5-1-2021

Clinical outcomes and healthcare expenditures in the real world with left ventricular assist devices - The CLEAR-LVAD study

Francis D. Pagani

Mandeep R. Mehra

Jennifer A. Cowger
Henry Ford Health, jcowger1@hfhs.org

Douglas A. Horstmanshof

Scott C. Silvestry

See next page for additional authors

Recommended Citation
Pagani FD, Mehra MR, Cowger JA, Horstmanshof DA, Silvestry SC, Atluri P, Cleveland JC, Jr., Lindenfeld J, Roberts GJ, Bharmi R, Dalal N, Kormos RL, and Rogers JG. Clinical outcomes and healthcare expenditures in the real world with left ventricular assist devices - The CLEAR-LVAD study. J Heart Lung Transplant 2021; 40(5):323-333.

Authors

Francis D. Pagani, Mandeep R. Mehra, Jennifer A. Cowger, Douglas A. Horstmanshof, Scott C. Silvestry, Pavan Atluri, Joseph C. Cleveland, JoAnn Lindenfeld, Gregory J. Roberts, Rupinder Bharmi, Nirav Dalal, Robert L. Kormos, and Joseph G. Rogers

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Clinical outcomes and healthcare expenditures in the real world with left ventricular assist devices — The CLEAR-LVAD study

Francis D. Pagani, MD, PhD,[a] Mandeep R. Mehra, MD, MSc,[b] Jennifer A. Cowger, MD, MS,[c] Douglas A. Horstmanshof, MD,[d] Scott C. Silvestry, MD,[e] Pavan Atluri, MD,[f] Joseph C. Cleveland, Jr., MD,[g] JoAnn Lindenfeld, MD,[h] Gregory J. Roberts, BS,[i] Rupinder Bharmi, MS,[i] Nirav Dalal, MS,[i] Robert L. Kormos, MD,[i] and Joseph G. Rogers, MD[j]

From the [a]Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan; [b]Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts; [c]Department of Cardiovascular Medicine, Henry Ford Hospitals, Detroit, Michigan; [d]INTEGRIS Advanced Cardiac Care, Oklahoma City, Oklahoma; [e]Advent Health Transplant Institute, Orlando, Florida; [f]Division of Cardiovascular Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [g]University of Colorado School of Medicine, Aurora, Colorado; [h]Section of Heart Failure and Cardiac Transplantation, Vanderbilt University Medical Center, Nashville, Tennessee; [i]Abbott Laboratories, Abbott Park, Illinois; and the [j]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina.

KEYWORDS:
left ventricular assist device;
heart failure;
healthcare expenditures;
medicare beneficiaries;
mechanical circulatory support

BACKGROUND: Several distinctly engineered left ventricular assist devices (LVADs) are in clinical use. However, contemporaneous real world comparisons have not been conducted, and clinical trials were not powered to evaluate differential survival outcomes across devices.

OBJECTIVES: Determine real world survival outcomes and healthcare expenditures for commercially available durable LVADs.

METHODS: Using a retrospective observational cohort design, Medicare claims files were linked to manufacturer device registration data to identify de-novo, durable LVAD implants performed between January 2014 and December 2018, with follow-up through December 2019. Survival outcomes were compared using a Cox proportional hazards model stratified by LVAD type and validated using propensity score matching. Healthcare resource utilization was analyzed across device types by using nonparametric bootstrap analysis methodology. Primary outcome was survival at 1-year and total Part A Medicare payments.

RESULTS: A total of 4,195 de-novo LVAD implants were identified in fee-for-service Medicare beneficiaries (821 HeartMate 3; 1,840 HeartMate II; and 1,534 Other-VADs). The adjusted hazard ratio for mortality at 1-year (confirmed in a propensity score matched analysis) for the HeartMate 3 vs HeartMate II was 0.64 (95% CI; 0.52−0.79, $p< 0.001$) and for the HeartMate 3 vs Other-VADs was 0.51 (95% CI; 0.42−0.63, $p < 0.001$). The HeartMate 3 cohort experienced fewer hospitalizations per patient-year vs Other-VADs (respectively, 2.8 vs 3.2 EPPY hospitalizations, $p < 0.01$) and 6.1 fewer hospital days on average (respectively, 25.2 vs 31.3 days, $p < 0.01$). The difference in Medicare expenditures, conditional on survival, for HeartMate 3 vs HeartMate II was -$10,722, $p < 0.001$ (17.4% reduction) and for HeartMate 3 vs Other-VADs was -$17,947, $p < 0.001$ (26.1% reduction).

Reprint requests: Otto Gago MD Endowed Professor of Cardiac Surgery Department of Cardiac Surgery 5161 Cardiovascular Center, SPC 5864 University of Michigan 1500 East Medical Center Drive Ann Arbor, Michigan 48109 Telephone: 734-647-2894; Fax: 734-764-2255
E-mail address: fpagani@umich.edu

https://doi.org/10.1016/j.healun.2021.02.010

CONCLUSIONS: In this analysis of a large, real world, United States. administrative dataset of durable LVADs, we observed that the HeartMate 3 had superior survival, reduced healthcare resource use, and lower healthcare expenditure compared to other contemporary commercially available LVADs.
J Heart Lung Transplant 2021;40:323−333

Abbreviations

CMS	Centers for Medicare and Medicaid Services
CPSY	Cost per study-year
ECMO	extracorporeal membrane oxygenation
EPPY	Events per patient-yea
FDA	United States Food and Drug Administration
HeartMate 3	HM3
HeartMate II	HMII
HMO	health maintenance organization
LVAD	left ventricular assist device
TCCS	Total cost conditional on survival

Condensed abstract

A real world comparative effectiveness study was conducted among commercially available durable left ventricular assist devices (LVADs). Medicare claims files were linked to manufacturer device registration data to identify de-novo, implants to assess 1-year survival and healthcare expenditures. Among 4,195 de-novo implants (821 HeartMate 3, (HM3); 1,840 HeartMate II, (HMII); and 1,534 Other-VADs), the adjusted mortality at 1-year for the HM3 was superior to HMII and Other-VADs. The HM3 cohort experienced fewer hospitalizations and less Medicare expenditures vs Other-VADs. In a large, real world, United States (U.S.) administrative dataset, we observed the HM3 to have superior survival and lower healthcare expenditures.

Introduction

The evidentiary basis for device selection in patients with advanced heart failure receiving durable left ventricular assist device (LVAD) support has largely accrued from randomized controlled clinical trials.[1-4] The largest such trial, the Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3 Investigational Device Exemption Clinical Study (MOMENTUM 3) evaluated 1028 patients and demonstrated that a fully magnetically levitated centrifugal continuous flow pump (HeartMate 3; HM3; Abbott Labs, Chicago, IL) was superior to a mechanical bearing axial continuous flow pump (HeartMate II; HMII; Abbott Labs, Chicago, IL) with regard to 2-year survival free of disabling stroke or need for device reoperation or replacement for a malfunctioning device.[3] Similarly, The HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure: the ENDURANCE Trial (ENDURANCE) compared a smaller intrapericardial device (i.e., HVAD System; Medtronic, Inc., Minneapolis, MN) to the HMII in 446 patients and demonstrated noninferiority of the primary end point of survival at 2 years free from disabling stroke or device removal for malfunction or failure.[4] These trials were not powered to evaluate the various LVADs on the end-point of mortality alone.

