Prevalence and Prognostic Importance of Changes in Renal Function Following Mechanical Circulatory Support

Brisco et al: MCS and Renal Function

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Abstract

Background—The long-term durability and prognostic significance of improvement in renal function following mechanical circulatory support (MCS) has yet to be characterized in a large multicenter population. The primary goals of this analysis were to describe serial post-MCS changes in estimated glomerular filtration rate (eGFR) and determine their association with all-cause mortality.

Methods and Results—Adult patients enrolled in INTERMACS with serial creatinine levels available (n=3,363) were studied. Early post-MCS, eGFR improved substantially (median improvement 48.9%, p<0.001) with 22.3% of the population improving their eGFR by ≥100% within the first few weeks. However, in the majority of patients this improvement was transient, and by one year, eGFR was only 6.7% above the pre-MCS value (p<0.001). This pattern of early improvement followed by deterioration in eGFR was observed with both pulsatile and continuous-flow devices. Interestingly, poor survival was associated with both marked improvement (adjusted HR=1.64, 1.19-2.26, p=0.002) and worsening in eGFR (adjusted HR=1.63, 1.15-2.13, p=0.004).

Conclusions—Post-MCS, early improvement in renal function is common but appears to be largely transient and not necessarily indicative of an improved prognosis. This pattern was observed with both pulsatile and continuous-flow devices. Additional research is necessary to better understand the mechanistic basis for these complex post-MCS changes in renal function and their associated survival disadvantage.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00119834.

Key Words: renal function, ventricular assist device, heart failure, cardio-renal syndrome, transplantation
Renal dysfunction (RD) is common in patients with heart failure (HF) and has emerged as one of the most important prognostic indicators. In patients requiring mechanical circulatory support (MCS), the prevalence of RD is particularly high, often negatively influencing patient selection for advanced therapies. Notably, many of the factors thought causal of HF-induced RD likely stem from the hemodynamic perturbations characteristic of severe HF, abnormalities which improve after initiation of MCS. Perhaps as a result, marked early improvement in renal function post-MCS has now been described in several publications.

As the durability of MCS devices has improved, the cumulative effects of long-term support on non-cardiac organ function have become an important area of interest. Notably, two small single-center studies in patients with continuous-flow devices have recently reported a signal for significant late deterioration in renal function. To date, the long-term durability of post-MCS improvement in renal function (IRF) and the association with subsequent mortality has yet to be studied in a large multicenter population.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a national registry for patients implanted with a Food and Drug Administration-approved MCS device designed for long-term mechanical support. The primary goals of this study were to describe the early and late changes in renal function after MCS and to determine the potential clinical importance of these changes with respect to mortality in the large multicenter INTERMACS population.
Methods

INTERMACS Registry

INTERMACS is an audited registry of FDA-approved mechanical circulatory assist devices. Registry participation is mandatory for all Centers for Medicare and Medicaid Services-approved “destination” MCS implantation centers. The registry was created and maintained by the University of Alabama at Birmingham INTERMACS Data Coordinating Center since June 2005 and is supported by the National Heart, Lung and Blood Institute, the FDA, and Centers for Medicare and Medicaid Services. Participating centers are required to obtain institutional review board approval before initiating data collection, and data are transmitted from sites using a Web-based system to a secure server provided by the United Network for Organ Sharing. Contributing centers to INTERMACS can be found on the INTERMACS Web site (www.INTERMACS.org). The INTERMACS data were checked for completeness by the central collection facility. Values that fell outside of predetermined limits were validated with their site of origin; however, source documents are not routinely checked against the data submitted to INTERMACS. A Medical Events Committee reviewed primary cause of death as well as neurologic dysfunction, infection, bleeding and device malfunction.

