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Outcomes of Durable Mechanical Circulatory Support in Myocarditis: Analysis of the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support Registry

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Myocarditis can be refractory to medical therapy and require durable mechanical circulatory support (MCS). The characteristics and outcomes of these patients are not known. We identified all patients with clinically-diagnosed or pathology-proven myocarditis who underwent mechanical circulatory support in the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support registry (2013–2016). The characteristics and outcomes of these patients were compared to those of patients with nonischemic cardiomyopathy (NICM). Out of 14,062 patients in the registry, 180 (1.2%) had myocarditis and 6,602 (46.9%) had NICM. Among patients with myocarditis, duration of heart failure was <1 month in 22%, 1–12 months in 22.6%, and >1 year in 55.4%. Compared with NICM, patients with myocarditis were younger (45 *vs.* 52 years, $P < 0.001$) and were more often implanted with Interagency Registry for Mechanically Assisted Circulatory Support profile 1 (30% *vs.* 15%, $P < 0.001$). Biventricular mechanical support (biventricular ventricular assist device [BIVAD] or total artificial heart) was implanted more frequently in myocarditis (18% *vs.* 6.7%, $P < 0.001$). Overall postimplant survival was not different between myocarditis and NICM (left ventricular assist device: $P = 0.27$, BIVAD: $P = 0.50$). The proportion of myocarditis patients that have recovered by 12 months postimplant was significantly higher in myocarditis compared to that of NICM (5% *vs.* 1.7%, $P = 0.0003$). Adverse events (bleeding, infection, and neurologic dysfunction) were all lower in the myocarditis than NICM. In conclusion, although myocarditis patients who receive durable MCS are sicker preoperatively with higher needs for biventricular MCS, their overall MCS survival is noninferior to NICM. Patients who received MCS for myocarditis are more likely than NICM to have MCS explanted due to recovery, however, the absolute rates of recovery were low. *ASAIO Journal* 2021; XX;00–00

Key Words: myocarditis, mechanical circulatory support, left ventricular assist device, total artificial heart, outcomes

Myocarditis is an inflammatory process that affects the myocardium and most commonly caused by viruses.[1,2] Acute myocarditis can lead to a chronic dilated cardiomyopathy in 20% of the cases.[1,2] Once ensues, heart failure (HF) related to myocarditis carries mortality rates of approximately 50% at 4 years.[3,4] Although majority of patients with acute myocarditis recover,[5,6] a subset of these patients progress to advanced HF and require heart transplantation.[7] A contemporary cohort study showed that ventricular assist devices were used in 5% of myocarditis patients during index hospitalization, and heart transplantation is required in approximately 5% of patients with myocarditis for more than 5 years.[8]

We have previously shown that patients with myocarditis listed for heart transplantation in the United Network for Organ Sharing (UNOS)/Organ Procurement Transplantation Network Registry have a higher acuity at listing, and a twofold increase in requirement for biventricular mechanical support compared with other NICMs.[7] We also observed that patients with myocarditis who are listed for heart transplantation had a higher rate of improvement and delisting, and once transplanted, their posttransplantation survival is comparable to that of other listed patients. Contemporary data on the need and outcomes of durable mechanical circulatory support in this group of patients is lacking.

Thus, we aimed to review the baseline characteristics and clinical presentation of patients with a diagnosis of myocarditis who received mechanical circulatory support (MCS) and compare

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them to those with nonischemic cardiomyopathies (NICMs). We also sought to review the types of mechanical circulatory support systems and the outcomes of patients with a diagnosis of myocarditis namely rates of death, transplantation, recovery and device explanation, and assess the rate of adverse events (device malfunction, bleeding, infection, neurologic dysfunction, respiratory failure, and right HF) of patients with a diagnosis of myocarditis after MCS and compare them to those with NICMs.

Methods

The International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support

The International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) is an international registry that follows patients who receive durable mechanically assisted circulatory support devices internationally. The registry currently includes data on more than 14,000 implants from 35 countries.[9] Data sources include implanting hospitals as well as national registries (the European Registry for Patients with Mechanical Circulatory Support [Europe], the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS, United States], the Japanese Registry for Mechanically Assisted Circulatory Support [Japan], and the United Kingdom Registry [United Kingdom]). The registry records preimplant patient information, device information and tracks major postimplant clinical events. This study was approved by the University of Alabama Institutional Review Board (IRB-120521006).