With the real world use and dissemination of LVAD therapy beyond clinical trial-defined populations, device performance and outcomes have differed from those observed within clinical trials.[5-7] Conversely, increasing surgical experience has demonstrated improved outcomes beyond those of the early clinical trials.[8] Real world data can provide important opportunities for comparative effectiveness analyses when data is lacking or to supplement findings from randomized clinical trials.[9,10]

Medicare is the federal health insurance program in the U.S. for those aged ≥65 years, <65 years of age with disabilities, or with end-stage renal disease. Administrative claims files from Medicare have been used to perform comparative effectiveness studies of various therapies and to describe their associated patterns of morbidity and mortality, and healthcare expenditures associated with care.[11]

In the *C*linica*L* Outcom*E*s and Healthc*A*re Expenditures in the *R*eal World with *L*eft *V*entricular *A*ssist *D*evices (CLEAR-LVAD) study, we used a combination of Medicare claims files and manufacturer device registration data to: (1) investigate the real world effectiveness of commercially available durable LVADs on survival and post-implant hospitalizations; and (2) investigate differences in healthcare resource utilization and attendant expenditure among commercially available LVADs. We hypothesized that newer LVAD technology which in clinical trials has been shown to improve clinical outcomes would, in this real-world effectiveness analysis, demonstrate significant survival and healthcare expenditure benefits.

Methods

Study Design: We conducted a retrospective cohort study of de-novo durable LVADs implanted in the U.S. to assess comparative effectiveness across different LVAD systems. The goal was to compare the survival, hospitalization rate, and length-of-stay, and overall healthcare expenditures in patients implanted with different LVADs; (1) mechanical bearing axial-flow pump (HMII; Abbott Labs., Chicago, IL); (2) fully magnetically levitated centrifugal flow pump (HM3; Abbott Labs, Chicago, IL); and (3) other durable LVAD technologies (Other-VADs).

Data Sources: The data for baseline characteristics and outcomes were retrieved from the Centers for Medicare and Medicaid Services (CMS) longitudinal administrative claims files.[12,13] The data for pump technology type, for 2 LVADs; the HM3 and HMII, were retrieved from the Abbott device registration data. Linking of the manufacturer device registration data and the Medicare administrative claims files enabled labeling of the LVAD type for

each implant common to the manufacturer device registration database and Medicare claims files.[14] Please refer to the *Supplemental Appendix* for a detailed description of each data source and linkage methodology.

The use of Medicare records and linkage to the manufacturer device registration database was approved through a data use agreement, RSCH-2018-52161, with CMS. The methods for linking data from the manufacturer device registration database to Medicare claims files and the research protocol were reviewed by Western Institutional Review Board (Puyallup, WA) and were granted an exemption determination, a full waiver of informed consent, and a Health Insurance Portability & Accountability Act waiver.

Participants: We studied patients with heart failure implanted with a denovo, durable LVAD between January 1, 2014 and December 31, 2018. The last date of implant was based on the availability of Medicare data to ensure that each patient had a minimum of 12 months of postimplant follow-up. As of May 2020, CMS data was available through Dec 31, 2019.

Cohort Derivation: A total of 7109 LVAD implants were identified over the study period, with 5,643 implants representing de-novo or primary LVAD implants in the Medicare files that were not associated with a heart transplant procedure during the LVAD index hospitalization (Figure 1A & B). Please refer to the *Supplemental Appendix* for criteria to define de-novo primary VAD implants (eTable 1).

The identification of LVADs as HM3 or HMII was done based on the linkage to the manufacturer device registration database. Other-VADs were deemed to be implants that were not linked between the manufacturer device registration database and Medicare claims files. Starting with the de-novo implants, patients were then excluded based on 5 criteria in the following sequence: (1) extracorporeal membrane oxygenation (ECMO) during the index hospitalization; (2) incomplete Part A/B enrollment at index hospitalization; (3) absence of continuous medical coverage 3 months before the index hospitalization; (4) Health Maintenance Organization (HMO) insurance; and, (5) participation in a pre-market clinical trial. Patients receiving ECMO were excluded due to possible confounding from the high mortality associated with LVAD implantation in these patients and the different rates of ECMO use among the cohort groups. The status of pre-market clinical trial study participation was determined using the Clinical Trial Number field in the CMS data [https://www.resdac.org/cms-data/variables/clinical-trial-number] and the device registration database (Figure 1B). The availability of this field was used to exclude all patients participating in Investigational Device Exemption trials, whereas post-market study participation of registry participation was not used as an exclusion for participation in CLEAR-LVAD. Further, biventricular assist device status was not used as an exclusion criterium because of the low prevalence of biventricular assist device usage in the time period between VAD implant and discharge. eTable 2 documents the frequency of biventricular assist device usage across the different type of heart pumps. The final study cohort consisted of 4,195 patients (821 HM3 pumps, 1,840 HMII pumps and 1,534 Other-VADs) ensuring that none of the patients represented here were enrolled in MOMENTUM-3 Investigational Device Exemption clinical trial. A sensitivity analysis to evaluate the influence of exclusion criteria on survival outcomes at 1-year is presented in eTable 3. The only information provided by the linkage was the device name. All other information was obtained from Medicare claims files on the VRDC.

Healthcare Utilization and Expenditure Analysis: The healthcare burden was assessed in the postimplant period by quantifying the aggregate number of hospitalizations, number of days spent in hospital and the payer expenditures associated with these hospitalizations. The in-patient hospitalizations and corresponding expenditures were observed using Part A Medicare claims data only. Part B Medicare claims data were not used to determine total healthcare expenditures. The healthcare expenditure analysis was performed using 2 time-horizons to answer the following questions. (1) "What are the expenditures associated with hospitalizations while patients are ongoing on the original device?" − aggregate of hospitalizations in the 1-year post discharge - censored at VAD explant, heart transplant or death. This analysis focused on healthcare encounters for the patient while the individual was on the original device. 2. "What is the expected expenditures of hospitalizations for 1-year post implant depending on choice of initial VAD?" − aggregate of hospitalizations in the 1-year post discharge until and including death. This analysis focused on healthcare encounters for the patient until death and includes encounters wherein the original device may be removed or replaced. Procedure Codes for hospitalizations related to VAD explant and heart transplant are described in eTable 1.

Payments from hospitals from the dataset were standardized to 2019 U.S. dollars based on the medical (Consumer Price Index) inflation from the Bureau of Labor Statistics [https://fred.stlouisfed.org/series/CPIMEDSL]. Standardization to account for geographic differences was not attempted for 2 reasons. Firstly, the goal of the economic analysis was to report on the actual expenditures incurred by Medicare (payer), and secondly, geographic price standardization would effectively be a modeling exercise that would illustrate the relative cost differential between geographic regions and not actual expenditures.