Patient Population

Between June 23, 2006 until March 31, 2011, 4,108 adult patients were prospectively enrolled into the INTERMACS database for primary implantation of a durable ventricular assist device. Approximately 10% of patients eligible for inclusion in INTERMACS are not enrolled most often secondary to either their refusal to consent or their inability to consent secondary to critical illness. Patients receiving a total artificial heart or right ventricular support only (n=152) and
those with serum creatinine levels unavailable at baseline and one month (n=591) were excluded. Patients who received an LVAD and RVAD in the same OR visit were included (n=267).

Estimated glomerular filtration rate (eGFR) was calculated using the four variable Modified Diet and Renal Disease equation. As only age group is collected in INTERMACS, the median age of each group (i.e., 50 for 40-59 etc.) was used for calculation of eGFR. Renal function was evaluated pre-implant (referred to as pre-MCS or baseline) and at 1-week, 1-month, 3-months, 6-months and 1-year post-MCS. The minority of patients that were discharged from the hospital significantly before or after the 1-month post-MCS “visit” had both a discharge and one-month case report form available, and thus serum creatinine levels available were available at both time points in some patients (n=1,089). The primary outcome in the survival analyses was all-cause mortality and censoring occurred at the time of cardiac transplantation, device explantation, or if the patient was alive with the device in place at the end of follow-up (March 31, 2011).

Statistical Analysis

The primary focus of the analysis was 1) serial changes in eGFR post-MCS in the cohort and 2) the association of these changes with mortality. As such, the primary endpoints were 1) the magnitude and direction of serial post-MCS changes in eGFR and 2) the association between these changes and mortality. Given the large amount of missing data beyond 3 months post MCS, much of which is likely missing not at random, the primary approach to analysis #1 was descriptive. Plots were constructed based on initial device strategy (i.e., destination vs. bridge to transplant), patients that did or did not ultimately undergo cardiac transplantation, and device flow (pulsatile vs. continuous). Plots were also constructed for only patients without missing
data at the various time points to confirm that data missing not at random were not driving the
results (data not shown). Values reported are mean ± SD or medians (interquartile range, IQR)
for continuous variables and percentile for categorical variables. Independent Student’s t test or
the Wilcoxon Rank Sum test was used to compare continuous variables. Pearson’s Chi-Square
was used to evaluate associations between categorical variables. To examine renal function over
time, mean eGFR at each interval was examined graphically for all patients, in patients stratified
according to device strategy and device flow, in patients stratified according to baseline renal
dysfunction, and in patients with complete data through 1 year.

Cox models were used to evaluate the association between all-cause mortality and
changes in eGFR. The primary analysis focused on the percent change in eGFR from baseline to
1-month post MCS and time zero of this analysis was 1-month post implant. As the percent
change in eGFR variable included a number of extreme outliers, values beyond the largest and
smallest 1% of the data were truncated at these percentiles. To capture nonlinearities in the
relationship between change in eGFR and subsequent mortality, the predictor was modeled with
a cubic spline using three degrees of freedom. This model gave substantially better Akaike’s
Information Criteria (AIC) than a simple linear model. For a more relevant clinical interpretation
of this relationship, we divided eGFR into five quintiles of percent change in eGFR. Although
interpretation is limited somewhat by missing data, these processes were repeated to examine the
association between mortality and percent change in eGFR between 1-month and three months
as an exploratory analysis. Time zero of this survival analysis was 3-months post implant and
only included patients who survived to this point (n=2,416). Models were further adjusted for
eGFR at various time intervals. Additional candidate covariates for multivariate modeling were
selected by a combination of clinical judgment and precedence in the literature. Given the large
number of events in this population, we employed a low threshold to include any covariate with theoretical basis for impacting mortality or renal function which included all baseline covariates presented in Table 1. Covariates ultimately entered into the models can be found in the text preceding the results of the model. Kaplan-Meier survival curves for all cause mortality were constructed according to quintile of percent change in eGFR from baseline to 1-month post MCS. These survival curves were also plotted excluding those patients with greater than 200% improvement in renal function (top 5% of population) as a sensitivity analysis. Statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA) and R software version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline and early changes in renal function

