10-19-2021

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Recommended Citation

Cogswell R, Cantor RS, Vorovich E, Kilic A, Stehlik J, Cowger JA, Habib RH, Kirklin JK, Pagani FD, and Atluri P. HVAD(TM) to Heartmate 3(TM) Device Exchange: A Society of Thoracic Surgeons Intermacs Analysis. Ann Thorac Surg 2021.

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2021.09.031

HVAD to Heartmate 3 Device Exchange: A Society of Thoracic Surgeons Intermacs Analysis

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ABSTRACT

BACKGROUND On June 3, 2021 Medtronic, Inc announced discontinuation of the HVAD left ventricular assist device. The purpose of this analysis was to provide summary data on surgical risks of HVAD to HeartMate 3 exchange and compare survival after HVAD to HeartMate 3 exchange to survival after primary HVAD implantation.

METHODS Three cohorts within The Society of Thoracic Surgeons Intermacs database were identified: primary HVAD implant cohort (January 2017 to March 2021, n = 3797), HVAD to HeartMate 3 exchange cohort (December 2017 to March 2021, n = 45), and HVAD to HVAD exchange cohort (January 2017 to March 2021, n = 234). Mortality after HVAD to HeartMate 3 exchange was modeled and compared with the constant hazard phase for risk of mortality while on continued HVAD support. As a secondary analysis outcomes and survival were compared between patients who underwent HVAD to HeartMate 3 and HVAD to HVAD exchange.

RESULTS HVAD to HeartMate 3 exchange was associated with significantly reduced survival compared with survival while remaining on HVAD support (6 months after exchange, 73.8% [70% confidence interval, 68.6-77.8] vs 79.0% [70% confidence interval, 78.3-79] for continued HVAD support). Compared with HVAD to HVAD exchange, survival was higher after replacement with HeartMate 3 (1 year: 85.9% [70% confidence interval, 79.5-90.5] vs 66.6% [70% confidence interval, 63.0-70.0], $P = .009$).

CONCLUSIONS Compared with continued support on HVAD, an exchange to HeartMate 3 was found to be associated with a significant increase in mortality. For patients who required pump exchange on HVAD support, exchange to HeartMate 3 demonstrated superior survival. Currently there is insufficient evidence to support elective exchange from an HVAD to HeartMate 3.

(Ann Thorac Surg 2021;■:■-■)

On June 3, 2021 Medtronic, Inc (Minneapolis, MN) discontinued the sale and commercial distribution of the HVAD left ventricular assist device (LVAD). Medtronic cited several reasons for this decision including an increased risk of stroke and mortality compared with the more contemporary HeartMate 3 pump (Abbott Laboratories, Chicago, IL)[1,2] and critical device malfunctions of the HVAD causing the device to delay or fail to restart.[3] The first communication by

Dr Cogswell discloses a financial relationship with Abbott Lab and Medtronic; Dr Vorovich with Abiomed, Sibel, and Cricket Innovations; Dr Kilic with Abiomed and Abbott; Dr Stehlik with Medtronic; Dr Cowger with Abbott, Medtronic, Endotronix, Procyrion, and Abbott; Dr Kirklin with STS Intermacs D.C.; Dr Pagani with the STS Intermacs Task Force; and Dr Atluri with Edwards Lifesciences, Medtronic, and Abbott.

The Supplemental Tables and Supplemental Figures can be viewed in the online version of this article [10.1016/j.athoracsur.2021.09.031] on http://www.annalsthoracicsurgery.org.

Accepted for publication Sep 14, 2021.

Presented at the Fifty-seventh Annual Meeting of The Society of Thoracic Surgeons, Virtual Meeting, Jan 29-31, 2021.

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Medtronic relating to this specific device malfunction occurred in December 2020. At that time an internal pump component, the impellor, was believed to be responsible for this specific failure mode, and the responsible device components were traced to 3 isolated lots of HVAD devices. Subsequently reports of device failures continued beyond the 3 lots initially identified, and a common root cause of this problem could not be determined in all cases. The rate of device malfunction for this mode of failure, outside of the 3 specified lots, was reported as 0.4%. With the inability to address these HVAD critical device malfunctions, coupled with data demonstrating the clinical superiority of the HeartMate 3,[1,2] Medtronic stopped the distribution and sale of the HVAD system.