Statistical Methods: As the primary end point, we compared the survival at 1-year following pump implantation. Kaplan−Meier survival estimates were calculated, censoring patients at the time of replacement, explant, or transplantation. The hazard of death for each pump type (relative to HeartMate-3), after adjusting for patient factors (which included age, sex, race (White), pre-implant transplant listing status, pre-implant short-term mechanical circulatory support, preimplant inotrope use, diabetes, hypertension, renal disease, obesity, coagulopathy, cerebral vascular disease, myocardial infarction, atrial fibrillation, ventricular tachycardia/fibrillation, peripheral vascular disease, liver disease, pulmonary disease, pulmonary circulation disorder) were compared using a Cox proportional-hazards model (Figure 2A). The comorbidity burden of LVAD recipients was quantified using the Elixhauser score distribution.[15,16]

Competing-risk curves for the total cohort reflect the cumulative percentages of patients in each group who had an outcome of ongoing device support, heart transplant, device explant/replacement, or death through 1 year and 2 years (eFigure (1). To analyze survival in the presence of competing outcomes, the Fine−Grey model was used to calculate the hazard ratio for death while accounting for the competing risk of heart transplantation. All tests were 2-tailed, and *p*values of .05 or less were considered significant.

Healthcare utilization among the implanted cohort was assessed using the Part A Medicare claims data (in-patient hospitalizations) in the time-period following post-implant until censoring. The events include in-patient hospitalization for any reason, including LVAD replacement; and follow-up continued until a patient received a heart transplant, VAD explant, VAD replacement, or death (Figure 3). The all-cause in-patient hospitalizations events and cumulative length of stay were compared using the nonparametric bootstrap model.[17] The primary end-point comparison is provided at the 1-year timepoint. In this non-parametric bootstrap analysis, the 2-sided P-values were estimated using the prepivoting technique for comparisons of event per patient-year (EPPY) and cumulative length of stay across the pairs of groups: HM3 vs HMII; HM3 vs Other-VADs. The bootstrap was

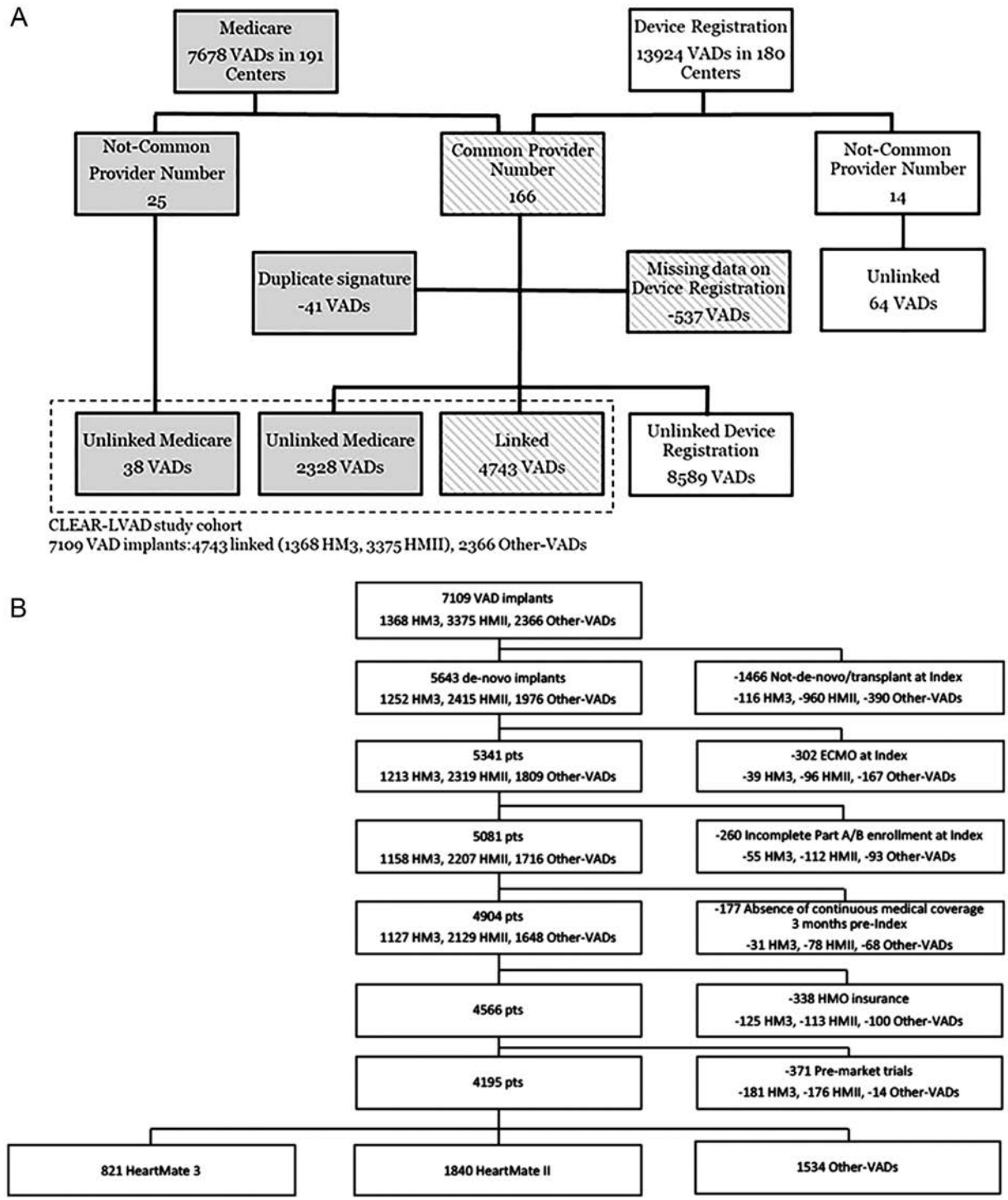
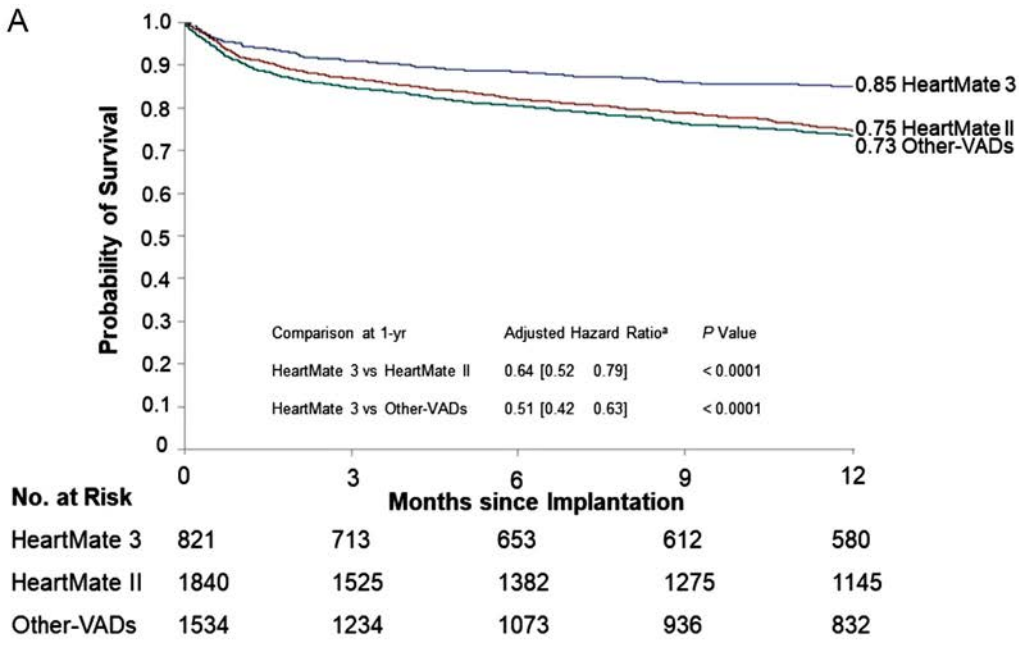