Overall 3,363 patients (81.9%) had data available to calculate pre-MCS and 1-month post-MCS eGFR. Baseline characteristics of this subset of the INTERMACS population are presented in Table 1. Pre-implant renal dysfunction was prevalent, with a mean pre-MCS eGFR of 60.9 ± 34.7 ml/min/1.73m², encompassing a broad spectrum of National Kidney Foundation chronic kidney disease stages (Table 1). Similar to prior reports, renal function improved substantially early post-MCS (Figure 1). The pattern of early rise in eGFR was consistent across subgroups of patients irrespective of initial device strategy (i.e., destination vs. bridge to transplant), patients that did or did not ultimately undergo cardiac transplantation, baseline INTERMACS profile, and device flow (pulsatile vs. continuous) (Figures 1A, 1B and 1C). Furthermore, this pattern of early changes in eGFR persisted amongst subgroups without missing data (data not shown). At one week, eGFR had improved to 79.6 ± 42.6 ml/min/1.73m² (p<0.001) and at one month eGFR
was 82.8 ± 46.1 ml/min/1.73m² (p<0.001). Notably, 61.3% of the population had an improvement of their eGFR by ≥20%, 39.3% improved by ≥50% and 16.7% improved by ≥100% within one-month post-MCS. Significant early deterioration in renal function was less common during this time period, with a worsening in eGFR of ≥25% in 10.0%, and worsening of ≥50% in only 3.1% of patients.

**Longer-term changes in renal function**

Although post-MCS mean eGFR remained above the mean baseline value (p<0.0001 for all time points), after an initial small increase from one week to one month (p<0.0001), eGFR declined at all time points subsequent to one month (Figure 1). In those patients with data available at one year, the median improvement in eGFR was only 2.6 ml/min/1.73m² (IQR -10.1 - 17.2 ml/min/1.73m²) or 6.7% (IQR -15 - 35.8%) above the pre-MCS value. Similar to the early improvement, the pattern of late decline in eGFR was consistent across subgroups of patients based on initial device strategy, ultimate cardiac transplantation status, device flow and amongst subgroups without missing data (Figure 1).

The prevalence of a ≥50% improvement in eGFR decreased over time from 39.3% at 1-month post-MCS to 27.6% at three months, 21.2% at six months, and 18.7% at one year. Similarly, late declines in eGFR ≥25% from one-month-post-MCS were also relatively common occurring in 28.0% at three months, 39.0% at 6 months, and 41.4% at one year. In the overall population, larger reductions in eGFR (≥50%) from the 1-month time point occurred in 3.9% by three months, 7.2% by 6 months, and 8.9% by one year. An important observation was that the late decline in eGFR was predominantly restricted to patients with early IRF (Figure 2).

Ultimately, eGFR at both six months and one year was not different between patients that did or
did not have a ≥50% IRF at 1-month (p ≥0.23, Figure 2). However, in the group with IRF, despite a substantial decline subsequent to one month, eGFR remained meaningfully improved over the baseline value throughout the follow-up period (Figure 2). A significant pre-MCS to late post-MCS deterioration in eGFR was relatively uncommon with only 10.6% with ≥ 25% deterioration at 3 months, 14.8% at 6 months and 15.7% at one year (in those patients surviving with the device in place free of transplant to the respective time points). Only 3.5% of patients experienced a ≥50% worsening from the pre-MCS eGFR to one year.

