6-1-2021

Concordance of Treatment Effect: An Analysis of The Society of Thoracic Surgeons Intermacs Database

Francis D. Pagani

Ryan Cantor

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

Daniel Goldstein

Jeffrey Teuteberg

See next page for additional authors

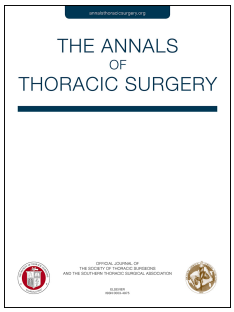
Recommended Citation

Pagani FD, Cantor R, Cowger J, Goldstein D, Teuteberg J, Mahr C, Atluri P, Kilic A, Maozami N, Habib R, Naftel D, and Kirklin JK. Concordance of Treatment Effect: An Analysis of The Society of Thoracic Surgeons Intermacs Database. Ann Thorac Surg 2021.

Authors

Francis D. Pagani, Ryan Cantor, Jennifer A. Cowger, Daniel Goldstein, Jeffrey Teuteberg, Claudius Mahr, Pavan Atluri, Arman Kilic, Nader Maozami, Robert Habib, David Naftel, and James K. Kirklin

Journal Pre-proof



Concordance of Treatment Effect: An Analysis of The Society of Thoracic Surgeons Intermacs Database

Francis D. Pagani, MD PhD, Ryan Cantor, PhD, Jennifer Cowger, MD, MS, Daniel Goldstein, MD, Jeffrey Teuteberg, MD, Claudius Mahr, DO, Pavan Atluri, MD, Arman Kilic, MD, Nader Maozami, MD, Robert Habib, PhD, David Naftel, PhD, James K. Kirklin, MD

PII: S0003-4975(21)00929-2

DOI: https://doi.org/10.1016/j.athoracsur.2021.05.017

Reference: ATS 35283

To appear in: *The Annals of Thoracic Surgery*

Received Date: 28 March 2021

Revised Date: 28 April 2021

Accepted Date: 2 May 2021

Please cite this article as: Pagani FD, Cantor R, Cowger J, Goldstein D, Teuteberg J, Mahr C, Atluri P, Kilic A, Maozami N, Habib R, Naftel D, Kirklin JK, Concordance of Treatment Effect: An Analysis of The Society of Thoracic Surgeons Intermacs Database, *The Annals of Thoracic Surgery* (2021), doi: https://doi.org/10.1016/j.athoracsur.2021.05.017.

Concordance of Treatment Effect: An Analysis of The Society of Thoracic Surgeons Intermacs Database

Running Head: Concordance of Treatment in Intermacs

Francis D. Pagani, MD PhD[1]; Ryan Cantor, PhD[2]; Jennifer Cowger, MD, MS[3]; Daniel Goldstein, MD[4]; Jeffrey Teuteberg MD[5]; Claudius Mahr, DO[6]; Pavan Atluri, MD[7]; Arman Kilic, MD[8]; Nader Maozami, MD[9]; Robert Habib, PhD[10]; David Naftel, PhD[2]; James K. Kirklin, MD[2]

[1]Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI; [2]Kirklin Institute for Research in Surgical Outcomes, University of Alabama at Birmingham, Birmingham, AL; [3]Henry Ford Health System, Detroit, MI; [4]Montefiore Einstein Center for Heart and Vascular Care, New York, NY; [5]Division of Cardiovascular Medicine, Stanford University Medical Center, Stanford, CA; [6]Department of Medicine, University of Washington Medical Center, Seattle, WA; [7]Division of Cardiothoracic Surgery, Department of Surgery, University of Pennsylvania, Philadelphia, PA; [8]Division of Cardiac Surgery, Medical University of South Carolina, Charleston, SC; [9]Department of Cardiothoracic Surgery, Langone Medical Center, New York University, New York, NY; [10]The Society of Thoracic Surgeons Research Center, The Society of Thoracic Surgeons, Chicago, IL.

Word Count: 4500

Corresponding Author:

Francis D. Pagani, MD, PhD, Department of Cardiac Surgery, Frankel Cardiovascular Center, 5161 Cardiovascular Center, SPC 5864, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109; email: fpagani@umich.edu

Abstract

Background: The Society of Thoracic Surgeons (STS) Intermacs Registry represents a real-world data source of durable, left ventricular assist devices that can address knowledge gaps not informed through randomized clinical trials. We sought to compare survival with contemporary left ventricular assist device technologies using multiple analytic approaches to assess concordance of treatment effects and to validate prior STS Intermacs observations.

Methods: Patients (aged $\geq$ 19 years) enrolled into STS Intermacs between August 2017 - June 2019 were stratified by device type (centrifugal device with hybrid levitation [CF-HL] or full magnetic levitation [CF-FML]). The primary outcome was 1-year survival assessed by three statistical methodologies (multivariable regression, propensity score matching, and instrumental variable analysis).

Results: Of 4,448 patients, 2,012 (45.2%) received CF-HL and 2,436 (54.8%) received CF-FML. One-year survival for CF-FML was 88% vs. 79% for CF-HL (overall $p < .001$), with a hazard ratio for mortality of 3.18 for CF-HL ($p<0.0001$) after risk adjustment. With propensity score matching (n=1400 each cohort), 1-year survival was 87% for CF-FML vs. 80% for CF-HL, with a hazard ratio of 3.20 for mortality with CF-HL ($p<0.0001$) after risk adjustment. With an instrumental variable analysis, the probability of receiving CF-HL was associated with a hazard ratio of 3.11 ($p<0.0001$).

Conclusions: Statistical methodology using propensity score matching and instrumental variable analysis increased the robustness of observations derived from real-world data and demonstrates the feasibility of performing comparative effectiveness research using STS Intermacs. These analyses provide additional evidence supporting a survival benefit of CF-FML versus CF-HL.