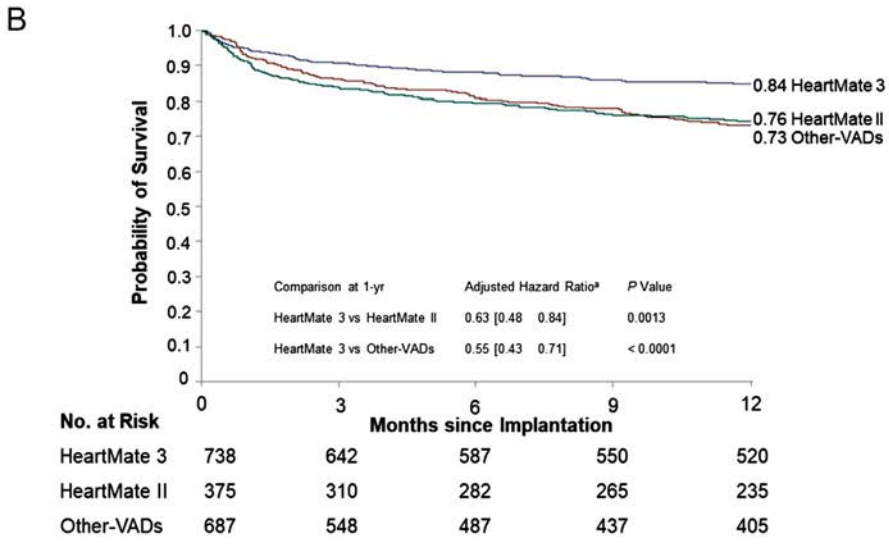
Figure 1 Study population and cohort derivation. (A) Consolidated diagram of the study population. (B) Cohort derivation. (A) Consolidated diagram of the study population. The CLEAR-LVAD study cohort included 7109 VAD implants, of which 4,743 were linked (1,368 HeartMate 3 and 3375 HeartMate II) and 2,366 Other-VADs were not linked. Abbreviations: HeartMate II, HMII; HeartMate 3, HM3; VAD, Ventricular assist device Consolidated diagram of the study population. Medicare VAD implants consists of all heart pump types in Medicare fee for service enrollees only. The heart pumps in the manufacturer device registration consist of HM3 and HMII implants conducted, amongst all Insurance types (Medicare FFS, Medicare Advantage, Private Insurance, No Insurance). (B) Cohort Derivation Abbreviations: ECMO - extracorporeal membrane oxygenation; HMO, Health maintenance organization; HMII, HeartMate II; HM3, HeartMate 3; VAD, Ventricular assist device. Index Hospitalization is defined as hospitalization for de novo implant.

conducted 10,000 times to quantify the variability in the observation and estimate the confidence interval.[18]

Supporting Analysis using Propensity Matching: We further conducted a supporting analysis to characterize the outcomes in a propensity-matched cohort.[19,20] Please refer to the ***Supplemental Appendix*** for details of the propensity matching methodology.

All analyses were conducted on the CMS Virtual Research Data Center (VRDC) using SAS Enterprise Guide version 7.15 HF3 (SAS Institute Inc., Cary, NC).





Number of LVAD Implants by Year and By Device Type

LVAD Type \ Implant Year	2016	2017	2018
Heart Mate 3	83	317	421
Heart Mate II	383	286	89
Other-VADs	232	300	387

Figure 2 Primary end point of overall 1-year survival. (A) Durable LVAD implants Jan 2014-Dec 2018. (B) Durable LVAD implants Jan 2017-Dec 2018. (A) Durable LVAD implants Jan 2014-Dec 2018 (A) The hazard ratios were adjusted for age, sex, race (White), preimplant transplant listing status, preimplant short-term mechanical circulatory support, pre-implant inotrope use, diabetes, hypertension, renal disease, obesity, coagulopathy, cerebral vascular disease, myocardial infarction, atrial fibrillation, ventricular tachycardia and/or fibrillation, peripheral vascular disease, liver disease, pulmonary disease, pulmonary circulation disorder. (B) Durable LVAD implants Jan 2017-Dec 2018.

Results

Baseline Characteristics: The study cohort consisted of 821 HM3, 1,840 HMII and 1534 Other-VADs patients. Demographics and comorbidities for the study cohort are reported in **Table 1**. Average age was 63.6 years (57.9% ≥ 65 years) with a majority being male (78.4%), white (69.6%), and with a high comorbidity burden (93.9% of patients having an Elixhauser comorbidity burden > 4; 20.7 ± 11.7). The comorbidity burden was similar across all 3 groups. The average length of stay for the index VAD hospitalization was 35.0 ± 24.1 days, with a length of stay from VAD