**Pre-MCS renal dysfunction and post-MCS changes in renal function**

Patients with moderate to severe pre-MCS renal dysfunction (eGFR < 60 ml/min/1.73m²; 57.6% of the population) were also likely to experience significant early improvements in renal function by one month (p<0.0001) followed by a progressive decline in eGFR through 1-year post implant (Figure 2, Supplementary Figure 1). In both patients with or without pre-MCS renal dysfunction, the majority of the late decline in eGFR was derived from the group that experienced early-IRF (Figure 2). Despite the late decline in eGFR, patients with pre-MCS renal dysfunction had a 1-year mean eGFR that remained significantly above their pre-MCS baseline (Figure 2 and Supplementary Figure 1, p<0.001), whereas those without renal dysfunction sustained a relative decrement in mean eGFR compared to pre-MCS (p<0.0001, Figure 2 and Supplementary Figure 1). Although limited by smaller numbers of patients with both normal (eGFR >90ml/min/1.73m²) and severely reduced baseline renal function (eGFR <30 ml/min/1.73m²), further examination of renal function over time stratified by pre-MCS chronic kidney disease stage generally revealed similar patterns of early improvement followed by progressive decline (Figure 3, Supplementary Figure 1). However, patients with normal pre-
MCS renal function (eGFR $\geq 90$ ml/min/1.73m$^2$) were more likely to experience WRF 1-month-post-MCS (p<0.001; Figure 3) and less likely to experience marked IRF (p<0.001; Figure 3). Patients with severe renal dysfunction (eGFR<30 ml/min/1.73m$^2$) who received MCS were more likely to experience IRF at 1-month-post-MCS and at 3-months-post-MCS (p<0.001 for both, Figure 3).

Changes in renal function and survival:

Out of 3,363 subjects surviving to one month after implantation, 562 died (16.7%) during a median follow-up of 7.0 (IQR 3.4-12.7) months. The association between the pre-MCS to 1-month-post-MCS change in renal function and the risk for mortality was roughly U-shaped with a nadir in the region of a small improvement in eGFR and higher risk associated with the extremes of both improvement and worsening in eGFR. Consistent with this non-linear association, quintiles of pre-MCS to 1-month post-MCS change in eGFR were strongly associated with mortality (p<0.00001; Table 2). Notably, both the top quintile (>88% improvement) and the bottom quintile (<0% improvement, i.e. any worsening) were both strongly and similarly associated with mortality, with 178 deaths in the bottom quintile and 137 deaths in the top quintiles of improvement respectively (Table 2, Figure 4). Interestingly, patients in quintile 2 (<22% improvement) or quintile 4 (47-88% improvement) tended to have inferior survival compared to patients in quintile 3 (22-47% improvement) who had the best outcome with only 67 deaths during the study period (Table 2, Figure 4). The increased mortality associated with large improvements in renal function (>88%) persisted despite exclusion of those patients with greater than 200% improvement (top ~5% of population) (p<0.001; data not shown). Furthermore, the association between early post-MCS changes in renal function and
mortality was only minimally affected by adjusting for patient and device characteristics [age, race, sex, history of diabetes, history of pulmonary disease, ischemic disease, New York Heart Association class, baseline medication use, device strategy (i.e., destination or bridge to transplant), device type, device implant year, device flow, INTERMACS profile and need for hemodialysis] or by adjusting for pre-MCS or 1-month post-MCS eGFR (i.e., time zero of the survival analysis; Table 2). Additionally, the magnitude of the mortality disadvantage associated with the various quintiles of percent change in eGFR did not differ when baseline renal function was dichotomized into greater or less than 60 ml/min/1.73m2 (p-interaction=0.77) or based on baseline stage of chronic kidney disease (p-interaction=0.48). Moreover, there was no significant interaction between baseline eGFR as a continuous parameter and quintiles of percent change in eGFR (p-interaction=0.27). In a sensitivity analysis utilizing quintiles of absolute change in eGFR, again, the top quintile of improvement (≥45 ml/min/1.73m2 improvement, adjusted HR= 1.49, 95% CI 1.06-2.09, p= 0.021) and the bottom quintile (any worsening, adjusted HR=1.35, 95% CI 1.01-1.80, p=0.040) were similarly associated with reduced survival.