Patient Population

We identified all patients with clinically-diagnosed or pathology-proven myocarditis who underwent mechanical circulatory support in the IMACS registry (2013–2016). The characteristics and outcomes of these patients were compared to those of patients with NICM.

Patient characteristics and outcomes

We compared preimplant patient characteristics (demographics, clinical history, laboratory data), type of device, and device strategy by etiology. Patient outcomes of interest were rates of death, recovery and device explant, need for RVAD, transplantation, and recovery. Adverse events of interest included neurologic events, arterial thromboembolism, device malfunction, infection, and respiratory failure. Early adverse events were defined as those that happened within 3 months of implant, while late adverse events were defined as those that happened after 3 months of implant. The duration of HF was obtained from the case report form (pre_implant.DUR_HRT_FAIL: duration of HF – length of time patient has endured HF).

Statistical Analyses

Categorical variables are presented as numbers and percentages, and compared using χ^2 test. Continuous variables are presented as means and SDs and compared using *t*-test. Time-related events (death, transplantation, and device explant) were estimated using the Kaplan-Meier method with competing risk outcomes. Comparisons of events were done using log-rank (Mantel-Cox) test. All analyses were performed using SAS software version 9.4 (Cary, NC).

Results

Baseline Characteristics

Out of 14,062 patients in the registry, 180 (1.2%) had myocarditis and 6,602 (46.9%) had NICM. Compared with NICM,

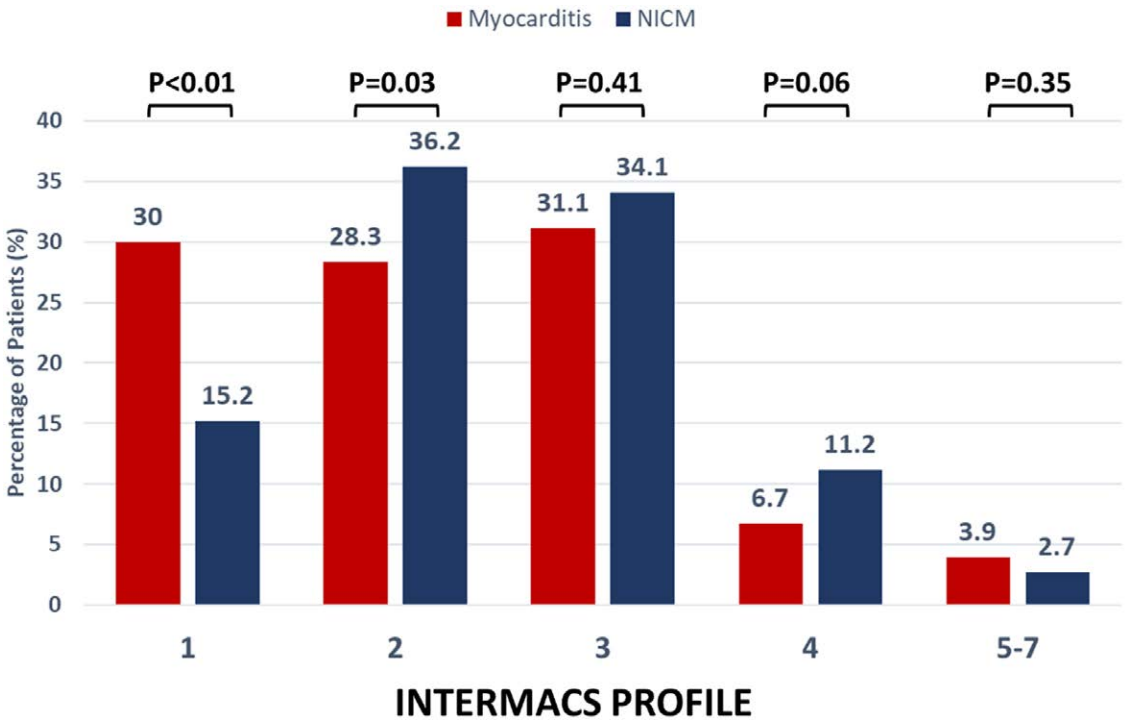

Figure 1. INTERMACS profile by etiology of heart failure. Patients with myocarditis who are implanted with durable MCS are more likely to be INTERMACS profiles 1 and 2 than patients with NICM. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; NICM, nonischemic cardiomyopathy.