With Medtronic's decision the HeartMate 3 is now the only US Food and Drug Administration-approved durable LVAD in the United States for both new implants and pump exchanges. This also holds true for a large part of the global community. A number of important issues have arisen as to how to manage patients currently supported with the HVAD pump with little data for guidance. Should patients on HVAD support be offered exchange for a device-related complication only (ie, pump thrombosis), or should HVAD pumps be electively changed to the HeartMate 3 to reduce the risk of patient harm from a potential device malfunction related to a failure to restart event? In addition little data have been published with respect to the surgical risks and mortality expected after an HVAD to HeartMate 3 exchange, particularly when considering the additional surgical complexity of device exchange and associated morbidity.

The objective of the present study was to provide summary data of the surgical risks of an HVAD to HeartMate 3 exchange and to compare survival after an HVAD to HeartMate 3 exchange to survival after a contemporary, primary HVAD implant. We also compared surgical outcomes and survival between HVAD to HeartMate 3 and HVAD to HVAD exchange populations. We hypothesized that survival after an HVAD to HeartMate 3 exchange would not be superior to survival on continued HVAD support.

PATIENTS AND METHODS

This retrospective analysis of The Society of Thoracic Surgeons (STS) Intermacs registry was performed by the Data Coordinating Center at the University of Alabama at Birmingham. The primary analysis compared survival after an HVAD to HeartMate 3 exchange to survival after a contemporary, primary HVAD implant. A secondary analysis compared survival after an HVAD to HeartMate 3 exchange to survival after an HVAD to HVAD exchange. To complete these comparisons 3 study cohorts were identified: a contemporary cohort undergoing primary HVAD implant (n = 3797, implant dates January 2017 to March 2021), an HVAD to HeartMate 3 exchange cohort (n = 45 [first occurrence of an HVAD to HeartMate 3 exchange reported in STS Intermacs was in December 2017], implant dates December 2017 to March 2021), and a contemporary cohort consisting of patients undergoing an HVAD to HVAD exchange (n = 234, implant dates January 2017 to March 2021) (Figure 1).

Patients were excluded if age at the time of surgery was <19 years. For the first cohort (primary HVAD implant), patients receiving concomitant right ventricular assist device (RVAD) support concomitant with the initial LVAD implant were excluded from the study cohort. Patients receiving a subsequent RVAD after leaving the operating room from the initial LVAD implant were included. Patients receiving a concomitant RVAD at the time of LVAD exchange were included for the second (HVAD to HeartMate 3 exchange; 2/42 [4.7%] received a concomitant RVAD at the first exchange) and third (HVAD to HVAD exchange; 9/234 [3.8%] received a concomitant RVAD at the first exchange) study cohorts. Patients receiving any other type of durable mechanical circulatory support device were excluded from the analysis. The study period was limited to January 2017 to April 30, 2021 to match the time period when HVAD to HeartMate 3 exchanges were reported to the STS Intermacs.

For each cohort baseline characteristics at the time of exchange (exchange cohorts) or the time of first implantation (primary HVAD cohort) are presented in Table 1. Continuous variables were evaluated for normality and are presented as mean ± SD or median (interquartile range), as appropriate. Categorical variables are displayed as counts and percents.

For the primary HVAD implant cohort, follow-up began at initial device implant, and patients were censored at transplant, device exchange, cessation of device support, or device explant without exchange. For the exchange subgroups, follow-up began at the device exchange and continued while the exchange device was in place. Additional LVAD exchange procedures in the exchange subgroups were not considered as censoring events in the analysis unless the device was switched to a different brand of device. Of the 234 patients undergoing an HVAD to HVAD exchange 5 patients went on to receive a subsequent exchange to a HeartMate 3 (third device). These patients were censored at the time of the second exchange. The last date of follow-up was June 15, 2021. STS Intermacs subject status (alive on support, exchanged, transplanted) and dates were verified with clinical sites as of June 15, 2021 for the 45 patients undergoing HVAD to HeartMate 3 exchange.