Table of Abbreviations

CF-HL – Continuous flow left ventricular assist device with hybrid levitation

CF-FML – Continuous flow left ventricular assist device with full magnetic levitation

DT – Destination therapy

ECMO – Extracorporeal membrane oxygenation

HR – Hazard ratio

IQR – Interquartile range

IV – Instrumental variable

IVA – Instrumental variable analysis

LVAD – Left ventricular assist device

MCS – Mechanical circulatory support

RCT – Randomized control trial

RVAD – Right ventricular assist device

RV – Right ventricle

SD – Standard deviation

STS – The Society of Thoracic Surgeons

UNOS – United Network for Organ Sharing

To date, evidence to support durable left ventricular assist device (LVAD) selection has been developed through randomized clinical trials (RCTs).**(1-5)** However, previous RCTs have not been powered to assess mortality benefit alone, nor reflect real-world populations that may differ from patients participating in RCTs.**(6-8)** Thus, real-world experience becomes a complimentary data source.**(8)** Mitigating the impact of confounding from inferences derived from real-world data becomes an important goal in order to utilize these data in clinical decision-making.**(9-11)**

The Society of Thoracic Surgeons (STS) Intermacs National Database is a U.S. registry of patients receiving commercially-available, durable mechanical circulatory support (MCS) devices and provides a real-world experience.**(12-14)** Recent observations from STS Intermacs demonstrated that patients receiving a continuous flow, centrifugal LVAD with hybrid levitation (CF-HL) had a 3.01 higher hazard for mortality compared to those receiving a continuous flow, centrifugal LVAD with full magnetic levitation (CF-FML).**(12)** However, the reliability of these observations were called into question because of the potential for residual confounding and limited patient follow up for the newest available technology (i.e., CF-FML device).**(15,16)**

Statistical analytic methods to assess and mitigate confounding have developed over the past 30 years and include propensity scoring techniques, instrumental variable analyses (IVA), and multivariable regression analyses with time-related models.**(17-23)** These methods facilitate the appraisal of contemporary observational registry-based data to develop real-world observations.**(17-23)**. These statistical approaches address some of the limitations of real-world data that are problematic for use in comparative effectiveness research, most important the lack of treatment randomization causing substantial differences in baseline characteristics of comparative cohorts (i.e., treatment selection bias).

The objective of this study was to compare survival outcomes for patients receiving contemporary durable LVAD designs using; 1) multivariable, multiphase hazard function modeling, 2) propensity score matching; and 3) IVA. We hypothesized that the previously reported survival benefit of CF-FML design based on the analysis of the national experience in STS Intermacs using multiphase hazard function modeling only would be confirmed by propensity matching and IVA.

Patients and Methods

The study cohort consisted of all adult patients (age ≥ 19 years) in STS Intermacs undergoing primary (i.e., de novo), durable LVAD implantation (N = 4448) with either a continuous flow LVAD with centrifugal flow design and hybrid levitation (CF-HL; N = 2012; HVAD™, Medtronic, Inc., Minneapolis, MN) or a continuous flow LVAD with centrifugal flow design and full magnetic levitation (CF-FML; N = 2436; HeartMate 3™, Abbott Labs, Chicago, IL) between August 23, 2017 to June 30, 2019 with follow-up through December 31, 2019. **(Figure 1)** The August 2017 date was chosen as a starting point for this analysis as this date represented the first full month for which both the CF-HL and CF-HML devices were available for commercial use.**(24)** Followup was censored at heart transplantation, cessation of device support (with or without device explant), device exchange to another type of device, and study closeout (12/31,2019) or at 24 months of followup. Patients were not censored for device exchange to the same device type or addition of a right ventricular assist device (RVAD) after leaving the operating room following LVAD implant. Patients receiving a continuous flow LVAD with axial flow design (N=580) or receiving a concomitant RVAD (i.e., biventricular support [RVAD at time of LVAD implant]; N=194) were excluded from the study cohort. Patients who received any LVAD design not approved by the U.S. Food and Drug Administration and who were part of a clinical trial were not reported to STS Intermacs and not included in this analysis.

The cohort was broken down into 4 eras. Distribution of device implants by era and by device type is presented in the **Supplemental Appendix (Supplemental eFigure 1)**.

For descriptive purposes, categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means ± standard deviation (SD) or median with interquartile range (IQR) as appropriate for data distribution. Discrete variables were compared with the use of chi-square test. Kaplan-Meier survival estimations were calculated with censoring of patients at the time of heart transplantation, cessation of device support (either explant or device inactivation), or device exchange to another type of device. For all survival analyses, differences for specific subsets of data were compared with the use of log-rank testing. Outcomes associated with specified strategies at the time of

implant were examined using the Fine-Gray competing outcomes analysis, in which multiple mutually exclusive outcomes are tracked over time. At any point in time, the sum of the proportion (percentage) of patients in each outcome category equals 100%.

Please see the **Supplemental Appendix** for a detailed description **Supplemental Information on Statistical Methodology (page 3 of the Supplemental Appendix)** and supporting **Supplemental eFigures 1-10** and **Supplemental eTables 1-7** of the multivariable, multiphase hazard function modeling **(12-14)**, propensity score matching, and IVA. **(25-27)**

Statistical analysis was performed with SAS 9.4 software (SAS Institute, Inc, Cary, NC). The analyses reported here were approved by the STS Intermacs/PediMACS Committee of the STS Access and Publications Task Force under the Workforce on Research Development and the Workforce on National Databases. Patient consent for STS Intermacs data collection was obtained at enrolling centers according to the local Institutional Review Board requirements.