patients with myocarditis were younger (myocarditis 45.5 ± 13.6 years *vs.* NICM 52.4 ± 13.6, $P < 0.01$), have lower BMI (26.5 ± 5.6 *vs.* 28.5 ± 7.1, $P < 0.01$), less likely to have chronic kidney disease (*vs.* 13.1% *vs.*19.9%, $P = 0.03$), pulmonary disease (2.2% *vs.* 6.9%), but have higher serum creatinine (1.54 ± 1.4 mg/dl *vs.* 1.38 ± 0.71, $P < 0.001$). There was no difference in sex distribution (76.7% *vs.* 76.9%, $P = 0.94$), diabetes (8.3% *vs.* 7.6%, $P = 0.74$), prior cardiac surgery, or serum albumin.

Duration of Heart Failure

Among patients with myocarditis, duration of HF was <1 month in 22%, 1–12 months in 22.6%, and >1 year in 55.4%, which was different from NICM (3.5%, 12.6%, and 83.9%, respectively, $P < 0.01$ for all comparisons).

Preimplantation Profile

Compared with NICM, patients with myocarditis were more often implanted with INTERMACS profile 1 (30% *vs.* 15%, $P < 0.01$), and less likely to be implanted with INTERMACS profile 2 (28.3% *vs.* 36.2%, $P = 0.03$) (Figure 1). Patients with myocarditis were more likely to have preimplant extracorporeal membrane oxygenator (27% *vs.* 4.8%, $P < 0.01$), but no difference in intraaortic balloon pump use (24.2% *vs.* 25.2%, $P = 0.75$) or preimplant inotrope (82.2% *vs.* 82.6%, $P = 0.83$).