To compare survival after an HVAD to HeartMate 3 exchange with that of survival after a primary HVAD implant, a multiphase parametric survival curve was fit to the data of the primary HVAD implant cohort and HVAD to HeartMate 3 exchange cohort (Supplemental Figures 1 and 2). This technique displays the changing hazard for an event over time[4] and identifies when

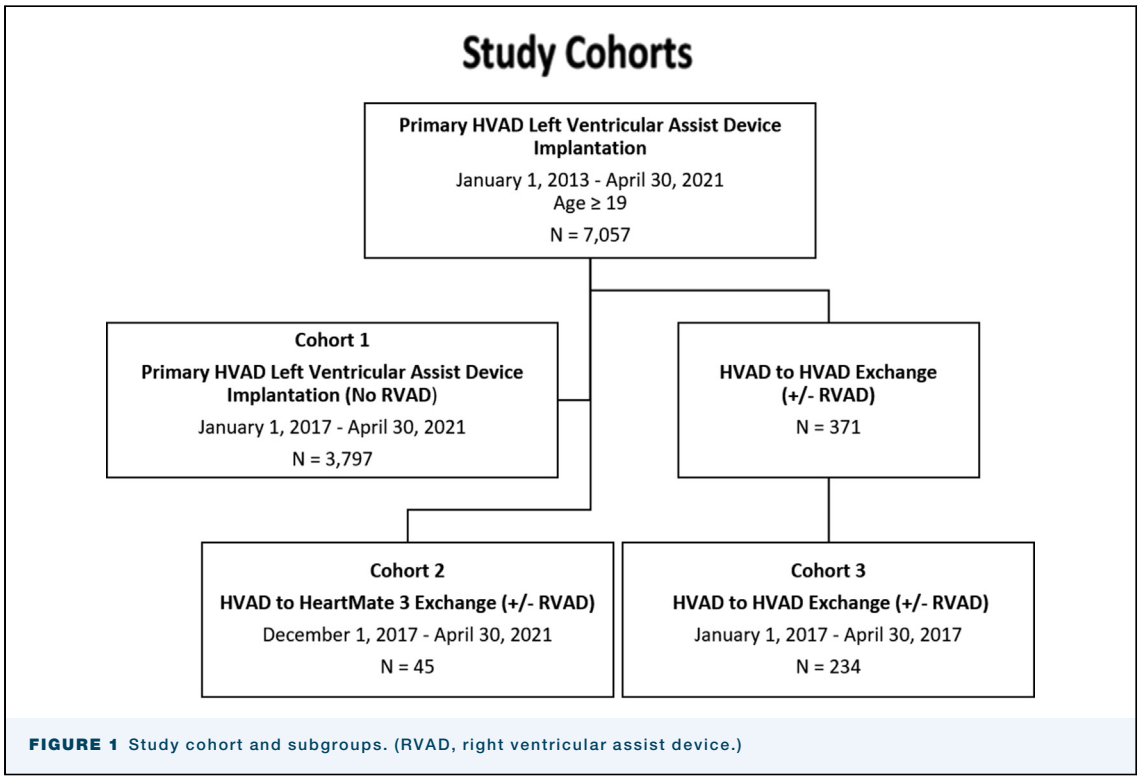

FIGURE 1 Study cohort and subgroups. (RVAD, right ventricular assist device.)

survival reaches a constant hazard phase for risk of mortality for the primary HVAD cohort (starting at approximately 6 months after primary HVAD implant). Parametric survival after an HVAD to HeartMate 3 exchange was then overlaid onto the parametric survival of the HVAD curve at 6 months. Seventy percent confidence intervals were included to indicate statistical significance of approximately $P = .05$ (Figure 2 and Supplemental Figure 3).[5,6]

HVAD to HeartMate 3 and HVAD to HVAD exchange patient characteristics at the time of exchange were compared. Normally distributed continuous variables were compared with Student t tests and nonnormally distributed variables with the Mann-Whitney tests. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Survival probabilities after exchange were calculated using the Kaplan-Meier method, and survival was compared using the log rank test. Additionally outcomes were examined using the Fine-Gray competing outcomes analysis in which multiple mutually exclusive outcomes (alive on LVAD support, death, cessation of support, and transplant) are tracked over time. At any point in time the sum of the proportion (%) of patients in each outcome category equals 100%. Finally survival after an HVAD to HVAD exchange was stratified by year of exchange (2017, 2018-2019, 2020-2021). All analyses were completed with SAS 9.4 (SAS Institute Inc, Cary, NC), and a $P < .05$ was considered statistically significant.

