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Regional differences in use and outcomes of left ventricular assist devices: Insights from the Interagency Registry for Mechanically Assisted Circulatory Support Registry

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continuous-flow;
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BACKGROUND: We examined whether characteristics, implant strategy, and outcomes in patients who receive continuous-flow left ventricular assist devices (CF-LVAD) differ across geographic regions in the United States.

METHODS: A total of 7,404 CF-LVAD patients enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) from 134 participating institutions were analyzed from 4 distinct regions: Northeast, 2,605 (35%); Midwest, 2,210 (30%); West, 973 (13%); and South, 1,616 (22%).

RESULTS: At baseline, patients in the Northeast and South were more likely to have INTERMACS risk profiles 1 and 2. A bridge-to-transplant (BTT) strategy was more common in the Northeast (31.7%; West, 18.5%; South, 26.9%; Midwest, 25.5%; $p < 0.0001$). In contrast, destination therapy (DT) was more likely in the South (40.6%; Northeast, 32.3%; Midwest, 27.3%; West, 27.3%; $p < 0.0001$). Although all regions showed a high 1-year survival rate, some regional differences in long-term mortality were observed. Notably, survival beyond 1 year after LVAD implant was significantly lower in the South. However, when stratified by device strategy, no significant differences in survival for BTT or DT patients were found among the regions. Finally, with the exception of right ventricular failure, which was more common in the South, no other significant differences in causes of death were observed among the regions.

CONCLUSIONS: Regional differences in clinical profile and LVAD strategy exist in the United States. Despite an overall high survival rate at 1 year, differences in mortality among the regions were noted. The lower survival rate in the South may be attributed to patient characteristics and higher use of LVAD as DT.

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With a limited number of heart donors, left ventricular assist devices (LVADs) are increasingly used in patients with advanced heart failure as a bridge to transplantation (BTT) or destination therapy (DT).[1–10]

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Current data from the United Network for Organ Sharing (UNOS) suggest regional disparities in waiting times for patients awaiting heart transplantation in the United States (U.S.).[11–13] Although this may theoretically affect the use of LVADs, particularly as a BTT strategy, no studies have been performed to carefully evaluate this issue. Furthermore, there have been no reports on potential differences in LVAD use as DT across geographic regions in the U.S.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a database sponsored by the National Heart, Lung and Blood Institute, has collected data on more than 6,000 patients supported with LVAD and is currently the largest registry for mechanical circulatory support (MCS) in the U.S.[14] Examining data from this registry may provide important insights into regional variations in current patterns of LVAD use and outcomes in the U.S. Our hypothesis is that significant variations in LVAD use and outcomes exist among U.S. regions, and this study aimed to (1) describe demographic and clinical characteristics among LVAD patients enrolled in the INTERMACS registry from 4 distinct geographic regions: Northeast, Midwest, South, and West; (2) compare device strategy (BTT vs DT) among regions; and (3) explore regional differences in outcomes among patients receiving a continuous-flow (CF) LVAD.

Methods

Data sources

The primary data source for this study was the INTERMACS registry, an ongoing national registry for patients implanted with a U.S. Food and Drug Administration–approved MCS device designed to support patients for long periods. Details and objectives of this database have previously been described.[15] In summary, the registry was launched in 2005 with the collaborative effort the National Heart, Lung, and Blood Institute, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services and has been maintained by The University of Alabama INTERMACS Data Coordinating Center since its creation. Data, including patient characteristics, medical history, medications, laboratory data, INTERMACS profile, device type, and patient outcomes are collected using an interactive, Internet-based system to a secure server provided by the UNOS. Data analysis was done at The University of Alabama, which serves as the data analysis center, and has Institutional Review Board approval for analyzing the aggregate deidentified data for research purposes.

Study population

In this study, we selected patients who received a CF-LVAD only. Between June 2006 and March 2013, 8,609 adults (age $\geq$19 years at implant) received a heart device from 134 hospitals participating in the INTERMACS registry. After excluding 79 pediatric patients and 1,127 patients with pulsatile-flow devices, the final study population comprised 7,404 patients from 4 geographic regions.

Definitions of variables and outcomes

The following 4 geographic regions were defined from the UNOS regions: Northeast (UNOS regions 1, 2, 9, and 11), Midwest (regions 7, 8 and 10), South (regions 3 and 4), and West (regions 5 and 6). The rationale for choosing a UNOS-based distribution was that it would allow us to align with the UNOS data. The BTT strategy was used for patients listed for cardiac transplantation at the time of LVAD implant, bridge to candidacy (BTC) was used for patients who were considered eligible for heart transplant but not listed at the time of implantation, and DT was designated as a permanent therapy for patients who were not eligible for transplant.