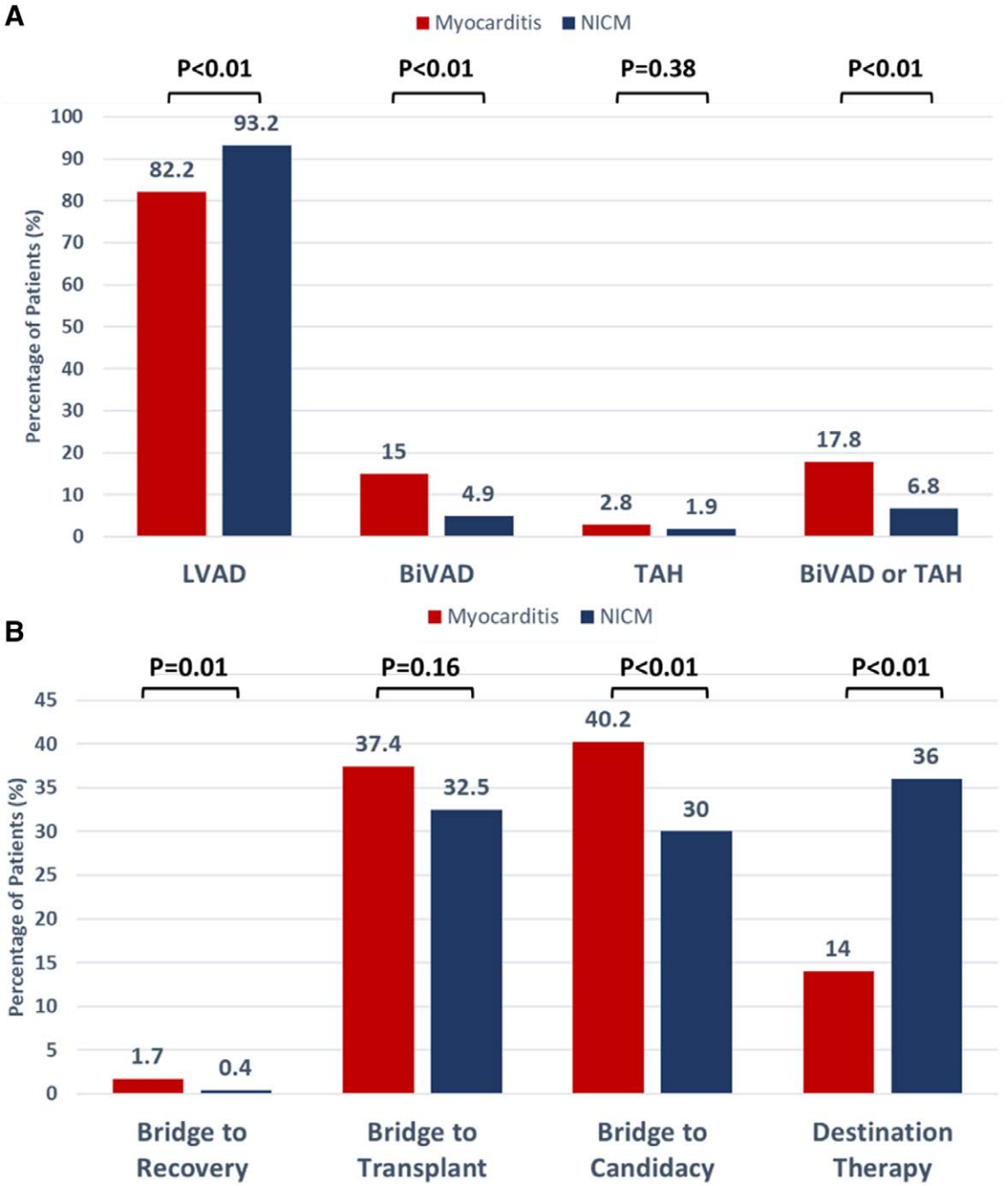

Figure 2. Device type (**A**) and strategy (**B**) by etiology of heart failure. Patients with myocarditis have increased needs for biventricular support, resulting in decreased percentage of isolated left ventricular assist devices, and were more likely to be implanted as bridge to recovery or candidacy.