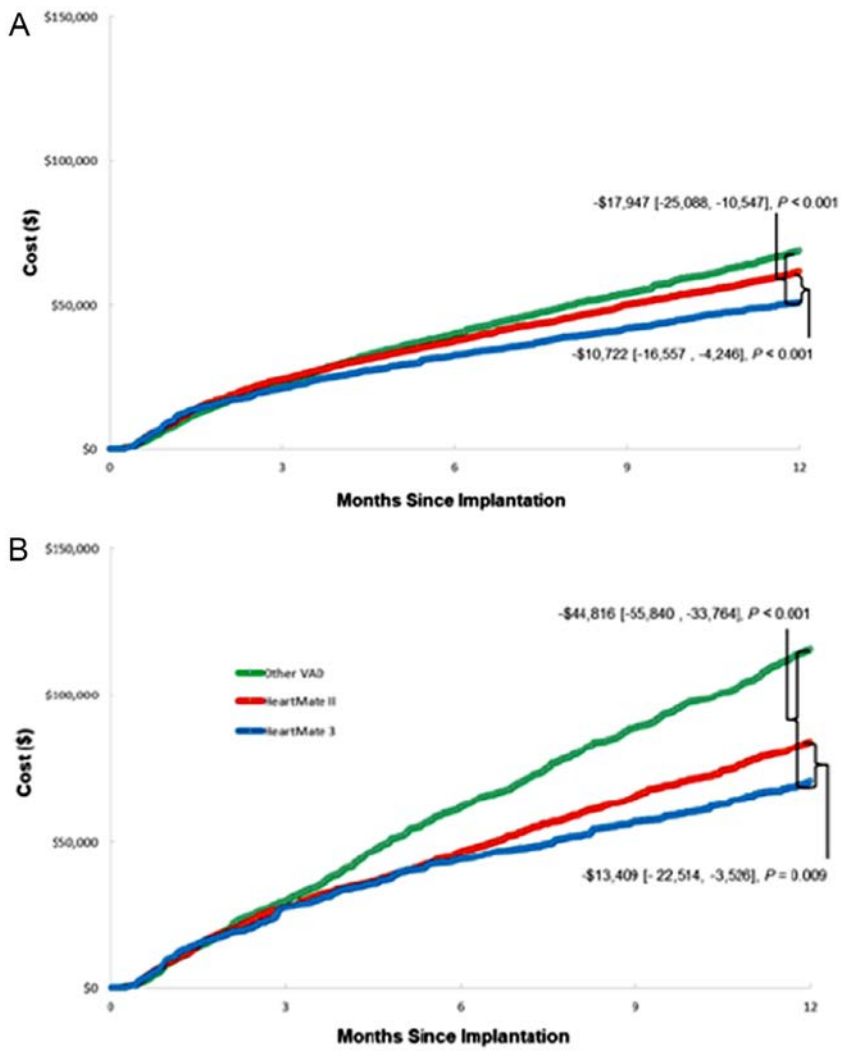


Figure 3 Total healthcare expenditure conditional on survival over time. (A) Hospitalization expenditures while patients are ongoing on the original device. (B) Hospitalization expenditures post discharge until death. The plot shows the expected cumulative cost at each time point, conditional on the subject remaining in the study at that point. *p* values derived from bootstrap simulation (x10,000). CI - pivotal confidence intervals from non-parametric bootstrap model (x10,000) (A) Hospitalization expenditures while patients are ongoing on the original device. (B) Hospitalization expenditures post discharge until death.

implant to discharge of 25.0 ± 21.2 days. Clinical management at baseline was characterized by determining the presence of pre-implant short-term mechanical circulatory support, organ transplant status, and inotrope usage (**eTable 4**). Preimplant short-term mechanical circulatory support was used in 25.9% of HM3 patients, 35.1% of HMII patients, and 37.3% of patients with Other-VADs. Heart transplant listing before VAD implant was present in 17.4% of HM3 patients, 10.2% of HMII patients and 24.9% of Other-VADs. Preimplant inotrope usage, estimated using the Healthcare Common Procedure Coding System and National Drug Code codes (**eTable 1**) from all healthcare encounters, was present in 28.7% of HM3 patients, 28.8% of HMII patients, and 24.8% of Other-VADs.

Primary Outcomes: Each patient had a minimum follow-up time of 1 year. There were 117 (14.3%) deaths among 821 HM3 patients, 375 (20.4%) deaths among 1840 HMII patients, and 375 (24.5%) deaths among 1534 Other-VADs. The mortality rate at 1-year was significantly lower in patients with HM3 vs HMII devices (unadjusted hazard ratio (HR) = 0.57 [95% CI, 0.47-0.70]) and in patients with HM3 vs Other-VADs (unadjusted HR = 0.53 [95% CI; 0.43 −0.66]). When adjusted for covariates (**eTable 5**), the 1-year HM3 vs HMII HR was 0.64 (95% CI; 0.52−0.79), $p<$ 0.0001; and the 1-year HM3 vs Other-VADs HR was 0.51 (95% CI; 0.42−0.63), $p < 0.0001$ (Figure 2A). To investigate era effect, a sensitivity analysis was performed limiting survival analysis to Jan 2017-Dec 2018 (Figure 2B).

The 2-year mortality rate was significantly lower in HM3 vs HMII, with an unadjusted HR = 0.57 (95% CI; 0.47−0.70); and in HM3 vs Other-VADs, with an unadjusted HR = 0.53 (95% CI; 0.43−0.66). When adjusted for covariates, the 2-year HR for HM3 vs Other-VADs was 0.62 (95% CI; 0.52−0.75), $p < 0.001$, and the 2-year HR for HM3 vs Other-VADs was 0.51 (95% CI, 0.42−0.61), $p < 0.001$. The hazards were proportional, and the survival outcomes were consistent over the 2-year period (**e**Figure 2 **and eTable 5**).

Table 1 Demographics and Comorbidities at Index Implant

Variable	HeartMate 3 ($n = 821$)	HeartMate II ($n = 1,840$)	Other-VADs ($n = 1,534$)	p value[a]
Age, mean (SD), y	63.6 (11.0)	64.6 (10.8)	62.3 (11.2)	< 0.0001
Age ≥ 65 years, No. (%)	479 (58.3)	1152 (62.6)	800 (52.2)	< 0.0001
Female, No. (%)	182 (22.2)	341 (18.5)	383 (25.0)	< 0.0001
Race, No. (%)				0.48
White	573 (69.8)	1310 (70.7)	1045 (68.1)	
Black	193 (23.5)	418 (22.7)	362 (23.6)	
Hispanic	16 (1.9)	35 (1.9)	42 (2.7)	
Other\Unknown	39 (4.8)	86 (4.7)	85 (5.5)	
Comorbidity history, No. (%)[b]				
Diabetes[c]	404 (49.2)	1016 (55.2)	757 (49.3)	0.0007
Hypertension[c]	703 (85.6)	1584 (86.1)	1270 (82.8)	0.0223
Renal disease[c]	490 (59.7)	1175 (63.9)	844 (55.0)	<0.0001
Obesity[c]	282 (34.3)	490 (26.6)	396 (25.8)	<0.0001
Coagulopathy[c]	85 (10.4)	285 (15.5)	210 (13.7)	0.0018
Cerebral vascular disease[c,d]	225 (27.4)	534 (29.0)	395 (25.7)	0.1056
Myocardial infarction[d]	342 (41.7)	792 (43.0)	593 (38.7)	0.0343
Atrial fibrillation	418 (50.9)	983 (53.4)	735 (47.9)	0.0062
Ventricular tachycardia/fibrillation	435 (53.0)	886 (48.2)	736 (48.0)	0.0411
Peripheral vascular disease[c]	244 (29.7)	575 (31.3)	413 (26.9)	0.0222
Liver disease[c]	108 (13.2)	294 (16.0)	179 (11.7)	0.0012
Pulmonary disease[c]	302 (36.7)	994 (54.0)	692 (45.1)	<0.0001
Pulmonary circulation disorder[c]	92 (11.2)	627 (34.1)	380 (24.8)	<0.0001
Elixhauser score 0-1, No. (%)	37 (4.5)	47 (2.6)	75 (4.9)	<0.0001
Elixhauser score 2-3, No. (%)	24 (2.9)	28 (1.5)	44 (2.9)	
Elixhauser score ≥ 4, No. (%)	760 (92.6)	1765 (95.9)	1415 (92.2)	
Elixhauser comorbidity score, mean (SD) [Q1, Q3]	18.6 (11.1) [10, 26]	22.4 (12.0) [13, 30]	19.8 (11.7) [11, 27]	

[a] p-values derived using ANOVA for discrete variables and Chi-square test.
[b] All comorbidities were assessed in the 3 months before index.
[c] When definitions were available as both Elixhauser and Charleson, preference was given to the Elixhauser comorbidity definition.
[d] Charleson comorbidity code definition used.