Results

Baseline Characteristics of the Patients based on Durable Mechanical Circulatory Support Type

The study cohort consisted of 4,448 patients, with 2,012 (45.2%) patients receiving the CF-HL device and 2,436 (54.8%) receiving the CF-FML device. **(Table 1)** The mean age of the study cohort was 56.7+/-12.9 years with no significant difference in age between device types. Patients receiving CF-HL were more likely to be female, supported for destination therapy (DT), have smaller body surface areas, with a higher prevalence of comorbidity, including severe diabetes, prior cancer, alcohol and/or tobacco abuse, and prior cardiac surgery. Patients on CF-HL vs. CF-FML had laboratory evidence of greater preoperative hepatic dysfunction/congestion (higher alanine aminotransferase and aspartate aminotransferase) and echocardiographic evidence of greater preoperative right ventricular (RV) dysfunction (severe tricuspid regurgitation and severe RV dysfunction). Patients receiving CF-HL were more commonly STS Intermacs Profile 1 (19.8% vs. 14.8%) or Profile 2 (34.9% vs. 32.3%). While there were no differences between cohorts in need for dialysis, mechanical ventilation, or extracorporeal

membrane oxygenation (ECMO) prior to device implant, intra-aortic balloon pump (17.9% vs. 13.6%) and temporary MCS (37.3% vs. 29.9%) were more frequently employed in those patients receiving the CF-HL device.

More CF-HL patients received a device in Era 1 (20.9% vs. 7.6%) and Era 2 (36.5% vs. 17.4%). **(Table 1; Supplemental eFigure 1)** At the time of surgical implantation, more patients receiving the CF-FML underwent a sternotomy approach (90.0% vs. 82.5%). Cardiopulmonary bypass time was longer for patients receiving the CF-FML device (100.1+/-104.6 vs. 89.1+/-47.0 minutes).

Survival According to Device Type

Cumulative follow-up for the entire study cohort was 4,357 years with a median follow-up of 11 (6.9 – 16.9) months. Median follow-up was 10.3 (7.3 – 14.2) months for the CF-FML device and 12.9 (6.3 – 19.0) months for the CF-HL device.

The Kaplan-Meier survival (risk unadjusted) estimates for CF-FML and CF-HL are compared in **Figure 2**. Overall survival was significantly higher for patients with CF-FML (log rank p= 0.0001), with a survival at 1-year of 88% versus 79% with CF-HL. A competing outcomes analysis at 1-year demonstrated that for patients receiving CF-HL, 15.1% underwent heart transplantation, 19.6% died, 1.6% underwent device explant (or cessation of support), and 63.7% remained alive on device support. **(Supplemental eFigure 2A)** For patients receiving the CF-FML device, at 1-year, 10.6% received a heart transplantation, 11.7% died, 0.6% underwent device explant (or cessation of support), and 77.1% remained alive on device support. **(Supplemental eFigure 2B)** Gray's test comparing outcomes between groups demonstrated significant differences between CF-HL and CF-FML for transplant (p=0.0006), death on device support (p<0.0001), and explant or cessation of device support (p=0.0001).

Multivariable, Multiphase Hazard Function Modeling of Mortality According to Device Type

On adjusted analyses, the risk factors for death in the early and constant hazard phases are listed in **Table 2**. Device type was not associated with an early increased risk of death. In contrast, the strongest

risk factor for death in the long-term (constant phase) was a CF-HL device (hazard ratio (HR) of 3.18, $p<0.001$).

Propensity Score Matching and Mortality Assessment

Propensity score matching identified 1400 patient pairs within the CF-HL and CF-FML cohorts, defined through use of 60 matched variables. **(Supplemental eTable 1)** These arms represented 69.5% of the original CF-HL cohort and 57.4% of the original CF-FML cohort. Distribution of the propensity scores before and following matching are presented in the **Supplemental eFigure 3**. Patient characteristics of the propensity score matched cohorts are presented in **Supplemental eTable 2**. Characteristics of the patients not matched in the propensity score matching analysis are presented in the **Supplemental eTable 3**.

A Kaplan-Meier analysis for the propensity score matched cohorts demonstrated a survival at 1-year of 87% for CF-FML device and 80% for CF-HL ($p<0.0001$). **(Figure 3)** A Kaplan-Meier survival estimate for the patients not matched in the propensity score matching showed similar survival differences. (**Supplemental eFigure 4)** A competing outcomes analysis at 1-year for the propensity score matched cohorts demonstrated that for patients receiving CF-HL, 15.9% underwent heart transplantation, 18.7% died, 1.7% underwent device explantation (or cessation of support; i.e., device inactivation), and 63.7% remained alive on device support. **(Supplemental eFigure 5A)** For patients receiving CF-FML, at 1-year, 10.9% received a heart transplantation, 12.8% died, 0.6% underwent device explantation (or cessation of support; i.e., device inactivation), and 75.6% remained alive on device support. **(Supplemental eFigure 5B)** Gray's test comparing outcomes between groups demonstrated significant differences between CF-HL and CF-FML for transplant ($p=0.0013$), death on device ($p<0.0001$), and explant or cessation of support ($p=0.0007$).

A multiphase hazard multivariable analysis to identify pre-implant risk factors associated with death within the propensity score matched cohort again identified CF-HL device as a significant risk factor for death in the long-term (constant phase), with a HR of 3.20 (p<0.0001). **(Table 2)**

Instrumental Variable Analysis

The IVA first generated a probability for device therapy (expressed as the probability of receiving a CF-HL device) using all of the prior covariables in the multivariable model plus the potential instrumental variable; i.e., era. The distribution of the predicted probability of receiving the device ~~to~~ actual device received is displayed in the **Supplemental eFigure 6**. Multiphase hazard multivariable modeling was then performed for the entire cohort (n = 4,448) using the probability of receiving the CF-HL device and prior covariates **(Supplemental eTable 1)** used in the previous multiphase hazard multivariable modeling but not including the instrumental variables as covariates. The HR for the CF-HL device in the multiphase multivariable modeling using the probability of receiving the CF-HL device was 3.11 **(Table 2; Supplemental eFigure 7)**.