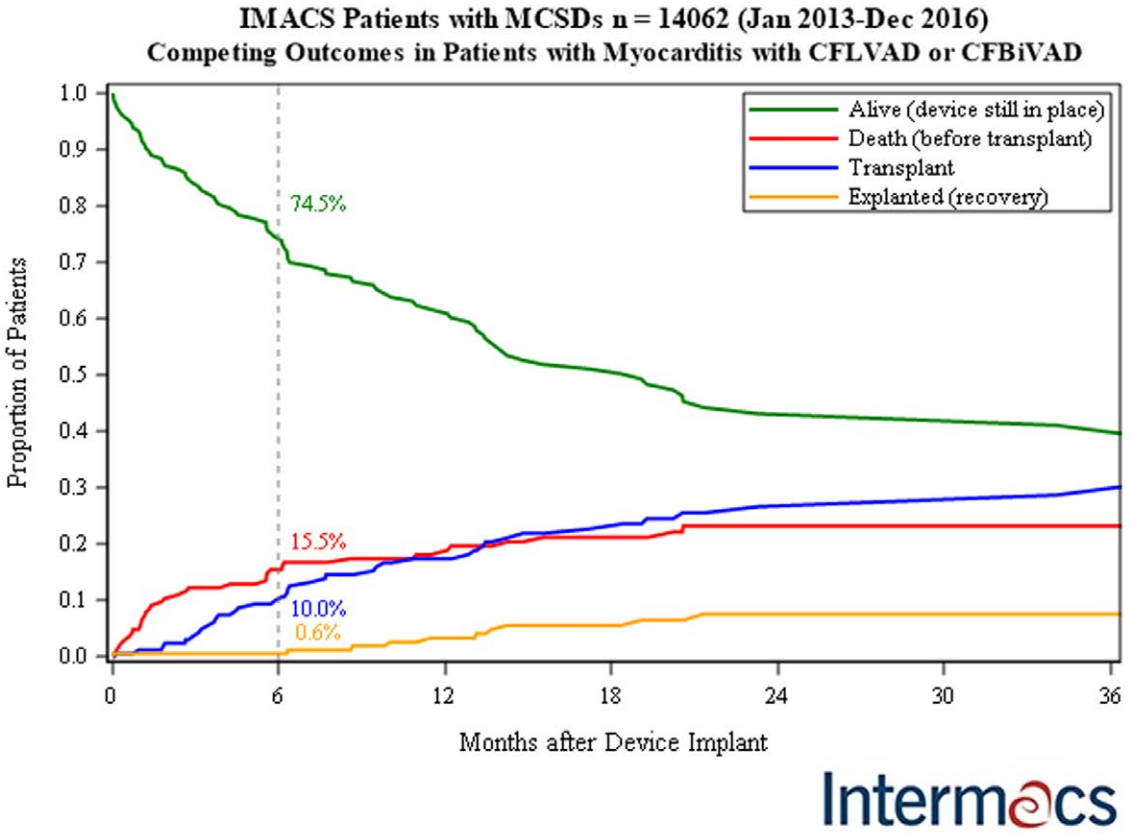

Figure 3. Competing risk outcomes of all patients with myocarditis receiving MCSD. MCSD, mechanical circulatory support device.

Biventricular mechanical support (biventricular ventricular assist device [BIVAD] or total artificial heart) were implanted more frequently in myocarditis *versus* NICM (18% *vs.* 6.7%, $P < 0.001$) (Figure 2A). Patients with myocarditis were more likely to be implanted as bridge to recovery (1.7% *vs.* 0.4%, $P = 0.01$), bridge to candidacy (40.2% *vs.* 30%, $P < 0.01$), and less likely to be implanted as a destination therapy (14% *vs.* 36%, $P < 0.01$) (Figure 2B).

They also had higher levels of liver transaminases (ALT 315 *vs.* 82 μ/L and AST 372 *vs.* 78 μ/L, $P < 0.001$ for both), lower systolic blood pressure (99 *vs.* 104 mm Hg, $P < 0.001$), lower systolic pulmonary artery pressures (45 *vs.* 50 mm Hg, $P < 0.001$), and smaller LV end-diastolic diameters (6.8 *vs.* 7.1, $P = 0.004$).

Postimplantation Outcome

Competing outcomes among myocarditis patients are shown in Figure 3 (all myocarditis) and 4A (continuous flow left ventricular assist device myocarditis). Overall postimplant survival was not different between myocarditis and NICM (left ventricular assist device [LVAD]: $P = 0.27$, BIVAD: $P = 0.50$) (Figure 4, B and C). The proportion of myocarditis patients that have recovered and explanted by 12 months postimplant was significantly higher in myocarditis compared to that of NICM (5% *vs.* 1.7%, $P = <0.001$) (Figure 4D). Adverse events (bleeding, infection, neurologic dysfunction, and respiratory failure) were all lower in the myocarditis than NICM with no difference in non-CNS thromboembolism or device malfunction (Figure 5 and Figure 1, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A633). After adjusting for various characteristics (age, body mass index, serum creatinine, blood urea nitrogen, pre-MCS IABP, blood type, INTERMACS profile, peripheral vascular disease, and smoking status), myocarditis was not associated with mortality (hazard ratio 0.95, 95% confidence interval: 0.62–1.45, $P = 0.84$).

Discussion

To our knowledge, this is the first large analysis of outcomes of durable MCS in myocarditis. We show that myocarditis patients form 1.3% of all patients who received MCS in the IMACS registry. Compared with NICM, patients with myocarditis are younger, present more acutely, and are approximately three times more likely to receive biventricular mechanical support, however, have lower risk of adverse events and similar long-term survival after MCS. Additionally, we observed a significantly higher recovery and LVAD explant in patients with myocarditis compared with NICM.