In the supporting propensity-score matched analysis of 2,232 patients (744 HM3, 744 HMII, and 744 Other-VADs), the survival rate in the HM3 patients at 1-year was 0.84, and at 2-years was 0.76. Among the matched HMII patients, the survival at 1-year was 0.76, and at 2-years was 0.64. Among the matched Other-VADs, the survival at 1-year was 0.73, and at 2-years was 0.59 (**e**Figure 3 **and eTable 6**). The mortality rate at 1-year was significantly lower in HM3 vs HMII, with a HR = 0.62 [95% CI; 0.49−0.79], and in HM3 vs Other-VADs, with a HR = 0.53 [95% CI; 0.42−0.67]. Propensity score density plots show matching between the cohorts based on the match criteria (**eFigure 4**). The patients were well matched with standardized mean difference estimates < 10% for all match parameters (**eTable 6**). A quartile-based analysis showed the survival trend was maintained across the four quartiles of propensity scores (**eTable 7**).

Competing-risk curves that reflect the cumulative percentages of patients in each group who had an outcome of ongoing device support, heart transplant, device explant, device replacement, or death are shown in **e**Figure 1. At the end of 1 year, 78.0% of HM3, 66.5% of HMII and 58.5% of Other-VADs were ongoing on the original implanted device. The Fine-Grey model-based HR for death while accounting for competing risk of heart transplantation at 1 year was 0.64 [95% CI; 0.52−0.79], $p < 0.001$ for HM3 vs HMII; and was 0.53 [95% CI; 0.43−0.65], $p < 0.001$ for HM3 vs Other-VADs. At the end of 2 years, 70.3% of HM3, 51.3% of HMII and 43.4% of Other-VADs were ongoing on the original implanted device (**e**Figure 1). The Fine-Grey model-based HR for death while accounting for competing risk of heart transplantation at 2 years was 0.63 [95% CI; 0.53−0.76], $p < 0.001$ for HM3 vs HMII; and was 0.54 [95% CI; 0.45−0.65], $p < 0.001$ for HM3 vs Other VADs.

Healthcare Encounters: Over 72.6% of patients had hospitalization for any cause in the first year while supported on the original device, with an event rate of 3.0 events per patient-year (EPPY). The all-cause hospitalization rates and cumulative length of stay associated with these in-patient hospitalizations are reported in **Table 2**, at the 1-year timepoint. When controlled for time in the study (by patient-years), the HM3 group experienced fewer hospitalizations per patient-year vs Other-VADs (respectively, 2.8 vs 3.2 EPPY hospitalizations, $p = 0.005$) and 6.1 fewer hospital days on average (respectively, 25.2 vs 31.3 days, $p < 0.001$), as well. As determined from the administrative claims database, the HM3 patients had the lowest device explant or replacement rate of 2.6% vs 4.0% for HMII and 3.9% for Other VADs ($p < 0.01$).

Healthcare Expenditure Analysis: The average expenditures related to these hospitalizations are summarized in

Table 2 Postimplant Healthcare Encounters Within First Year After Implant

	HeartMate 3 ($n = 812$)	HeartMate II ($n = 1,840$)	Other-VADs ($n = 1,534$)
Number of hospitalized patients N (%)	600 (73.9)	1,347 (73.2)	1,093 (71.3)
All-cause hospitalization[a], Events per patient year [95% CI]	2.8 [2.6 - 3.0]	3.0 [2.9 - 3.2]	3.2 [3.1 - 3.4]
Cumulative LOS for All-cause hospitalizations a, Days per patient year [95% CI]	25.2 [23.0 - 27.8]	28.5 [26.9 — 30.3]	31.3 [29.0 - 33.9]
Reimbursement for Index Implant Hospitalization, $ [95% CI]	$ 249,561 [$243,656- $256,383]	$ 266,752 [$261,767- $272,300]	$ 280,0128 [$272,902- $287,395]
Hospitalization cost while patients are ongoing on original device			
Average cost at 1-year (CPSY), $ [95% CI]	$ 52,583 [$47,970- $58,025]	$ 63,717 [$60,141 - $67,825]	$70,838 [$65,942 - $76,097]
Total cost conditional on survival (TCCS) at 1-year, $ [95% CI]	$ 50,885 [$46,371 - $56,359]	$ 61,607 [$57,993 - $65,545]	$ 68,832 [$64,215 - $74,100]
Hospitalization cost in the 1-year post discharge until death			
Average cost at 1-year (CPSY), $ [95% CI]	$ 71,846 [$64,438- $81,785]	$ 84,942 [$79,376 - $90,805]	$115,574 [$108,300 - $123,877]
Total cost conditional on survival (TCCS) at 1-year, $ [95% CI]	$ 70,566 [$63,465 - $78,964]	$ 83,975 [$78,895 - $89,659]	$ 115,382 [$108,617 - $123,968]

Abbreviations: EPPY, events per patient year; LOS, length of stay; CI, pivotal confidence intervals from non-parametric bootstrap model (x100,000); CPSY, cost per study year; TCCS, total cost conditional on survival

[a]Aggregate of hospitalizations in the 1-year post discharge - censored at VAD explant, heart transplant or death.

Table 2. The reimbursement related to the index LVAD implant for HM3, HMII and Other-VADs was observed to be $249,561, $266,752 and $280,127 respectively (Table 2). The difference for HM3 vs HMII was -$17,191, $p < 0.001$ and for the HM3 vs Other-VADs was -$30,566, $p < 0.001$. The cost per study-year (CPSY) associated with the hospitalizations at 1-year for the HM3, HMII, and Other-VADs were $52,583, $63,717 and $70,838/patient-year respectively. The CPSY difference for the HM3 vs HMII was -$11,134, $p < 0.001$ (17.5% reduction) and for the HM3 vs Other-VADs was -$18,255, $p < 0.001$ (25.8% reduction).