In a subset of patients with data on baseline right ventricular (RV) function available (n=1,544), both the top quintile (>88% Improvement; HR=2.25, 95% CI 1.44-3.51, p<0.001) and the bottom quintile (Any Worsening; HR=1.89, 95% CI 1.22-2.93, p=0.004) in eGFR were similarly associated with increased mortality. Adjustment for the presence of baseline moderate to severe RV dysfunction had minimal impact on these associations, with large improvements in renal function (>88% IRF; HR=2.20, p<0.001) and any WRF (HR=1.90, p=0.004) still conferring a substantially increased mortality risk.
Late changes in eGFR and survival

A total of 2,416 (71.8% of the initial cohort) survived to the three-month time point (i.e., alive, free of transplant, without missing eGFR data) and were available for exploratory analysis of the change in eGFR from one-month post MCS to 3-months. In this subset of patients, 430 deaths were observed. Once again, there was a non-linear relationship between percent change in eGFR and mortality (Table 2). Similar to the early changes in renal function, extreme improvement (80 deaths observed) and extreme worsening in renal function (86 deaths observed) were associated with increased mortality as compared to 42 deaths in the middle quintile (0-16% worsening). Unlike the early post-MCS changes, worsening in renal function appeared to predominate this association as substantial improvement was rare (Table 2). These associations remained significant after adjustment for either 1-month eGFR (the “baseline” eGFR of this analysis; p<0.0001) or 3-month eGFR (i.e., time zero of this survival analysis; p=0.003) and persisted with adjustment for patient and device characteristics (Table 2). Importantly, the significant survival disadvantage associated with significant worsening in eGFR from one to three months (both with ≥25% and ≥50% WRF) was similar regardless if a patient had experienced an early ≥50% improvement in renal function (p-interaction >0.44 for both).

Discussion

The principal findings of this study are that: 1) post-MCS, most patients experience a substantial early improvement in kidney function; 2) much of this early improvement is sustained only for a few weeks to months 3) large early and late changes in renal function, regardless whether a worsening or improvement, are associated with worsened survival. Overall these results reveal
that dynamic changes in renal function post-MCS are common, and given the strong association with mortality, potentially of clinical importance.

Mechanical circulatory support results in significant resolution of the hemodynamic perturbations thought ultimately responsible for HF-induced RD. As such, it is not unexpected that significant IRF early after MCS has been described by several authors. Since much of the hemodynamic improvement post MCS is presumed to be sustained, one might expect that the IRF would be as well, but recent single center studies of continuous flow populations have raised the possibility of significant long-term decline in eGFR during continued support.\textsuperscript{6,11,12} The current analysis of the large multicenter INTERMACS registry confirms that a decline in eGFR is commonly observed in the large majority of patients. However, an important incremental finding from this study is the observation that the long-term deterioration in renal function appears predominantly confined to patients who experienced significant early improvement. Although this group has a substantial decline from their peak eGFR and ultimately ends up with an eGFR similar to patients that did not experience early IRF, the long-term eGFR in these patients remains meaningfully higher than the baseline value. There are important potential mechanistic implications in the above observations. For example, if the sole driver of the late deterioration were a direct adverse effect of the device on the kidney, unless early improvement confers or identifies a specific vulnerability, a late decline would be expected to occur in all patients and not be primarily restricted to those with marked early improvement. Furthermore, the observation that a late deterioration in renal function is associated with worsened survival makes it unlikely that change in body composition (leading to non-renal increases in serum creatinine) is the sole mechanism responsible for the late worsening given that increases in skeletal muscle mass would be expected to associate with neutral or improved survival.
The mortality disadvantage associated with early post-MCS worsening renal function (WRF) is not surprising considering the large body of epidemiologic evidence linking post cardiac surgery acute kidney injury with worsened outcomes.\textsuperscript{16-18} Interestingly, a significant worsening in eGFR occurring late after MCS implantation was also associated with worsened survival, despite the fact that eGFR remained above the pre-MCS level. The finding that the risk persisted despite adjustment for either the pre or post-worsening eGFR suggests that the risk is not simply a reflection of the eGFR ultimately achieved but factors related to the change itself.