This study was reviewed and approved by the STS Research Center. The findings and conclusions herein represent those of the authors and not those of the STS (Chicago, IL), Abbott Labs, Medtronic, Inc, or the US Food and Drug Administration.

RESULTS

STUDY COHORTS. For the primary HVAD implant subgroup (n = 3797) mean age was 56 ± 13.2 years and 73% were men (2768/3797), with 22.9% (869/3797) STS Intermacs Profile 1 (Table 1). The mean age of the HVAD to HeartMate 3 exchange subgroup (n = 45) was 53 ± 13 years, 69% were men (31/45), and 16% (7/45) were STS Intermacs Profile 1. Overall there was a relatively high proportion of patients on an intraaortic balloon pump (9% [4/45]) and/or ventilator support (9% [4/45]) at the time of the LVAD exchange (Table 1). The HVAD to HVAD exchange subgroup (n = 234) was similar in age and acuity to both the HVAD to HeartMate 3 exchange and the primary HVAD implant subgroups (Table 1). The median follow-up for the 3 cohorts was 14.5 months (interquartile range, 7.6-23.9) for the HVAD to HeartMate 3 subgroup, 13.0 months (interquartile range, 5.0-27.2) for the primary HVAD implant subgroup, and 8.3 months (interquartile range, 2.7-17.1) for the HVAD to HVAD subgroup.

TABLE 1 Patient Characteristics of the Study Cohorts

	HVAD to HeartMate Exchange Cohort Exchange (n = 45)	Contemporary Primary HVAD Implant Cohort[a] (n = 3797	HVAD to HVAD Exchange Cohort (n = 234)
Age, y	53.2 ± 13.2[b]	56.0 ± 13.2	54.1 ± 13.6[b]
Male	31 (68.9)	2768 (72.9)	175 (74.8)
White	26 (57.8)	2336 (61.5)	160 (68.4)
Bridge to transplant, listed	10 (22.2%)[b]	740 (19.5)	62 (26.6)[b]
Body surface area	2.2 ± 0.3[b]	2.0 ± 0.3	2.1 ± 0.3[b]
Body mass index, kg/m^2	30.8 ± 6.8[b]	28 ± 7.6	30.3 ± 7.9[b]
Ischemic cardiomyopathy	24 (53.3)[b]	1569 (41.3)	103 (44.0)[b]
Society of Thoracic Surgeons Intermacs Profile			
1	7 (15.6)[b]	869 (22.9)	53 (22.8)[b]
2	6 (13.3)[b]	1315 (34.6)	64 (27.5)[b]
3	2 (4.4)[b]	1240 (32.7)	28 (12.0)[b]
4-7	30 (66.7)[b]	373 (9.8)	88 (37.8)[b]
Prior coronary artery bypass graft	7 (15.6)	641 (16.9)	39 (16.7)
Intraaortic balloon pump	4 (8.9)[b]	1299 (34.2)	18 (7.7)[b]
Extracorporeal membrane oxygenation	1 (2.2)[b]	324 (8.5)	18 (7.7)[b]
Dialysis	2 (4.4)[b]	174 (4.6)	13 (5.6)[b]
Ventilator	4 (8.9)[b]	558 (14.7)	23 (9.9)[b]
Creatinine, mg/dL	1.4 ± 0.7[b]	1.4 ± 0.6	1.8 ± 1.0[b]
Blood urea nitrogen, mg/dL	21.4 ± 11.5[b]	29.5 ± 17.4	27.9 ± 17.4[b]
Albumin, g/dL	3.5 ± 0.6[b]	3.4 ± 0.6	3.5 ± 0.6[b]
Bilirubin, mg/dL	1.6 ± 1.3[b]	1.3 ± 1.6	2.0 ± 1.8[b]

[a]All data for the cohort were reported at the time of primary HVAD implant; [b]Reported at the time of exchange. Values are mean ± SD or n (%).