The primary outcome was all-cause mortality by region (overall and by device strategy), with data censored at transplantation or device removal after recovery of myocardial function. Regional mortality was further compared during the early or late/constant phases if death occurred before or after 3 months from implantation, respectively. The mean follow-up for this study was 12.74 months. The causes of death identified were right heart failure, major bleeding, cardiac arrhythmia, hemolysis, end-stage cardiomyopathy, major infection, device malfunction, hepatic dysfunction, renal dysfunction, neurologic dysfunction, and other/unknown. The definitions of these adverse events can be found on the INTERMACS Web site (http://www.intermacs.org).

Statistical analysis

Baseline patient characteristics were compared among regions. Mean values with standard deviations (SDs) are used to describe continuous variables and numbers (percentages) are reported for categoric variables. The chi-square test was used for categoric variables, and the 2 independent sample *t*-test or 1-way analysis of variance Wilcoxon rank sum tests were used for continuous variables. Actuarial survival while on MCS was calculated from the date of LVAD implant to death, and patients were censored at the time of cardiac transplantation or LVAD explantation.

Time-related event data were analyzed using Kaplan-Meier methodology, and the effect of survival by geographic region was made univariately and multivariately by a parametric hazard regression analysis. The adjusted effect of these variables was assessed after adjustment for the following pre-implant parameters: age, sex, race/ethnicity, college education, body mass index, smoking, alcohol use, INTERMACS profile, previous cancer, chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, peripheral vascular disease, coronary artery disease, history of coronary artery bypass graft, history of valve surgery, ascites, implantable cardiac defibrillator, serum sodium, albumin, total bilirubin, blood urea nitrogen, creatinine, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, cholesterol, white blood cell count, use of an intraaortic balloon pump, left ventricular ejection fraction $<$20%, left ventricular end-diastolic diameter, severe right ventricular dysfunction, biventricular assist device use, concomitant surgery, inotrope use, and pre-implant invasive hemodynamics, including cardiac output, cardiac index, right atrial pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance. These significant pre-implant variables were selected based on prior studies.[16–18]

All tests were 2 sided, and *p*-values of <0.05 were considered statistically significant. Analyses were performed using SAS 8.2 software (SAS Institute Inc, Cary, NC).

Results

Patient characteristics

The study included 7,404 CF-LVAD patients from 134 participating institutions: Northeast, 2,605 (35%); Midwest, 2,210 (30%); West, 973 (13%), and South, 1,616 (22%). Patient characteristics are summarized in Table 1. At baseline, there were no significant regional differences in patient age, sex, or body mass index. The Northeast had more diabetic patients than other regions. Patients from the Northeast and South were more likely to have INTERMACS risk profiles 1 and 2 compared with those from the Midwest and West. The South had more black patients, and the West had more Hispanic patients. Similarly, patients in the South and West were more likely to be on dialysis. The South had a higher proportion of patients with blood type O compared with other regions.

BTT strategy was more common in the Northeast (31.7%) compared with the West (18.5%), South (26.9%), and Midwest (25.5%; $p < 0.0001$). In contrast, DT was more likely in the South (40.6%) than in the Northeast (32.3%), Midwest (27.3%), and West (27.3%; $p < 0.0001$). A higher proportion of patients with INTERMACS profile 1 in the Northeast received short-term MCS before LVAD implant compared with other regions. Patients in the Northeast were also more likely to receive a biventricular assist device or extracorporeal membrane oxygenation compared with other regions.

Hospital characteristics

This cohort included 134 participating hospitals, with 53 in the Northeast, 33 in the Midwest, 23 in the West, and 25 in the South. Most of the LVAD implanting centers were cardiac transplant centers. The Northeast had more non-transplant LVAD implanting centers, and the South had the highest number of DT certified centers (Table 1).

Outcomes

Overall mortality by region

There were a total of 1,653 deaths (22.3%) in the study group. Unadjusted analysis showed that the South had a lower survival than the other regions (Figure 1). Figures 2 and 3 highlight the competing outcomes in the overall cohort and among regions. Mortality at 1 year was significantly higher in the South region than in the other regions. Furthermore, these regional differences in survival persisted at 2 years (South, 65%; Northeast, 72%; Midwest, 71%; West, 70%; adjusted $p = 0.001$). In addition, LVAD patients in the South were less likely to have received a transplant at 1 year (South, 18%; Northeast, 23%; Midwest, 23%; West, 21%; $p = 0.001$). Overall, rates of myocardial recovery were low (1%), with no significant difference among the regions (Figure 2).