Remarkably, large improvements in kidney function were actually associated with reduced survival of a similar magnitude to WRF. This seemingly counterintuitive finding may stem from the fact that there was no true “control” group (e.g., patients with the potential for IRF who did not undergo MCS), and thus the comparison was to those patients receiving MCS that had relatively stable post-MCS renal function. A requisite for treatment-induced recovery of renal function is to have a reversible form of RD at baseline, with the most likely etiology being HF-induced RD. As a result, it is not surprising that comparison of patients with substantial improvement to patients with relatively stable renal function (indicative of a lesser degree of pre-MCS HF-induced renal dysfunction and thus lower pre-MCS disease severity) revealed greater mortality in patients with larger degrees of IRF.

Another notable observation from this data is that people with the most severe RD at baseline tended to have the most durable improvement in renal function. An important caveat in the interpretation of the above observation is that many of the patients with severe RD who undergo MCS are a highly selected group that was thought to have reversible RD at the time of MCS evaluation. As such, caution must be exercised prior to concluding that unselected HF patients (i.e., patients being considered for MCS) with severe RD would have similar renal
outcomes to the few patients in INTERMACS who were ultimately selected to receive MCS.

Lastly, there are several biologically plausible mechanisms by which chronic exposure to non-pulsatile flow might directly cause a deterioration of renal function including periarteritis, hyperplasia of renal arterial smooth muscle cells and activation of the renin-angiotensin-aldosterone system.\(^{19-22}\) Although multiple limitations in this dataset preclude formal comparison of changes in renal function between device flow types, qualitatively, a substantial early improvement followed by late decline in renal function was observed with both pulsatile and continuous-flow devices. As such, it would seem unlikely that the late decline in renal function can be entirely attributed to direct adverse effects of continuous flow. Furthermore, the superior survival in patients with continuous-flow devices highlights that many factors beyond renal function ultimately contribute to patient outcomes.

**Study Limitations**

While INTERMACS represents high-quality registry data, limitations inherent to the retrospective analyses of such data apply and causality is impossible to demonstrate. Due to the inclusion of only patients with FDA-approved devices, device selection was driven primarily by approval status at the time of implant, leading to the prevalence of pulsatile flow devices clustered in the early portion of the registry, and exclusion of a relatively large population of patients with investigational devices. Furthermore, confounding by indication amongst approved devices (i.e., anticipation of the potential requirement for biventricular support) likely occurred. Patients with significant renal dysfunction deemed irreversible are often not referred for MCS limiting generalizability, particularly in the subgroup of patients with baseline renal dysfunction. Additionally, the probability for informative censoring exists since significant improvements in
renal function may contribute to the decision to list a patient for cardiac transplantation. As such, the survival analyses should be interpreted as hypothesis-generating only. In order to maintain confidentiality, protected health information was largely not collected and therefore the registry cannot confirm death or cardiac transplantation status, possibly under-estimating the frequency of these events. Moreover, information on age was limited to age ranges spanning ~20 years, potentially leading to both over and underestimates of static eGFR; however, as all estimates of GFR in an individual patient utilized the same numeric age, relative differences in GFR over time are likely less biased. Still, INTERMACS was not specifically designed to examine serial changes in renal function. Physicians were not blinded to the renal function data and likely altered treatment based on this information. Furthermore, the interval between renal function data points is relatively long in the context of how quickly changes in renal function can occur and thus may not encapsulate the fluctuations in renal function that may have occurred between them. Given the limited data available, we were also unable to adjust for the potential effects of post-operative right ventricular dysfunction or ultrafiltration on these fluctuations. Furthermore, at 3 months post-MCS there is a significantly different level of medical supervision, therapies and adverse events such as gastrointestinal bleeding/infection compared to 1 month when many patients are still in the hospital or recently discharged. These differences may have played a role in the observed changes in renal function. Additionally, competing pathophysiologic events may occur such that a patient could have both some resolution of HF-induced renal dysfunction and peri-operative acute tubular necrosis (which has been reported to occur in a substantial proportion of cardiac surgery patients), leading to an unpredictable net effect on eGFR.17, 23