Causes of Death

Please see the **Supplemental Appendix** for a description of causes death for each device type.

Sensitivity Analyses

A number of important sensitivity analyses were performed to determine if the risk associated with the CF-HL device in the overall study cohort (N = 4448) was generalizable to specific subgroups. For each subgroup of interest, a multiphase hazard, multivariable model was performed to determine if CF-HL device remained an important risk factor for mortality. Co-variates included in the model included those listed in Supplemental eTable 1. The subgroups of interest that were explored included: 1) Overall Study Cohort (N = 4448; 100% of the Study Cohort); 2) female sex (N = 1037; 23% of the Study Cohort); 3) body surface area less than 1.6 (N = 268; 6% of the Study Cohort); 4) thoracotomy approach (N = 595; 13% of the Study Cohort); 5) age less than 60 years (N = 2410; 54% of the Study

Cohort); and 6) age greater than or equal to 60 years (N = 2038; 46% of the Study Cohort). In each subgroup of interest, the CF-HL device remained an important risk factor for mortality. **(see Supplemental Appendix section on Sensitivity Analyses: Supplemental eFigures 11-16 and Supplemental eTables 8-13).**

Comment

In this analysis of STS Intermacs, a clinically robust source of real-world data for patients undergoing implantation of commercially available, durable MCS devices, we identified an important survival benefit for recipients receiving a durable LVAD with CF-FML design. The direction of the mortality ascription was consistent across all three statistical methodologies, and was consistent with prior observations from STS Intermacs.**(12)** The magnitude of the survival benefit was similar across all three statistical approaches which reflects the importance of considering all potential confounders when assessing the effectiveness of LVAD support using registry data. Since the HR (3.18) for the CF-HL device obtained from the multiphase hazard multivariable analysis using device received was similar to the HR (3.11) obtained from the multiphase hazard multivariable modeling using probability of receiving a CF-HL device, we infer that the instrumental variables (era; participation in the Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ Investigational Device Exemption Clinical Study (MOMENTUM 3); and United Network for Organ Sharing (UNOS) region) had little impact on the effect size of the CF-HL device as an independent risk factor for mortality. This registry-based analysis underscores the importance of real-world data in generating novel and incremental clinical evidence, informing clinical decision-making beyond what can be interpreted with the data generated in RCTs.

Data to support durable LVAD therapy derives largely from RCTs **(1-5)**, but inherent limitations imposed by pre-defined inclusion and exclusion criteria in RCTs restricts the generalizability of the conclusions. Thus, real-world studies provide additional evidence of therapeutic effectiveness in commercial use settings which typically include a broader profile of patient characteristics.**(8,9)** Recent

analyses from STS Intermacs have demonstrated that nearly 50% of patients receiving durable LVADs would not meet eligibility criteria of contemporary RCTs of durable LVADs and that the survival benefit of patients not meeting trial inclusion and exclusion criteria is less than patients who are trial eligible.**(6-8)** Thus, data from real-world sources provide an important source of complementary data that can provide valuable observations in assisting health care providers in making informed clinical decisions.**(8)**

In this study, we observed a 1-year risk-unadjusted survival of approximately 88% for CF-FML and nearly 79% for CF-HL. In the MOMENTUM 3 clinical study, 1-year unadjusted survival of 515 patients receiving CF-FML was approximately 86.6%, an observation that is consistent with the observations from our current study.**(1)** Approximately 61% of patients in the MOMENTUM 3 trial receiving the CF-FML device were implanted with DT intent compared to approximately 51% of patients in our current study who were implanted with DT intent. In the HeartWare™ Ventricular Assist System as Destination Therapy of Advanced Heart Failure: the ENDURANCE Trial (ENDURANCE), 296 patients received the CF-HL device with an observed unadjusted 1-year survival of approximately 77%, findings similar to the 79% 1-year survival observed in the present study.**(2,3)** A salient difference between the populations of ENDURANCE and that of CF-HL patients in our current study is that the ENDURANCE population represented patients ineligible for transplant while approximately 15.3% of patients receiving the CF-HL device in our current study were listed for heart transplantation at the time of implant and an additional 23.7% were listed as bridge to decision at the time of VAD implant. Thus, the small differences in survival observed in this study (88% vs. 86.6% for CF-FML and 79% vs. 77% for CF-HL) compared to those observed in the RCTs are likely attributable to differences in patient samples. Additionally, rates of transplantation between the different devices (CF-HL versus CF-FML) may have been impacted by the change in the UNOS heart allocation system in October of 2018 that assessed less priority to durable VADs compared to temporary MCS.**(29)** This change in allocation policy may have biased the CF-FML group to a greater degree (fewer transplants) as more CF-FML were implanted after the change in allocations policy.**(29)**

The conventional method used to adjust for baseline differences between treatment groups in observational databases is covariate adjustment, where all relevant patient characteristics are included in a regression model relating the outcome of interest to the alternative treatments. A commonly cited concern is that such models are overfitted when the number of covariates is large compared with the number of patients or outcome events. Techniques such as propensity score matching and IVA become important statistical methodologies to reduce selection bias by matching characteristics of patients in different cohorts of the study. **(22,30-32)** Using different statistical approaches to mitigate the risk of confounding and bias in our comparative effectiveness evaluation, we observed a numerically smaller yet clinically consistent survival benefit for CF-FML technology at 1-year with each statistical approach. We believe the comparative effectiveness evaluation is therefore strengthened by the consistency of each statistical approach to identify a similar survival benefit, and reduces the impact of confounding on the observation.