The cost implications of these hospitalizations are summarized in Figure 3**A**. The total cost conditional on survival (TCCS) associated with the hospitalizations at 1-year for the HM3, the HMII and Other-VADs were $50,885, $61,607 and $68,832 at 1-year, respectively. The TCCS difference for the HM3 vs HMII was -$10,722, $p < 0.001$ (17.4% reduction) and for HM3 vs Other-VADs was -$17,947, $p < 0.001$ (26.1% reduction). The economic analyses represent actual expenditure differences observed in the nationally representative Medicare fee for service population that were implanted with each pump type. The viewpoint most relevant to the payer is cost associated with choice of VAD type. This is summarized in Table 2 section titled "Hospitalization cost in the 1-year post discharge until death" which shows the CPSY associated with the hospitalizations at 1-year for the HM3, HMII, and Other VADs: $71,846, $84,942 and $115,574/patient-year respectively and TCCS of $70,566, $83,975 and $115,382/patient-year respectively. The TCCS difference at 11 year for the HM3 vs HMII was -$13,409, $p = 0.009$ (16.0% reduction) and for the HM3 vs Other-VADs was -$44,816, $p < 0.001$ (38.8% reduction) Figure 3**B**.

The healthcare expenditure impact was assessed in the propensity matched cohort and showed similar trends in cost difference. In the propensity score matched cohort, the reimbursement related to the index LVAD implant for HM3, HMII and Other-VADs was observed to be $ 250,685, $ 263,464and $ 276,746 respectively. The difference for HM3 vs HMII was -$12,779, $p = 0.020$ and for the HM3 vs Other-VADs was -$26,061, $p < 0.001$. We observed that the CPSY associated with hospitalizations at 1-year for the HM3, HMII, and Other-VADs were $53,089, $62,675 and $73,447 at 1-year respectively (**eTable 8**) with a CPSY difference for HM3 vs HMII of -$9,586 $p = 0.008$ (15.3% reduction) and for HM3 vs Other VADs -$20,358, $p < 0.001$ (27.7% reduction).

Discussion

The principal findings of the CLEAR-LVAD study demonstrate that; (1) the HM3 LVAD is associated with improved survival and decreased rate of postimplant hospitalizations and days spent in the hospital, when compared to the HMII LVAD, or with other commercially available VADs; and (2) healthcare expenditures (Part A claims) assessed from the perspective of Medicare payments are significantly lower with the HM3 LVAD, attributed to a reduction in post-implant hospitalizations.

Survival of patients with the HM3 LVAD in the CLEAR-LVAD study was similar to that observed within the MOMENTUM 3 clinical trial. These data suggest that real world adoption of this new technology continues to demonstrate device performance consistent with that observed in the clinical trial setting and further validates the within trial observations. We also demonstrated that the improved outcome on survival and rehospitalization was

associated with a healthcare expenditure benefit in favor of the HM3 LVAD, similar to what was reported in an early within-trial analysis.[21]

Survival on 1 of the comparator pumps, the HMII, was inferior to the HM3 in this real world experience at 2-years. This observation was not consistent with that observed in the MOMENTUM 3 clinical trial, but instead survival with the HMII was closer to the outcome noted in the ENDURANCE trial.[3,4] The real world experience analyzed in this study was restricted to the Medicare fee for service-eligible population, a population with a greater preponderance for lifelong LVAD therapy in and is more characteristic of the population enrolled in the ENDURANCE trial, whereas the MOMENTUM 3 trial included patients with either destination therapy or bridge to transplantation intent. Further, patients in the real world experience receiving the HMII could have included patients with characteristics that would have made them ineligible for MOMENTUM 3.

In addition to improved expenditures following discharge for the HM3, the reimbursement for the index implant admission is more for the Other-VAD than for the HM3 device. Even though the implants are associated with the same MS-DRGs, there are various contributing factors for the observed differences in Medicare expenditures and include Outlier payments, Geographic location of the Provider (inflation adjusted but not price-standardize Medicare expenditures), Short-term heart support and Length of stay. This observation held true in the propensity score matched cohort as well.

The methodology used in this study was designed to identify patients undergoing primary implantation of an FDA-approved, durable LVAD. Thus, the "Other VADs" cohort was presumably represented largely by the only other FDA-approved LVAD in the U.S., the centrifugal continuous flow pump with hybrid (hydrodynamic and magnetic) levitation (HVAD; Medtronic, Inc., Minneapolis, MN). Linkage of manufacturer data to Medicare beneficiary records was applied only to the HM3 and HMII arms of the study cohort. Linkage of the manufacturer database to the Medicare files served as validation of the methodology to identify patients receiving primary implantation of an FDA-approved durable VAD. However, this linkage was not feasible for the Other-VADs arm of the study cohort because manufacturer data for pumps in that group were not available. Thus, the number of administrative coding errors in this arm of the study cohort could potentially be higher than the other 2 study arms and could have permitted inclusion of some non-FDA-approved durable VADs in the Other-VADs arm of the study cohort. However, care was taken to ensure n1 of the Other-VADs were participants of an Investigational Device Exemption clinical trial by reviewing the Clinical Trial Number field in the CMS data.

Administrative datasets, such as Medicare, do not capture complete center implant activity and include only device implants among beneficiaries. Medicare fee for service beneficiaries represent approximately 45% of durable LVAD implants in the U.S.[22] Thus, the real world experience in this study excludes patients receiving the HM3 who were not Medicare eligible. Whether the real world experience in non-Medicare beneficiaries is similar to Medicare beneficiaries or similar to the clinical trial experience remains unknown. Recent data from The Society of Thoracic Surgeons Interagency Registry of Mechanically Assisted Circulatory Support (Intermacs) have demonstrated similar survival for the HM3 in a real world setting in a population including Medicare and non-Medicare patients.[10] In a recent trial analysis of MOMENTUM 3, Goldstein et al. compared patients by initial therapeutic intent and demonstrated that the survival and adverse events, such as stroke rates, were not materially different in the bridge-to- transplant population compared with the older destination-therapy cohort.[2]

There are several limitations to this study. This was a real world analysis of patients receiving durable VAD therapy and was a retrospective, observational study design involving nonrandomized treatment assignments. Thus, confounders not accounted for in the study analyses may contribute to differences in the outcomes of the 3 study arms. Rigorous comparison of comorbid conditions and status of transplant eligibility, inotrope use, and temporary mechanical circulatory support use were carefully assessed among study arms to minimize cofounders. Important, clinically relevant differences between the HM3 and the Other-VADs group were noted for pulmonary disease, pulmonary circulation disorders, and frequency of pre-implant short-term mechanical circulatory support between admission and durable device implant, which were more frequent for the Other-VADs cohort. However, the Other-VADs cohort was characterized by much greater representation of bridge-to-transplant candidates, of whom generally indicate a population with fewer comorbid conditions. The proportion of patients receiving a heart transplant at 2-years was twice that with the Other-VADs compared to the HM3. Administrative coding, however, may not be as precise as granular clinical data available from a clinical device registry in assessing risk of co-morbid conditions. Multiple statistical methodologies including propensity matching, were therefore used to minimize differences, where feasible, between groups. Additionally, more HM3 devices were placed in the later years of the study compared to HMII devices and Other-VADs. Thus, improvements in patient management strategies over time could have created confounding with respect to the cost associated with management of adverse events. We also do not report the adverse event profiles, nor do we evaluate the principal reasons for the observed survival benefit, or the causes of hospitalizations. We intentionally did not attempt to analyze this information since we deemed that level of evaluation to not provide sufficient robustness or granularity due to the introduction of coding errors, misclassification, and the fact that multiple adverse events tend to define most hospitalizations and it is difficult to adjudicate the principal drivers from such a database. We therefore maintained the evaluation to those areas of robustness including death rates, overall hospitalizations and days in the hospital and overall costs incurred.

