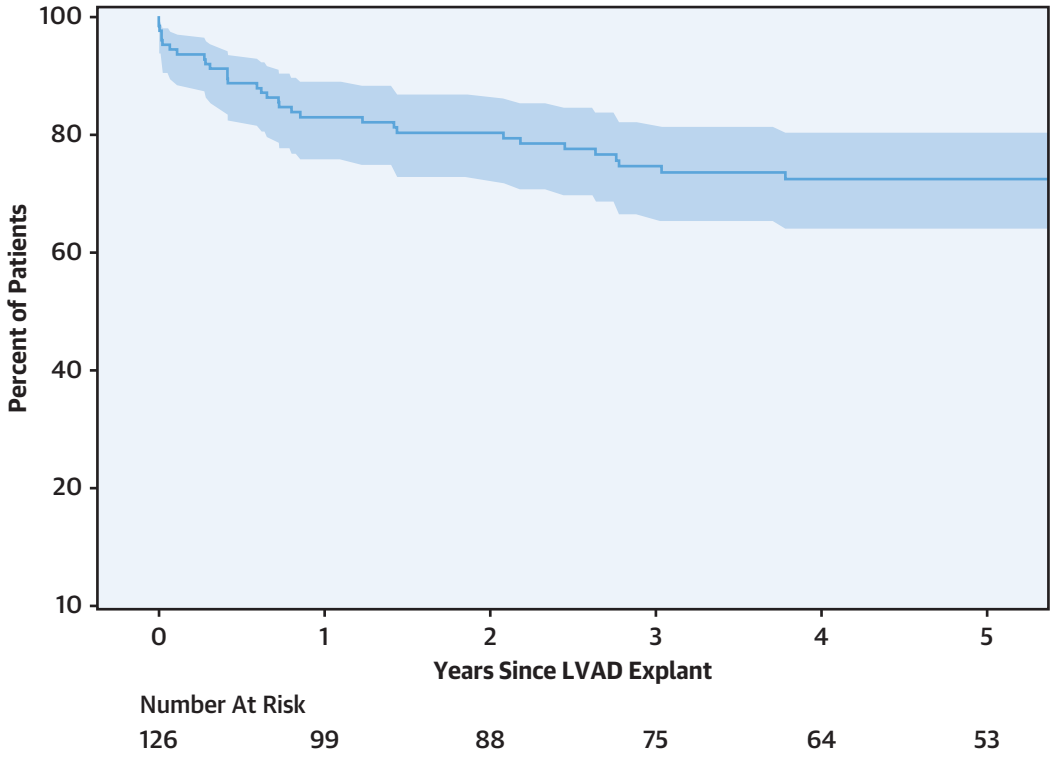


Approximately 60% of the patients were eventually removed from the list for sustained myocardial recovery and were never relisted. The remaining 40% of patients remained on the list or were relisted after some period of delisting. LVAD = left ventricular assist device.

centers having LVAD explant as a treatment option, the incidence rates were at the level of a practical reality, achieving as high as 10%. Myocardial recovery seems to be the purview of limited centers with academic interest in this otherwise rare event; moreover, the U.S. system may bias most centers toward not pursuing recovery strategies aggressively, as they could carry undesirable consequences for programmatic transplant volumes and finances. These may explain the dissociation between the "real-world" incidence and the true incidence, likely leading to the ongoing and substantial underappreciation of myocardial recovery under LVAD support, which only limits the enthusiasm for pursing it.

Our data added a new insight into the association of the LVAD device type and myocardial recovery. Among factors favoring myocardial recovery, most of which were shown in the previous studies, HeartMate II LVAD compared with HeartWare or HeartMate 3 was found to favor myocardial recovery. This interesting finding may implicate the effect of the LVAD flow mechanism, axial or centrifugal, on myocardial recovery or simply because HeartMate II is a device in which the ramp study creating no net flow was

CENTRAL ILLUSTRATION **Freedom From Heart Failure Relapse Events After Left Ventricular Assist Device Explant**



Itagaki S, et al. J Am Coll Cardiol HF. 2024;12(5):893-901.

The freedom rate from heart failure relapse events (relisting followed by delisting due to death, being too ill, or heart transplantation; and second durable left ventricular assist device [LVAD] implant) is plotted against time from LVAD explant. Shaded areas represent 95% CIs.

established most.[12] The cumulative experience on HeartMate 3 may change this trend in the future.

The present study is unique among those investigating the outcomes after LVAD explant as it had a large sample size and adequate follow-up time to capture heart failure relapse events. It has been challenging to draw any definitive conclusion from previous studies on how patients behave after LVAD explant because of the small sample size of patients who actually reach this endpoint,[7] the relatively short follow-up time,[5] or simply because no follow-up information was available.[10,11] Heart failure relapse is a legitimate concern for a cohort of patients whose heart failure was believed to be "end-stage," requiring a durable LVAD.[13] With an extended mean follow-up time of 4 years, we found that 60% of patients were delisted and remained that way, indicating sustained recovered cardiac function, and that 40% of patients remained on the list or were relisted, which may indicate some burden of residual advanced disease.