The need for biventricular support is not unexpected. Myocarditis affects both ventricles and thus have higher rates of right ventricular failure,[6,10] which is associated with worse outcomes.[11] Additionally, respiratory failure is common in myocarditis that may result from pulmonary edema, acute respiratory distress syndrome, and direct effect of viruses (*e.g.,* influenza A).[12,13] All of these can lead to RV failure requiring biventricular support.[14] We have previously shown that patients with myocarditis listed for heart transplantation had threefold increase in biventricular mechanical support compared with NICMs.[7] The relatively lower odds of biventricular support in the current

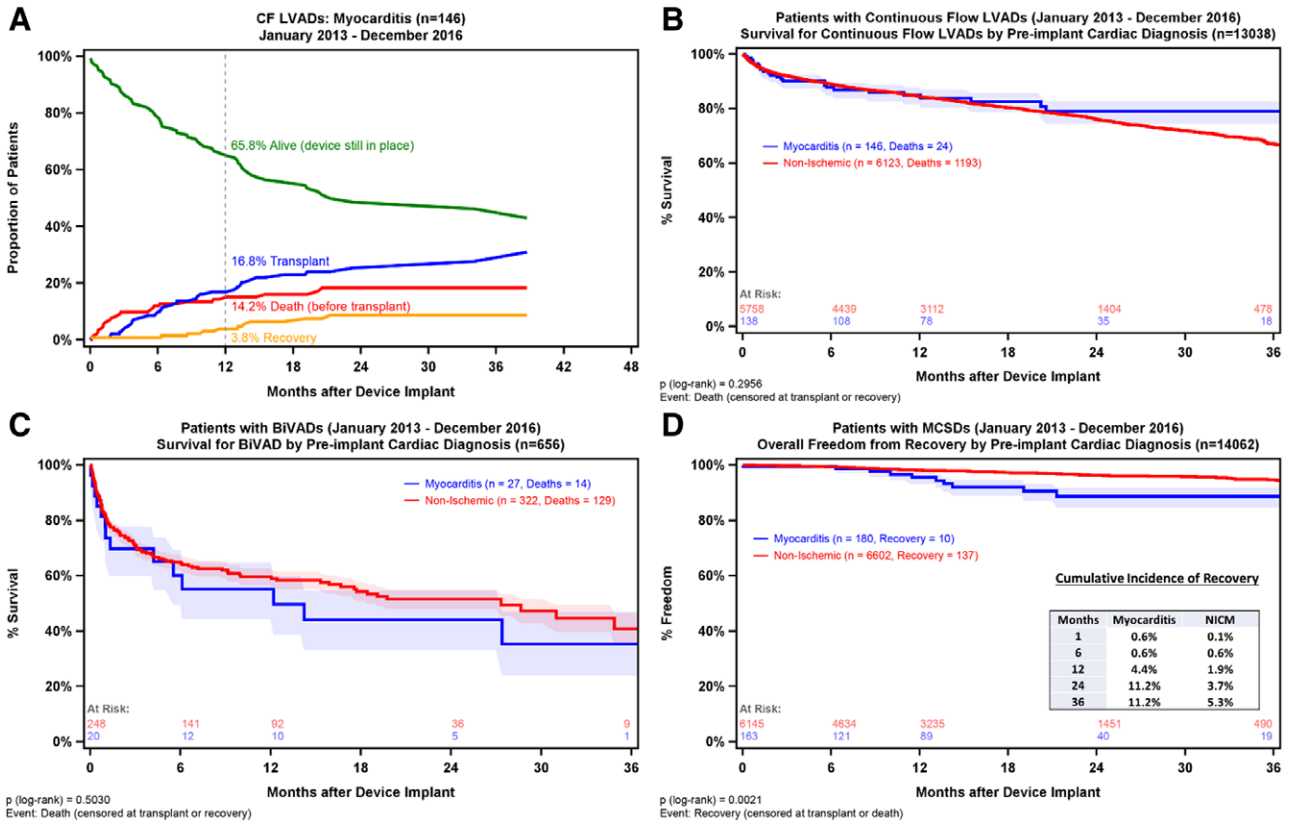

Figure 4. Long-term outcomes of patients with myocarditis supported with durable mechanical circulatory support. **A**: Competing-risk outcomes in patients with myocarditis supported with continuous-flow left ventricular assist devices. **B**: Overall survival among patients with myocarditis and nonischemic cardiomyopathies supported with continuous-flow left ventricular assist devices. **C**: Overall survival among patients with myocarditis and nonischemic cardiomyopathies supported with biventricular assist devices. **D**: Device explant among patients with myocarditis and nonischemic cardiomyopathies supported with mechanical circulatory support devices.