SURVIVAL COMPARISON BETWEEN HVAD TO HEARTMATE 3 EXCHANGE VS CONTEMPORARY HVAD SUPPORT. For a primary HVAD implantation there was a high early hazard for death followed by a rapidly declining postoperative hazard phase that transitioned to a constant mortality hazard at approximately 6 months (Figure 2 and Supplemental Figures 1 and 3). An HVAD to HeartMate 3 exchange was also characterized by an early hazard for risk of death with rapidly declining risk that quickly transitioned to a constant hazard of risk for death (Figure 2 and Supplemental Figures 2 and 3). Although the constant hazard of risk for mortality after an HVAD to HeartMate 3 exchange was less than the constant hazard of risk for mortality after a primary HVAD implant, there was a substantial early postoperative risk of death associated with the HVAD to HeartMate 3 exchange operation.

Comparison of these risks is depicted in Figure 2 for a hypothetical HVAD to HeartMate 3 device exchange occurring at 6 months vs continued support after a primary HVAD implant beyond 6 months. Mortality was highest early after primary HVAD implant, reaching a constant hazard phase of risk for mortality at approximately 6 months after LVAD implantation (Figure 2 and Supplemental Figures 1 and 3). In the subgroup of patients undergoing HVAD to HeartMate 3 exchange a statistically significant (ie, separation of the 70% confidence intervals between curves supporting a $P < .05$)[5,6] increase in mortality was noted, represented in Figure 2 as an increase in the early mortality hazard after exchange when compared with the constant hazard phase for risk of mortality of 0.1 for those maintained on HVAD support after primary implant.

SURGICAL COMPARISON BETWEEN PUMP EXCHANGE OUTCOMES: HVAD TO HEARTMATE 3 VS HVAD TO HVAD. The indication for pump exchange, length of stay, and postsurgical complications for both the HVAD to HeartMate 3 and HVAD to HVAD pump exchange cohorts are summarized in Supplemental Table 1. Of note given the ability to indicate multiple causes for exchange on STS Intermacs Adverse Event forms, the aggregate is >100%. For the HVAD to HeartMate 3 exchange subgroup the indications for exchange were pump thrombosis in 67%, device malfunction in 11%, device infection in 20%, and other in 1%. For the HVAD to HVAD exchange cohort indications were pump thrombosis in 61%, device malfunction in 36%, device infection in 6%, and other in 6%. Compared with the HVAD to HVAD exchange, bypass time for the HVAD to HeartMate 3 was considerably longer (median 139 minutes vs 75