It should not be understated that 6% of patients had a heart failure relapse event relatively early, within 30 days of explant. There are limited reports of follow-up after explant and even those found typically do not go beyond the anecdotal or descriptive level of analysis; however, one can find several reports of events occurring in the early phase after explant. These include dramatic presentations such as sudden death with arrhythmias, suicide, or cardiogenic shock requiring placement of mechanical support.[2-5,7] It is notable that these events occurred despite likely extensive assessments before explant that led expert centers to believe that these patients were acceptable candidates for device removal. The observation of these early events occurring should perhaps call our current methods of evaluation in question. The time period that is typically used, generally minutes to hours, for assessment on minimal LVAD support may not be sufficient to reveal the underlying cardiac vulnerability. In addition, this early hazard phase, observed in our series and others,

highlights the necessity that patients being considered for LVAD explant should have a planned bailout strategy, be able to undergo strict periodic surveillance, and accept a low threshold for relisting or reimplantation of LVAD if there are clinical indicators or heart failure relapse.

Nonetheless, following the relatively high hazard in the early phase, the rate of heart failure relapse seems to taper, and >70% of the patients remained free from relapsing at 4 years. This observation, along with indubitable underestimation of the true incidence of left ventricular recovery mentioned earlier, has important implications for the concept of LVAD-induced myocardial recovery in the era of organ shortage. There are certainly a subgroup of patients, and potentially more, who can have sustained recovery and benefit from the period free of complications related to immunosuppressant use or an LVAD device. This is especially relevant in younger patients with nonischemic etiology, and the focused LVAD explant strategy should continue to be explored and may be a key consideration leading to the concept of net prolongation of life in both individual patients and patients overall with advanced heart failure.[14]

STUDY LIMITATIONS. Given the features of the database we used, it only captured patients on LVAD support who were deemed to be bridge to transplantation at some point. The finding of this study may therefore not be generalizable to patients who underwent LVAD placement as destination therapy, a bridge to candidacy, or a bridge to recovery, which accounted for approximately 50% of all durable LVAD implanted, and may cause further underestimation of the true incidence of LVAD explant. The method of estimating the proportion of the study cohort to all implanted LVADs during the study period is described in the Supplemental Methods. Nonetheless, the feature of the UNOS registry provided us with a unique ability that other registry databases do not have: to track the outcomes after LVAD explant as all patients initially stayed on the transplant list after LVAD explant. Our study was also based on the assumption that a patient was considered free of a heart failure relapsing event if the patient was removed from the list for myocardial recovery and was never relisted until the end of the study period. It is possible that these patients had a heart failure relapse event but were never relisted for it or they died of noncardiac causes, which would not be captured. Therefore, our study may lead to an overestimation of success of LVAD explant. On the contrary, there was a risk of underestimating the outcomes after LVAD explant as mortality on the waitlist and delisting due to being too ill, despite being hard endpoints, cannot be completely stratified by the specific causes, some of which may have been unrelated to heart failure relapsing. The causes of death while on the waitlist are provided in Supplemental Table 5. The data on the method of LVAD support cessation (complete removal vs less invasive approaches such as decommission or defunctionalization) are not available in the UNOS registry, which is likely to have clinical implications. Finally, the interval estimates and *P* values were not adjusted for multiple comparisons and should be interpreted with caution.

CONCLUSIONS

In contemporary practice in the United States, LVAD explant for myocardial recovery was a practice that only occurred in a handful of implanting centers. The national overall incidence therefore appeared very low at <1%; however, in designated centers for selected patients, the incidence was at an achievable level ranging from 5% to 10%. After LVAD explant, more than one-half of the patients had sustained recovered cardiac function and were successfully removed and remained off the heart transplant waitlist. Although some heart failure relapse events occurred relatively early in 6% of patients after LVAD explant, the rate of relapse tapered off following, and 70% of patients were free from relapse at 4 years. Given these findings, the LVAD explant strategy seems to be substantially underutilized but has a potential to prolong the net lifespan of patients with advanced heart failure, especially in the young nonischemic cohort, and should likely be incorporated as one of the realistic options in the lifetime management of such patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with end-stage heart failure who underwent durable LVAD implant, myocardial recovery occurred but only a handful of centers explanted devices. After explant, with up to 4 years of follow-up, more than one-half of explanted patients showed sustained myocardial recovery, and the freedom of heart failure relapsing was >70% at 4 years.

TRANSLATIONAL OUTLOOK: Further work is needed to better identify who is expected to have myocardial recovery under durable LVAD support and who benefits from device explant.

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KEY WORDS end-stage heart failure, left ventricular assist device, myocardial recovery

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.

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