analysis, when compared with our previously reported number (3 times *vs*. 10 times), may be related to the fact that biventricular support is only approved as bridge to transplantation, and thus UNOS cohort may be enriched for patients receiving biventricular support. Prior case reports and small case series of acute myocarditis requiring mechanical circulatory support also show biventricular predominance.[15–19] Interestingly, in this analysis, there was no difference in overall survival between myocarditis and NICM whether they received isolated LVAD, suggesting that level of RV involvement varies among patients, and that carefully selected patients with myocarditis can do well with isolated LVAD, which has been previously suggested in isolated cases.[19–21] In 100 patients with myocarditis listed for heart transplantation with a mechanical circulatory device, 43% had isolated LVAD.[7] Further studies are needed to identify the subgroup of patients with myocarditis who do not require RV support, which may include investigation of RV function and involvement with cardiac magnetic resonance imaging.[10,22] This also has implications for management of patients with myocarditis-related cardiogenic shock, in whom careful RV assessment is warranted before use of percutaneous LV support devices.[23] Unfortunately, IMACS database does not have sufficient data to identify long-term right HF after LVAD due to heterogeneity in data capturing from different cohorts. It is particularly important to carefully assess the right ventricle when considering LVAD support in patients with myocarditis, given the high prevalence of RV failure in this group of patients.

Despite the high acuity and the higher need for biventricular support, patients with myocarditis who receive mechanical circulatory support device (MCSD) have excellent outcomes. This is possibly due to the fact that they are younger and have lower prevalence of comorbidities, which likely dictate long-term outcomes. Patients with myocarditis were more likely implanted as a bridge to candidacy and bridge to recovery, and less likely implanted as destination therapy, implying that the medical/surgical teams were still predicting some rate of recovery and explant. Indeed, patients with myocarditis who underwent MCSD were more likely to recover and have their device explanted than NICM. The absolute rates of recovery/explant, however, were very low with only 4% recovering at 1 year, with no difference by duration of HF. This suggests that once current criteria for advanced HF are met in patients with myocarditis, they are unlikely to recover. Heart transplantation, therefore, should not be delayed in these patients, especially given the risk of early and late right HF. It is possible that bridge to candidacy is also determined by acute organ dysfunction (*e.g.*, acute kidney injury, liver failure), with the hope that MCS may provide time for bystander organ recovery to meet eligibility criteria for heart transplantation.

The patients who have a preimplant diagnosis of myocarditis in this cohort had variable duration of HF, with approximately half have HF duration of >12 months, likely representing "burnt-out" myocarditis. These patients are more likely to resemble dilated cardiomyopathy. Approximately one-fifth of