Lastly, using creatinine-based estimates of GFR in a population known to have large fluctuations in body composition, such as post-MCS patients, is prone to produce biased results.
Conclusions

In a contemporary multicenter population, substantial early improvement in eGFR after MCS is common but appears to be largely transient. Large post-MCS changes in renal function, both in the form of improvement or worsening, identify patients at high risk of death. Further research is necessary to better understand these changes in eGFR, their associated mortality disadvantage, and if the adverse renal and clinical outcomes can be modified by changes in medical or device strategies.

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Disclosures

None.

References


3. Khot UN, Mishra M, Yamani MH, Smedira NG, Paganini E, Yeager M, Buda T, McCarthy PM, Young JB, Starling RC. Severe renal dysfunction complicating cardiogenic shock is not a contraindication to mechanical support as a bridge to cardiac transplantation. *Journal of the American College of Cardiology.* 2003;41:381-385.


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort (N=3,363)</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)</td>
<td>54.5 ± 13.8</td>
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<tr>
<td>White race</td>
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<td>Male</td>
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<td>Diabetes Mellitus</td>
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<td>Ischemic HF etiology</td>
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<td><strong>INTERMACS Profiles</strong></td>
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<tr>
<td>Profile 1</td>
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<tr>
<td>Profile 2</td>
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<td>Profile 3</td>
<td>19.8%</td>
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<tr>
<td>Profile 4</td>
<td>11.0%</td>
</tr>
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<td>Profiles 5-7</td>
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<tr>
<td><strong>Device-Related parameters</strong></td>
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<td>LVAD alone</td>
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<td>Continuous-flow device</td>
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<td>Destination Therapy</td>
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<td><strong>Medications</strong></td>
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<tr>
<td>β-Blockers</td>
<td>51.2%</td>
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<tr>
<td>ACE Inhibitors or ARBs</td>
<td>38.4%</td>
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<tr>
<td>Loop Diuretics</td>
<td>78.1%</td>
</tr>
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</table>
Inotropes 80.8%

Renal function

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73m²)</th>
<th>60.0 ± 34.7</th>
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<tbody>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.49 ± 0.83</td>
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<tr>
<td>eGFR ≥ 90 (mL/min/1.73m²)</td>
<td>11.7%</td>
</tr>
<tr>
<td>eGFR 60-89 (mL/min/1.73m²)</td>
<td>30.7%</td>
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<tr>
<td>eGFR 30-59 (mL/min/1.73m²)</td>
<td>46.6%</td>
</tr>
<tr>
<td>eGFR &lt;30 (mL/min/1.73m²)</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

HF: Heart Failure, NYHA: New York Heart Association, COPD: chronic obstructive pulmonary disease; LVAD: Left ventricular assist device, ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate.
### Table 2. Association of quintiles of percent change in eGFR over time and all-cause mortality