Given the potential for centers selecting the CF-HL or CF-FML device in a non-random fashion, the IVA was incorporated to examine the potential effect of covariates which might influence device selection without themselves directly affecting survival. Instrumental variable analysis is a technique designed to control for measured and unmeasured confounding. It utilizes an IV which is associated with outcome only through its correlation with choice of therapy, in this case device type. Of importance, the IV must be "strongly" associated with choice of therapy, but must have not independent effect on the outcome examined.**(25-27)** After considering a number of possible such variables (see Methods), the potential IV which best fulfilled these criteria (including a "strong" association with choice of device) was era. Given that we are basically judging the "effect" of the IV by comparing the hazard ratio of the risk factor "actual" device selected (standard analysis) versus the risk factor of "probability of getting a specific device" (IVA), the observed difference in the hazard ratios has importance for inferences. Since the IV is affecting the likelihood of selecting a device, the stronger the relationship, the lower the hazard ratio should be for the risk factor "probability of getting a specific device", since the IV itself has no effect on outcome. We interpret that small hazard ratio difference as a relatively mild effect of the IVs that was examined.

Limitations

Although propensity score matching and IVA provide additional statistical methods to control for confounding, the latter may persist in inferred observations. Propensity scores only assure relative balance of measured confounders and their validity is contingent upon the appropriate selection of covariates, matching techniques, and methods of final data analysis. The exclusion of some patients incurred by the use of the propensity matching may result in a loss of precision and generalizability. The target population may not be clinically relevant if large number of patients were excluded. In the analysis herein, propensity matching led to removal of 31% of patients in the original CF-HL cohort and 43% of the original CF-FML cohort. While the proportion of DT patients was reduced, the frequencies of other key characteristics (Intermacs 1 profile, ECMO support, age) remained stable. For IV analysis, it is important to realize that even if a valid instrumental variable is available, IV methods will not always be helpful. If the instrument is weak, an IVA study will be underpowered to detect anything less than a very strong effect, even with large samples. In the analysis here, the IV analysis demonstrated an impact on the hazard ratio, supporting its importance in the analytics.

Conclusions

In an analysis of STS Intermacs, a clinically robust source of real-world data for patients undergoing implantation of a commercially available durable MCS device, we confirmed a survival benefit at 1-year for recipients of durable LVADs designed with CF-FML technology using multiple contemporary statistical methodologies. Further studies are needed with longer durations of follow-up and careful analyses of adverse events to better understand the differences noted in herein.

Acknowledgement:

Francis D. Pagani is a member of the data safety monitoring board for Carmat, Inc., a 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. Jennifer Cowger is an unpaid member of the Endotronix, Inc., Steering Committee, unpaid member of the Procyrion, Inc., Steering Committee and receiving clinical trial funding to Henry Ford Health System from Abbott and Medtronic. Pavan Atluri reports membership on the Steering Committee for Abiomed and is Chair of the STS Intermacs Data Access and Publications and Participant User File task forces. James Kirklin reports receiving partial salary support from the STS to University of Alabama at Birmingham for his position as Director of the Data Center for STS Intermacs. Statistical analyses were performed at the Kirklin Institute for Research in Surgical Outcomes, University of Alabama at Birmingham, Birmingham, AL by Dr. Ryan Cantor under the direction of Dr. James Kirklin. All authors had access to summary statistical data. Funding for the study was provided by The Society of Thoracic Surgeons through the STS Access and Publications Task Force under the Workforce on Research Development and the Workforce on National Databases.

References

1. Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Left Ventricular Assist Device - Final Report. *N Engl J Med.* 2019;380:1618–1627.

2. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure. *N Engl J Med.* 2017;376:451–460.

3. Milano CA, Rogers JG, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Mokadam NA, Mahr C, Miller JS, Markham DW, Jeevanandam V, Uriel N, Aaronson KD, Vassiliades TA, Pagani FD; ENDURANCE Investigators. HVAD: The ENDURANCE Supplemental Trial. *JACC Heart Fail.* 2018;6:792-802.

4. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 2009;361:2241-51.

5. Rose EA, Gelijns AC, Moskowitz AJ, et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med.* 2001;345:1435-43.

6. Brescia AA, Watt TMF, Pagani FD, et al. Assessment of mortality among durable left ventricular assist device recipients ineligible for clinical trials. *JAMA Netw Open.* 2021 Jan 4;4(1):e2032865.

7. Mezzacappa C, Ravindra NG, Caraballo C, et al. Clinical implications of differences between real world can clinical trial usage of left ventricular assist devices for end stage heart failure. PLoS One. 2020;15:e0242928.

8. Rothwell P. External validity of randomized controlled trials: "To whom do the results of this trial apply?" *The Lancet.* 2005:365;82-93.

9. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - What is it and what can it tell us? *N Engl J Med.* 2016;375:2293-2297.

10. 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. https://www.fda.gov/media/99447/download. Assessed December 15, 2020.

11. Roche N, Reddel H, Martin R, et al. Quality Standards for Real-World Research. Focus on Observational Database Studies of Comparative Effectiveness. *Ann Am Thorac Soc*. 2014;11(Supplement 2):S99–S104.

12. Teuteberg JJ, Cleveland JC Jr, Cowger J, et al. The Society of Thoracic Surgeons Intermacs 2019 Annual Report: The Changing Landscape of Devices and Indications. *Ann Thorac Surg.* 2020;109:649-660.

13. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. *J Heart Lung Transplant.* 2017;36):1080-1086.

14. Kormos RL, Cowger J, Pagani FD, et al. The Society of Thoracic Surgeons Intermacs database annual report: Evolving indications, outcomes, and scientific partnerships. *J Heart Lung Transplant.* 2019;38:114-126.

15. Kon Z, Smith D, Moazami N. Letter on The Society of Thoracic Surgeons Intermacs 2019 Annual Report. *Ann Thorac Surg.* 2021;111:733-734.

16. Pagani FD, Teuteberg J, Cleveland J, Atluri P, Kirklin J. 2019 STS/Intermacs Annual Writing Committee's Response. *Ann Thorac Surg.* 2021;111:734.

17. Garbe E, Suissa S. Pharmacoepidemiology. In: Handbook of Epidemiology. Ahrens W, Pigeot I (Eds). Springer, NY, USA, 1875–925 (2014).

18. Hummel N, Debray TPA, Didden EM et al. Methodological guidance, recommendations and illustrative case studies for (network) meta-analysis and modelling to predict real-world effectiveness using individual participant and/or aggregate data (2017). www.imi-getreal.eu/Portals/1/Documents/

19. Efthimiou O, Mavridis D, Debray T et al. Combining randomized and non-randomized evidence in network meta-analysis. *Stat. Med*. 2017;36:1210–1226.

20. Sterne JA, Hernán MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Brit Med J*. 2016;355:i4919.

21. Elze MC, Gregson J, Baber U, et al. Comparison of propensity score methods and covariate adjustment. Evaluation in 4 cardiovascular studies. *J Am Coll Card*. 2017;69:345-57.

22. Yeh RW, Vasaiwala S, Forman DE, et al. Instrumental variable analysis to compare effectiveness of stents in the extremely elderly. *Circ Cardiovasc Qual Outcomes*. 2014;7:118-24.

23. Blackstone EH, Naftel DC, Turner ME. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615-624.

24. HeartMate 3™ Left Ventricular Assist System – P160054. United States Food and Drug Administration, Recently-Approved Devices. https://www.fda.gov/medical-devices/recently-approved-devices/heartmate-3tm-left-ventricular-assist-system-p160054. Assessed December 15, 2020.

25. Uddin MJ, Greonwold RH, Ton de Boer, Belitser SV, Roes KC, Klungel OH. Instrumental variable analysis in epidemiologic studies: An overview of the estimation methods. *Pharm Anal Acta.* 2015;6(4):1-9. DOI: 10.4172/2153-2435.1000353

26. Bosco JLF, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol.* 2010;63:64-74.

27. Ramirez SPB, Albert JM, Blayney MJ, et al. Rosiglitazone is associated with mortality in chronic hemodialysis patients. *J Am Soc Nephrol.* 2009;20:1094-1101.

28. McDowell BD, Chapman CG, Smith BJ, Button AM, Chrischilles EA, Mezhir JJ. Pancreatectomy predicts improved survival for pancreatic adenocarcinoma: Results of an instrumental variable analysis. *Ann Surg*. 2015;261:740-5.

29. Estep JD, Soltesz E, Cogswell R. The new heart transplant allocation system: Early observations and mechanical circulatory support considerations. *J Thorac Cardiovasc Surgery*. 2020. DOI:https://doi.org/10.1016/j.jtcvs.2020.08.113.

30. McMurry TL, Hu Y, Blackstone EH, Kozower BD. Propensity scores: methods, considerations, and applications. *J Thorac Cardiovasc Surg*. 2015;150:14–19.

31. Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. *JAMA*. 2020 Feb 4;323:466-467.

32. Ramos R, Garcá-Gil M, Comas-Cuf M, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol.* 2016;67:630–40.

Table 1: Patient Characteristics for the Study Cohort Stratified by CF-HL (N = 2012) and CF-FML (N = 2436) Device Type (Total Cohort Size; N = 4448)

Variable	CF-HL	CF-FML	P Value
Demographics			
Age at Implant (years)	56.6 +/- 13.2 (n= 2012)	56.7 +/- 12.7 (n= 2436)	0.8
Sex (Male)	1471 (73.1)	1940 (79.6)	<0.0001
Race (White)	1256 (62.4)	1526 (62.6)	0.9
Ethnicity (Hispanic)	149 (7.6)	125 (5.3)	0.0026
Married	1126 (57.1)	1417 (59.4)	0.1
Body mass index (Kg/M^2)	28.1 +/- 7.7 (n= 1998)	29.3 +/- 7.3 (n= 2429)	<0.0001
Body surface area (M^2)	2.0 +/- 0.3 (n= 1998)	2.1 +/- 0.3 (n= 2429)	<0.0001
Era of Implant			
1	420 (20.9)	185 (7.6)	<0.0001
2	734 (36.5)	425 (17.4)	<0.0001
3	567 (28.2)	670 (27.5)	0.6
4	291 (14.5)	1156 (47.5)	<0.0001
Intermacs Patient Profile			
1	398 (19.8)	361 (14.8)	<0.0001
2	702 (34.9)	787 (32.3)	0.07
3	692 (34.4)	918 (37.7)	0.02
4	180 (8.9)	307 (12.6)	0.0001
5	22 (1.1)	32 (1.3)	0.5
6	12 (0.6)	23 (0.9)	0.2
7	6 (0.3)	8 (0.3)	0.9
NYHA Class IV	1657 (84.8)	2011 (84.1)	0.6
Co-Morbidities			
History of Alcohol Abuse	180 (8.9)	164 (6.7)	0.0059
Ascities Pre-implant	104 (5.6)	70 (3.0)	<0.0001
Atrial Fibrillation	134 (6.9)	157 (6.7)	0.7
History of Cancer	117 (5.8)	95 (3.9)	0.0028