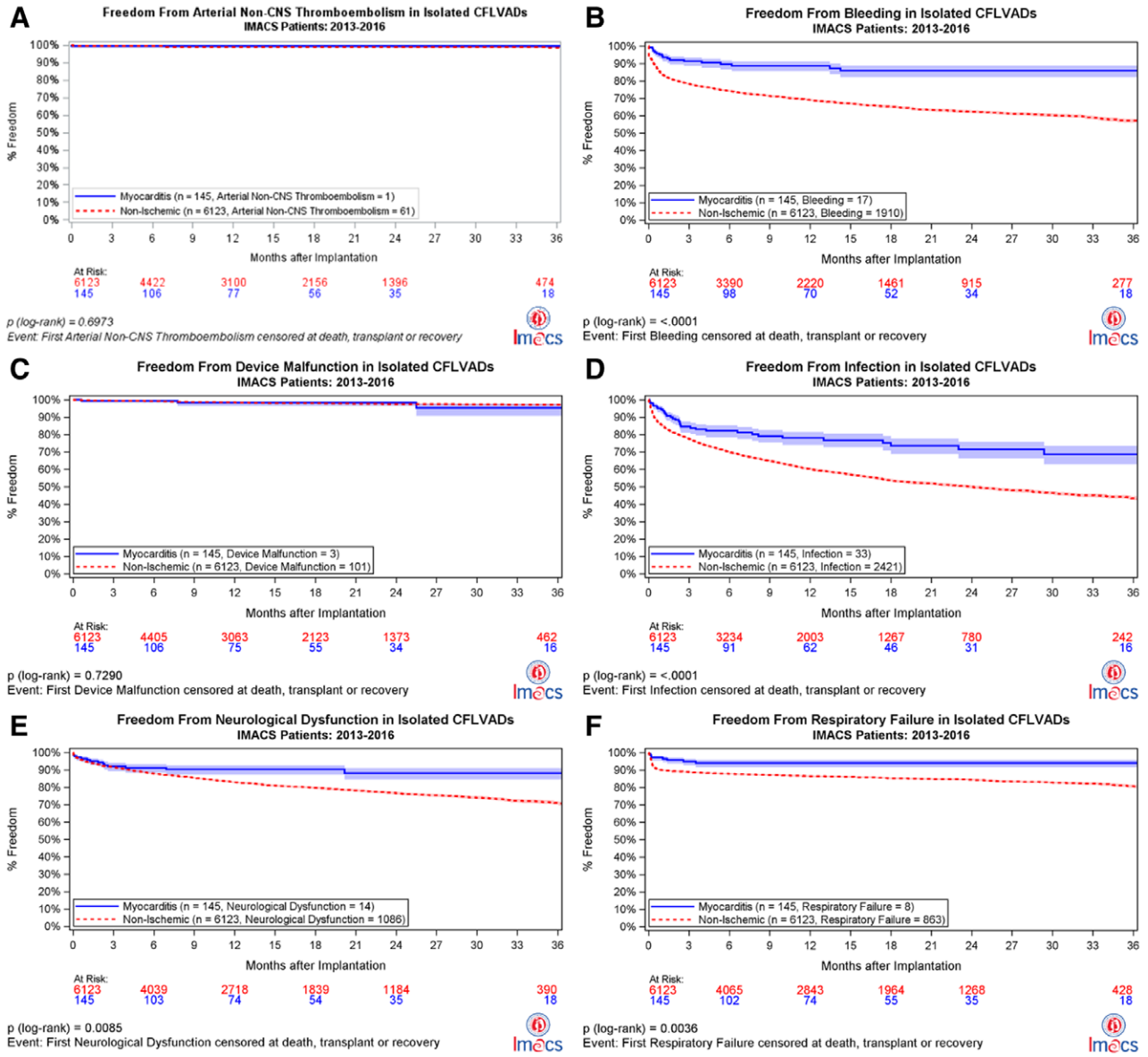

Figure 5. Long-term outcomes with myocarditis or NICM undergoing CF-LVAD (**A**) arterial thromboembolism; (**B**) bleeding; (**C**) device malfunction; (**D**) infection; (**E**) neurologic dysfunction; and (**F**) respiratory failure. CF-LVAD, continuous flow left ventricular assist device; NICM, nonischemic cardiomyopathy.

patients with myocarditis in this study had acute myocarditis (duration of symptoms <1 month). These patients did not differ in characteristics or outcomes.

This study has limitations that need to be acknowledged. We lack data on the diagnostic criteria and histopathology of myocarditis, and thus we are not able to make conclusions in regards to subtypes of myocarditis. There is no data on concomitant therapies for myocarditis (*e.g.*, immunosuppression) that may influence outcomes. The dataset lacks consistent reporting of echocardiographic or hemodynamic data that would have been informative. Due to the small number of events, we were unable to perform predictive modelling for recovery/device explant.

Conclusion

Although myocarditis patients who receive durable MCS are sicker preoperatively with higher needs for biventricular MCS, their overall MCS survival is not different from NICM. Patients who received MCS for myocarditis are more likely than NICM to have MCS explanted due to recovery, however, the absolute rates of recovery were low.

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