Conclusion

In this analysis of a large U.S. administrative dataset that details real world VAD therapy, we observed that the HM3 LVAD demonstrated better survival to that of other contemporary LVAD systems. Furthermore, we demonstrated that the HM3 is associated with fewer hospitalizations and hospital days incurred after implantation, and a reduction in overall expenditure, when compared to other commercially available LVADs. These data validate the efficacy of the HM3 in a real world experience and support previous clinical trial observations.

Perspectives

Competency in Medical Knowledge: In a real world setting of Medicare beneficiaries undergoing implantation of a durable LVAD, a totally magnetically levitated centrifugal continuous flow device (HeartMate 3), is associated with improved survival and lower hospital resource utilization and Medicare expenditures.

Translational Outlook: Further research is needed to understand the major benefits that contribute to reduction in hospital resource utilization, Medicare expenditures and survival for the HeartMate 3 left ventricular assist device.

Author contributions

Rupinder Bharmi and Gregory Roberts had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Rupinder Bharmi and Gregory Roberts are employees of Abbott. All authors have had access to aggregate data and summary statistics. All authors have read the manuscript, contributed to study design, and have provided critical review and have agreed to its submission for publication.

Disclosures

Dr. Pagani is a member of the Scientific Advisory Board for FineHeart, Inc., member of the data safety monitoring board for Carmat, Inc., member of the data safety monitoring board for the National Heart, Lung, and Blood Institute PumpKIN clinical trial, and Chair, The Society of Thoracic Surgeons Intermacs Task Force. Dr. Mehra reports receiving travel support and consulting fees, paid to Brigham and Women's Hospital, from Abbott, fees for serving on a steering committee from Medtronic and Janssen (Johnson & Johnson), fees for serving on a data and safety monitoring board from Mesoblast, consulting fees from Portola, Bayer, Triple gene, Baim Institute of Clinical Research, and fees for serving as a scientific board member from NuPulseCV, Leviticus and FineHeart. Dr. Cowger reports receiving consultant fees from Abbott and Medtronic, Inc.; Dr. Horstmanshof reports receiving consulting fees from Abbott; Dr. Silvestry reports receiving consulting fees from Abbott, Medtronic, and Syncardia.; Dr. Pavan reports no disclosures; Dr. Cleveland reports no disclosures.; Dr. Lindenfeld reports consulting for Abbott, AstraZeneca, CVRx, Boehringer Ingelheim, Edwards LifeSciences, Impulse Dynamics, and VWave and receives grants from AstraZeneca, Volumetric, and Sensible Medical.; Mr. Roberts, Ms. Bharmi, Mr. Dalal and Dr. Kormos are employees of Abbott.; Dr. Rogers reports no disclosures.

Funding/Support: Funding for this study was provided by Abbott.

Role of Funder/Sponsor: Abbott actively participated in the design and conduct of the study

Additional Contributions: N1

Acknowledgments

Rupinder Bharmi and Gregory Roberts had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Rupinder Bharmi and Gregory Roberts are employees of Abbott.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.02.010.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

References

1. Uriel N, Colombo PC, Cleveland JC, et al. Hemocompatibility-related outcomes in the MOMENTUM 3 trial at 6 months: a randomized controlled study of a fully magnetically levitated pump in advanced heart failure. Circulation 2017;135:2003-12.
2. Goldstein DJ, Naka Y, Horstmanshof D, et al. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the multicenter study of magLev technology in patients undergoing mechanical circulatory support therapy with heartMate 3 (MOMENTUM 3) randomized clinical trial. JAMA Cardiol. 2020;e195323.
3. Mehra MR, Uriel N, Naka Y, et al. A fully magnetically levitated left ventricular assist device - final report. N Engl J Med 2019;380:1618-27.
4. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med 2017;376:451-60.
5. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885-96. https://doi.org/10.1056/NEJMoa067758.
6. Kirklin JK, Naftel DC, Kormos RL, et al. Interagency registry for mechanically assisted circulatory support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. J Heart Lung Transplant 2014;33:12-22.
7. Kirklin JK, Naftel DC, Pagani FD, et al. Pump thrombosis in the thoratec heartMate II device: an update analysis of the INTERMACS registry. J Heart Lung Transplant 2015;34:1515-26.
8. Park SJ, Milano CA, Tatooles AJ, et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart Fail 2012;5:241-8.
9. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff. United States Food and Drug Administration; 2020. Available at: https://www.fda.gov/media/99447/download.

10. Teuteberg JJ, Jr Cleveland JC, Cowger J, et al. The society of thoracic surgeons intermacs 2019 annual report: the changing landscape of devices and indications. Ann Thorac Surg 2020;109:649-60. https://doi.org/10.1016/j.athoracsur.2019.12.005.
11. Fung V, Brand RJ, Newhouse JP, Hsu J. Using Medicare data for comparative effectiveness research: opportunities and challenges. Am J Manag Care 2011;17:488-96.
12. Research data assistance center (ResDAC). Available at: http://www.resdac.org.
13. Centers for medicare and medicaid services virtual research data center. Research Data Assistance Center. Available at: https://www.resdac.org/cms-virtual-research-data-center-vrdc.
14. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. Am Heart J 2009;157:995-1000. https://doi.org/10.1016/j.ahj.2009.04.002.
15. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130-9. https://doi.org/10.1097/01.mlr.0000182534.19832.83.
16. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ elixhauser comorbidity index. Med Care 2017;55:698-705.
17. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med 2000;19:3219-36.
18. Beran R. Prepivoting test statistics: a bootstrap view of asymptotic refinements. J Am Stat Ass 1988;83:687-97.
19. Austin P. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
20. Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research [published online ahead of print, 2020 Jan 10]. JAMA. 2020; 10.1001/jama.2019.21558. doi:10.1001/jama.2019.21558
21. Mehra MR, Salerno C, Cleveland JC, et al. Healthcare resource use and cost implications in the MOMENTUM 3 long-term outcome study. Circulation 2018;138:1923-34. https://doi.org/10.1161/CIRCULATIONAHA.118.035722.
22. Liang Q, Ward S, Pagani FD, et al. Linkage of medicare records to the interagency registry of mechanically assisted circulatory support. Ann Thorac Surg 2018;105:1397-402. https://doi.org/10.1016/j.athoracsur.2017.11.044.