Current Smoker	142 (7.1)	130 (5.3)	0.0171
Severe Diabetes	210 (10.4)	179 (7.3)	0.0003
Primary Diagnosis CAD	111 (5.6)	111 (4.6)	0.1
History of Stroke	74 (3.7)	67 (2.8)	0.08
History of other Cerebrovascular Disease	32 (1.6)	37 (1.5)	0.8
Hypertension	15 (0.8)	20 (0.80)	0.8
Implantable Cardio-defibrillator (ICD)	1494 (74.6)	1851 (76.5)	0.1
History of Repeated Non-compliance	93 (4.6)	78 (3.2)	0.01
History of Pulmonary Hypertension	304 (15.1)	377 (15.5)	0.7
Peripheral Vascular Disease	81 (4.0)	75 (3.1)	0.09
Previous Cardiac Surgery	573 (28.5)	609 (25.0)	0.009
Warfarin pre-implant	212 (10.5)	236 (9.7)	0.3
Arrhythmia at clinical presentation	449 (23.1)	639 (27.2)	0.0023
Laboratory Data			
Albumin (g/dL)	3.4 +/- 0.60 (n= 1927)	3.5 +/- 0.6 (n= 2349)	<0.0001
Total Bilirubin (mg/dL)	1.3 +/- 1.6 (n= 1946)	1.3 +/- 1.6 (n= 2363)	0.2
Blood Type O	980 (48.9)	1176 (48.6)	0.8
Blood Urea Nitrogen (mg/dL)	29.6 +/- 16.8 (n= 2010)	28.1 +/- 16.2 (n= 2432)	0.1
Creatinine (mg/dL)	1.4 +/- 0.6 (n= 2006)	1.4 +/- 0.7 (n= 2430)	0.5
INR	1.3 +/- 0.4 (n= 1934)	1.3 +/- 0.6 (n= 2350)	0.6
Aspartate Aminotransferase/AST (u/L)	54.2 +/- 249.2 (n= 1946)	42.5 +/- 74.9 (n= 2367)	0.03
Alanine Aminotransferase/ALT (u/L)	60.6 +/- 194.4 (n= 1940)	49.5 +/- 91.9 (n= 2369)	0.01
Sodium (mmol/L)	134.8 +/- 4.9 (n= 2007)	135.5 +/- 4.7 (n= 2431)	<0.0001
White Blood Cell	8.7 +/- 3.8 (n= 2004)	8.5 +/- 3.7 (n= 2429)	0.1

Count (x10^3/L)			
Echocardiography			
Aortic Regurgitation: moderate/severe	71 (4.1)	85 (4.0)	0.9
Tricuspid Regurgitation: moderate/severe	832 (44.6)	877 (38.9)	0.0002
Mitral Regurgitation: moderate/severe	1088 (58.3)	1261 (55.7)	0.09
LVEF < 20% (severe)	1385 (71.7)	1610 (69.2)	0.08
LVEDD	6.7 +/- 1.1 (n= 1632)	6.8 +/- 1.1 (n= 1990)	<0.0001
RVEF (severe)	309 (18.2)	253 (12.5)	<0.0001
Hemodynamics			
Heart rate (beats/min)	91.2 +/- 17.7 (n=2003)	89.8 +/- 17.5 (n=2425)	0.009
Cardiac Index (L/Kg/M^2)	2.1 +/- 0.8 (n= 1724)	2.1 +/- 0.8 (n= 2142)	0.9
Systolic Blood Pressure (mmHg)	106.2 +/- 16.9 (n= 1985)	107.3 +/- 16.2 (n= 2394)	0.0241
Diastolic Blood Pressure (mmHg)	66.4 +/- 11.7 (n= 1979)	67.4 +/- 11.8 (n= 2393)	0.0039
Pulmonary Artery Systolic Pressure (mmHg)	49.4 +/- 15.0 (n= 1794)	49.5 +/- 15.1 (n= 2228)	0.9
Pulmonary Artery Diastolic Pressure (mmHg)	24.9 +/- 9.2 (n= 1787)	24.7 +/- 8.9 (n= 2223)	0.4
Support at Implant			
Inotropes	1723 (86.2)	2018 (82.9)	0.0034
Phosphodiesterase-5 Inhibitor	135 (7.1)	177 (7.8)	0.4
Interventions with 48 Hours of Implant			
Dialysis	23 (1.1)	24 (1.0)	0.6
ECMO	49 (2.4)	44 (1.8)	0.1
IABP	360 (17.9)	332 (13.6)	<0.0001

Temporary Mechanical Circulatory Support	654 (37.3)	612 (29.9)	<0.0001
Ventilator	74 (3.7)	72 (3.0)	0.2
Indication for LVAD Therapy			
BTD	476 (23.7)	614 (25.2)	0.2
BTT; Listed	307 (15.3)	506 (20.8)	<0.0001
DT	1223 (60.8)	1249 (51.3)	<0.0001
Operative Details			
Cardiopulmonary bypass time (min)	89.1 +/- 47.0 (n= 1820)	100.1 +/- 104.6 (n= 2295)	<0.0001
Concomitant Surgical Procedures	804 (40.0)	1037 (42.6)	0.8
Surgical Approach			
Sternotomy	1657 (82.5)	2185 (90.0)	<0.0001
Thoracotomy	351 (17.5)	244 (10.0)	<0.0001

Abbreviations: CAD – coronary artery disease; CF-HL - Centrifugal flow-hybrid levitation; CF-FML - Centrifugal flow-full magnetic levitation; ECMO – extracorporeal membrane oxygenation; INR – International normalized ratio; IABP – intra-aortic balloon pump; LVEDD – Left ventricular end-diastolic dimension; NYHA – New York Heart Association; RVEF – Right ventricular ejection fraction; LVAD – left ventricular assist device.