#### Change in eGFR from Pre-MCS to 1-month-post MCS

<table>
<thead>
<tr>
<th>Quintile of eGFR Change</th>
<th>Unadjusted HR, 95% CI</th>
<th>Unadjusted p</th>
<th>Adjusted for Pre-MCS HR, 95% CI</th>
<th>Adjusted for Pre-MCS p</th>
<th>Adjusted for 1 Month HR, 95% CI</th>
<th>Adjusted for 1 Month p</th>
<th>Adjusted for patient HR, 95% CI</th>
<th>Adjusted for patient p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0%, Any Worsening)</td>
<td>1.96, 1.48-2.60</td>
<td>&lt;0.0001</td>
<td>2.22, 1.68-2.95</td>
<td>&lt;0.0001</td>
<td>1.72, 1.29-2.29</td>
<td>0.0002</td>
<td>1.63, 1.15-2.13</td>
<td>0.004</td>
</tr>
<tr>
<td>(0-22% Improvement)</td>
<td>1.31, 0.94-1.84</td>
<td>0.12</td>
<td>1.36, 0.97-1.90</td>
<td>0.08</td>
<td>1.25, 0.89-1.76</td>
<td>0.19</td>
<td>1.25, 0.87-1.78</td>
<td>0.22</td>
</tr>
<tr>
<td>(22-47% Improvement)</td>
<td>Reference group</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>(47-88% Improvement)</td>
<td>1.45, 1.07-1.96</td>
<td>0.02</td>
<td>1.36, 1.01-1.84</td>
<td>0.049</td>
<td>1.52, 1.12-2.06</td>
<td>0.007</td>
<td>1.40, 1.02-1.93</td>
<td>0.04</td>
</tr>
<tr>
<td>(&gt;88% Improvement)</td>
<td>2.02, 1.51-2.70</td>
<td>&lt;0.0001</td>
<td>1.61, 1.19-2.19</td>
<td>0.003</td>
<td>2.20, 1.64-2.96</td>
<td>&lt;0.0001</td>
<td>1.64, 1.19-2.26</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, diabetes, chronic lung disease, ischemic etiology, New York Heart Association class, device type, device strategy (destination vs. bridge to transplant), INTERMACS 1, year of MCS implant, baseline β-blocker use, baseline angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, baseline loop diuretic use, baseline inotrope use and dialysis requirement.

† Adjusted for 1-month eGFR; ‡ Adjusted for 3-month eGFR

eGFR: estimated glomerular filtration rate; MCS: mechanical circulatory support, CI: confidence interval.
Figure Legends

**Figure 1.** Mean eGFR over time grouped by device strategy, disease severity and device flow

**Panel A.** Mean eGFR over time by baseline device strategy or transplant status at end of follow-up.

**Panel B.** Mean eGFR over time by baseline INTERMACS profile.

**Panel C.** The slope of the lines reflects the rate of change in eGFR over time. Sample sizes (n) refer to the number of patients in each group through one month and sample sizes (N) refer to the number of patients with data available at each of the subsequent time points. eGFR: estimated glomerular filtration rate, MCS: mechanical circulatory support. Bridge to transplant defined as patients listed for transplantation or those deemed likely by the treating physician to be listed at the time of implantation.

**Figure 2.** Mean eGFR over time in patients with and without pre-MCS renal dysfunction and post-MCS improvement in renal function.

Mean eGFR according to presence or absence of baseline renal dysfunction further stratified by improvement in renal function at 1-month-post MCS. Renal dysfunction defined as a pre-MCS eGFR <60 ml/min/1.73 m². Improvement in renal function is defined as a ≥50% improvement in eGFR from pre-MCS to 1-month-post MCS. Sample sizes (N) refer to the number of patients with data available at all time points. eGFR: estimated glomerular filtration rate; IRF: improvement in renal function; MCS: mechanical circulatory support.

**Figure 3.** Proportion of patients across stages of renal function over time
Sample sizes (N) refer to the number of patients with data available at each time point. eGFR: estimated glomerular filtration rate mL/min/1.73m², MCS: mechanical circulatory support.

**Figure 4.** Relationship between early post-MCS changes in renal function and risk of death. Kaplan-Meier survival curves according to percent change in eGFR quintile. Percent change in eGFR is from pre-MCS to 1-month-post-MCS. eGFR: estimated glomerular filtration rate, MCS: mechanical circulatory support.
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Meredith A. Brisco, Stephen E. Kimmel, Steven G. Coca, Mary E. Putt, Mariell Jessup, W. H. Wilson Tang, Chirag R. Parikh and Jeffrey M. Testani

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Supplementary Figure 1: Mean eGFR over time in patients stratified by pre-MCS eGFR

Sample sizes (N) refer to the number of patients with data available at each time point encompassed by the respective line. eGFR: estimated glomerular filtration rate, MCS: mechanical circularity support, IRF: improvement in renal function.