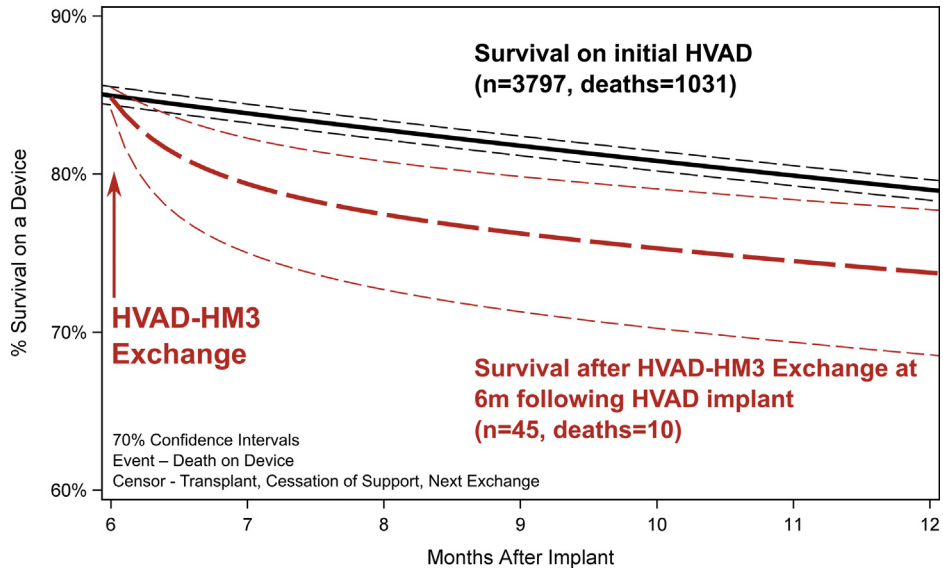

FIGURE 2 Parametric model estimate of survival after HVAD to HeartMate 3 (HM3) exchange and contemporary, primary HVAD implantation after survival for the primary HVAD implantation reaches the constant hazard phase of risk for death. Curves of parametric model survival estimates comparing the mortality of patients remaining on support with the HVAD left ventricular assist device (black) vs those who have undergone an exchange to the HM3 (red). Note that time begins at 6 months (6m) after primary implantation of the HVAD. The dash lines represent the 70% confidence intervals and do not overlap in the 6 months after HVAD to HM3 exchange supporting a statistical significance of $P = .05$.[5,6] Survival at 1-month after HVAD to HM3 exchange was 79.4% (70% confidence interval, 75.0-82.2) compared with survival of 83.8% (70% confidence interval, 83.2-84.4) if remaining on continued HVAD support (7 months from initial HVAD implant). Survival at 6-months after HVAD to HM3 exchange was 73.6% (70% confidence interval, 68.6-77.8) compared with survival of 79.0% (70% confidence interval, 78.3-79.6) if remaining on continued HVAD support (12 months from initial HVAD implant).

minutes, $P < .0001$), as was the need for concomitant surgery (71% vs 43%, $P < .001$). Postoperative RVAD use, prolonged inotrope use, infection, stroke, and need for dialysis were similar, with the HVAD to HeartMate 3 group requiring an RVAD in 6.7% (3/45) and prolonged inotropes in 33% (13/39) of cases. The occurrence of postoperative infection was 31% (14/45), need for dialysis was 12.9% (5/39), and stroke was 9% (4/45). Of the HVAD to HeartMate 3 exchanges 11% died (5/45) during the exchange hospitalization. Late survival after exchange was higher in those exchanged to a HeartMate 3 (1 year: 86% vs 67%, $P = .009$) (Supplemental Figure 4).

Survival after an HVAD to HVAD exchange stratified by year of device exchange (2017, 2018-2019, 2020-21) is shown in Supplemental Figure 5. There was no significant difference in survival across years.

COMPETING OUTCOMES. For patients undergoing an HVAD to HeartMate 3 exchange the proportion remaining alive on support at 12 months was 80.8%, with 5.2% receiving a transplant and 14% dying (Supplemental Figure 6A). For patients undergoing an HVAD to HVAD exchange only 51.9% remained alive on support at 12 months, with 14.9% receiving a transplant and 30.7% dying (Supplemental Figure 6B).

COMMENT

The ADVANCE, ENDURANCE, and ENDURANCE Supplemental clinical trials[7-9] established the long-term safety and efficacy of the HVAD system (Medtronic Inc) as durable LVAD support for patients with advanced heart failure. Initially manufactured by HeartWare, Inc the HVAD technology was subsequently acquired by Medtronic in 2016 with a focus to further advance HVAD development, including design of a totally implantable platform.[10] The HVAD served a key role in supporting thousands of patients, both for destination therapy and bridge to transplant applications. Several key design attributes advanced the application of this technology for both adult and pediatric patients, including an intrapericardial design that minimized surgical dissection and improved ease of surgical implant, reduced size permitting implantation in smaller patients, ease of application to novel support configurations including

use as a durable RVAD for biventricular assist, and potential to implant using a minimally invasive approach with an anterior lateral thoracotomy incision and without cardiopulmonary bypass.