Table 2: Summary of Multivariable Analyses Examining Mortality According to Device Type (CF-HL versus CF-FML)*

	Multiphase Hazard Multivariable Model Overall Cohort (N = 4,448)				Multiphase Hazard Multivariable Model Propensity Matched Cohort (N = 2880)				†Multiphase Hazard Multivariable Model with Instrumental Variable Overall Cohort (N = 4,448)			
	Early Hazard		Constant Hazard		Early Hazard		Constant Hazard		Early Hazard		Constant Hazard	
Pre-implant Risk Factors for Death	**HR**	***p*-value**	**HR**	***P***	**HR**	***p*-value**	***HR***	***p*-value**	**HR**	***p*-value**	**HR**	***p*-value**
Centrifugal Flow Pump with Hybrid Levitation (CF-HL)			3.18	<0.0001			3.20	<0.0001				
Probability of Receiving a CF-HL Device											3.11	<0.0001
Demographics												
Era 4: January – June 2019	0.73	0.014							0.75	0.0298		
Age at Implant (years)			1.02	0.0006			1.03	0.0004			1.02	0.0061
Age^2 (60 versus 50 years)	1.41	<.0001			1.41	<0.0001			1.47	<0.0001		
Male			1.49	0.0213							1.51	0.018
Body Mass Index (kg/M^2)	1.02	0.0363			1.02	0.0242			1.02	0.0190		
Clinical Status												
Device Strategy: Bridge to Decision			1.50	0.0055	0.59	0.0285	1.94	0.0003				
Device Strategy: Destination Therapy	1.31	0.0371										
Intermacs Patient Profile 1	2.15	<0.0001			1.92	<0.0001			2.18	<0.0001		
Intermacs Patient Profile 2	1.47	0.0095							1.47	0.0083		
Phosphodiesterase -5 Inhibitor Pre-implant	1.62	0.0059					2.02	0.0037	1.58	0.0098		
Cardiac Factors												
Right Ventricular Ejection Fraction: Severe	1.69	.0004			1.70	0.0042			1.69	0.0004		
Tricuspid Regurgitation: Moderate/Severe			1.37	0.0178			1.37	0.0482			1.42	0.0090

Mitral Regurgitation: Moderate/Severe	0.56	<0.0001			0.61	0.0011			0.56	<0.0001		
Aortic Regurgitation: Moderate/Severe	1.75	0.0209							1.77	0.0180		
LVEF < 20 (severe)	0.70	0.0041							0.72	0.0078		
Pulmonary artery diastolic pressure (mmHg)					1.03	0.0046						
LVEDD (cm)			0.85	0.0144	0.76	0.0008					0.81	0.0030
Non Cardiac Systems												
Intervention within 48 hours – Ventilation	1.84	0.0043							1.78	0.0059		
Intervention within 48 hours – Dialysis	2.62	0.0010			2.86	0.0063			2.58	0.0014		
Blood Urea Nitrogen (mg/dL)	1.02	<.0001	1.01	0.0044	1.02	<0.0001	1.01	0.0042	1.02	<0.0001	1.01	0.0185
Sodium (mmol/L)	0.96	.0005			0.95	0.0004			0.97	<0.0001		
International Normalized Ratio (INR)			1.23	0.0003							1.24	0.0002
Albumin			0.71	0.0009			0.59	<0.0001			0.76	0.0093
Aspartate Aminotransferase / AST (IU/L)					1.00	0.0160						
Severe Diabetes							1.61	0.0358				
Ascites Pre-implant							2.03	0.0200				
Surgical Complexities												
Cardiopulmonary Bypass Time (minutes)							1.01	<0.0001				
Previous Cardiac Operation	1.47	0.001			1.60	0.0020			1.51	0.0005		
Modifier: Temporary Circulatory Support	1.62	0.0012							1.62	0.0014		

†*Three Instrumental Variables (United Network of Organ Sharing (UNOS) Region; Participation in the MOMENTUM 3 clinical trial; and Era) and other covariates were used to predict the probability of receiving a CF-HL. The probability of receiving an CF-HL device (PS CF-HL) was expressed as a value between 0.0 and 1.0, where a probability of 1.0 means that receiving a CF-HL is certain to happen and 0.0 means that it is certain not to happen. The probability of receiving a CF-HL (PS CF-HL) was then used in the multiphase hazard multivariable model to produce the hazard ratio for mortality above.*

**Era of device implant was included as a potential risk factor in the multivariable hazard function analysis.*

Abbreviations: CF-HL: Centrifugal flow with hybrid levitation; CF-FML – Centrifugal flow with full magnetic levitation; LVEF – Left ventricular ejection fraction; LVEDD - Left ventricular end diastolic dimension; M – meter; mg - milligrams; dL - deciliter; L - liter

Figure Legends

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) Diagram Detailing Inclusion and Exclusion Criteria Used to Develop the Study Cohort.

Figure 2: Kaplan-Meier Survival Estimate (Risk Unadjusted) for the CF-HL (N = 2012) and CF-FML (N = 2436) Device Cohorts (Overall Study Cohort; n = 4,448) for the Time Period of Implants from August 2017 through June 2019.*

*****The shaded areas represent the 70% confidence intervals.

Figure 3: Kaplan-Meier Survival Estimate for the Propensity Score Matched Study Cohorts (CF-HL, N = 1400 and CF-FML, N = 1400) for the Time Period of Implants from August 2017 through June 2019.*

*****The shaded areas represent the 70% confidence intervals.