Since the commercial availability of the HVAD device in 2012 a next-generation device, the HeartMate 3 (Abbott Labs), has undergone evaluation in a large, multicenter, randomized, prospective clinical trial and received U.S. Food and Drug Administration approval for short-term circulatory support indication in 2017 and long-term support indication in 2019.[11,12] With commercial approval of the HeartMate 3 and in the absence of clinical trial data directly comparing the HVAD with HeartMate 3, a number of comparative effectiveness studies to the HVAD device have been performed from clinical registries and administrative databases and have demonstrated a significantly increased risk of stroke and mortality for the HVAD compared with the HeartMate 3.[1,2,13,14] Coupled with recent concerns over the potential of internal pump failures resulting in a delayed or failed restart in roughly 100 cases, Medtronic decided to remove the HVAD device from commercial distribution and sale.

The decision to remove the HVAD from commercial availability has raised concern regarding the optimal management of patients on existing HVAD support and the risk-to-benefit ratio of device exchange in those on uncomplicated device support to prevent future complications, including the potential for device restart failure. Data from this study demonstrate that compared with contemporary survival after primary implant of the HVAD System, exchange to a HeartMate 3 was associated with increased early-phase mortality, particularly in the initial 6 months after the exchange operation. When comparing outcomes after a nonelective HVAD to HeartMate 3 exchange with a nonelective HVAD to HVAD exchange postsurgical complications were similar, yet late survival was superior when an HVAD was changed to the HeartMate 3 vs exchanged with another HVAD.

Despite the increases in technical difficulty of exchanging an HVAD to HeartMate 3 compared with an HVAD to HVAD exchange and longer duration of cardiopulmonary bypass times, these data suggest that patients on HVAD support requiring a device exchange are not disadvantaged by replacement with the HeartMate 3 technology. In fact late survival appears to be superior and is consistent with previous observations of comparisons of overall survival when primary HVAD implants were compared with primary HeartMate 3 implants.[13,14] Thus the increase in surgical complexity in an HVAD to HeartMate 3 exchange compared with an HVAD to HVAD exchange does not increase operative risk. Collectively these data suggest there is insufficient evidence, to date, to support elective exchange from HVAD to HeartMate 3; however when an exchange is necessary, exchange to a HeartMate 3 is associated with late survival benefit.

LIMITATIONS. The results of the present analysis, however, must be interpreted acknowledging that the subgroup undergoing an HVAD to HeartMate 3 exchange underwent a device exchange for cause (ie, pump thrombosis or device infection) and were by definition sicker than patients who would be undergoing an elective device exchange. In addition because of the small sample size, we were not able to analyze outcomes by exchange indication or risk adjustment for severity of illness at the time of exchange. It is likely that surgical experience with device exchanges over time will lead to improved outcomes with an HVAD to HeartMate 3 exchange, as has been observed with other LVAD surgeries over time.[15] However when comparing survival after an HVAD to HVAD exchange, stratified by year of device exchange, significant improvements in survival were not observed with our data. Thus caution must be used in assessing the impact of surgical experience in improving outcomes after device exchanges. The exchange cohort analyzed in this study represents the first 45 patients who underwent this procedure and reported to STS Intermacs. For these reasons this analysis will likely need to be repeated as experience grows to understand the risk vs benefit of future exchanges.

The STS Intermacs registry relies on clinical sites for completeness and accuracy of data reporting and may not have included all events for the HVAD to HeartMate 3 exchange procedures and their related events and outcomes. However the STS Intermacs registry, a component of the STS National Databases, undergoes routine data audits for completeness and accuracy performed by independent auditors. Importantly this analysis was significantly limited by sample size, and there were insufficient numbers of patients to perform detailed statistical analyses to understand characteristics associated with poor outcomes or characteristics that may improve patient selection. Further because of sample size, risk adjustment of patient characteristics were not performed.

CONCLUSION. Compared with contemporary survival after primary HVAD implantation, an HVAD to HeartMate 3 exchange is associated with a significant increase in early mortality. Thus for patients currently supported on a normally functioning HVAD device, there is insufficient evidence to support a strategy of elective exchange to the HeartMate 3. For patients who required a device exchange while on HVAD support, exchange to the HeartMate 3 compared with exchange to an HVAD demonstrated superior late survival. Follow-up analyses are warranted to determine if changes to these current recommendations are necessary.

The data for this research were provided by The Society of Thoracic Surgeons' National Database Access and Publications Research Program.

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