Mortality among regions by device strategy

Survival curves by device strategy in the overall cohort and by regions are shown in Figures 3 and 4. The actuarial survival at 1 year was lower in DT patients (75.3%) than in BTT (85.5%) and BTC (81.7%) patients ($p < 0.0001$; Figure 3). This finding was consistent across regions (Figure 4). Tables 2 and 3 report adjusted hazard ratios (HRs) for mortality during the early high-risk phase and the late constant phase among the regions (using South as the reference group) categorized by device strategy. Some subtle regional differences were noted during the high-risk (early phase) and long-term period (constant phase). Notably, the lower mortality in the Northeast in the BTT group compared with the South was significant during the early phase (adjusted HR, 0.377; 95% CI, 0.1707–0.8339; $p = 0.02$) but not during the constant phase (adjusted HR, 0.817; 95% CI, 0.5765–1.1588; $p = 0.26$; Table 2). In the DT group, however, although a lower mortality was noted in the early phase in the Midwest and West, the Northeast did not show any statistically significant differences in mortality during the early and late phases compared with the South (Table 2). Similar to the BTT group, in the BTC group (Table 3) a significantly lower early mortality in the Northeast, Midwest, and West regions was noted compared with the South.

Causes of death

Infection and neurologic dysfunction were the most common causes of adverse events, with a similar distribution among the regions (Table 4). With the exception of right ventricular failure (RVF), which was more common in the South (7.9%) than in the Northeast (6.1%), Midwest (3.5%), and West (2.5%; adjusted $p = 0.01$), no other significant differences in causes of death were observed among the regions.

Discussion

This study explored the regional differences in use and outcomes of LVAD in the U.S. and offers important findings based on the INTERMACS database. First, at the time of LVAD implantation, patients from the Northeast and South were more likely to have INTERMACS risk profiles 1 and 2 compared with those from the Midwest and West. Second, BTT strategy was more common in the Northeast, whereas DT was more common in the South. Third, despite high overall 1-year survival rates across regions, patients from the South had a significantly lower survival after LVAD surgery.

Consistent with prior studies among LVAD patients,[9,19] our study population was composed predominantly of middle-aged white men with no regional variation in age or sex distribution. In regard to minorities, the largest Hispanic and black populations came from the West and South, respectively. In addition to previous INTERMACS data showing that more than 50% of patients had

Table 1 Baseline Characteristics by Geographic Region

Pre-implant characteristics	Total (n = 7,404)	Northeast (n = 2,605)	Midwest (n = 2,210)	West (n = 973)	South (n = 1,616)	p-value
Age at implant, mean ± SD years	56.7 ± 12.9	56.7 ± 12.9	56.5 ± 12.7	57.8 ± 18.7	56.4 ± 12.7	0.04
Male, %	79.10	77.70	79.00	82.00	79.50	0.04
Ethnicity, %						
White	70.0	65.8	75.3	73.9	67.3	<0.0001
Hispanic	6.3	5.5	2.6	11.6	9.3	<0.0001
Black	22.2	25.9	20.1	8.8	27.2	<0.0001
Other	6.4	6.7	3.5	14.7	5.1	<0.0001
Medical history, %						
Ischemic	48.0	47.5	48.5	48.2	48.0	0.93
Non-ischemic	51.0	51.5	50.4	50.2	51.4	0.8
Congenital diagnosis	0.5	0.42	0.68	0.72	0.19	0.11
Diabetes	27.1	29.2	27.2	24.0	25.6	0.005
CVA/TIA	5.4	5.5	5.6	5.3	5.2	0.96
Dialysis	7.9	1.0	1.2	3.1	2.0	<0.0001
ICD	81.5	79.3	81.2	82.2	85.1	<0.0001
CABG	23.6	22.1	22.9	24.6	26.3	0.01
Valve surgery	7.5	7.8	7.7	8.2	6.3	0.19
ECMO	2.0	3.0	2.0	1.2	1.1	<0.0001
IABP	28.6	26.5	34.7	21.6	31.9	<0.0001
Short-term MCS						
INTERMACS 1	50.1	64.5	43.5	58.3	59.7	0.0035
INTERMACS 2	19.1	12.9	19.5	31.5	28	<.0001
INTERMACS 3	10.7	9.45	7.8	17.2	12.4	0.04
Mechanical ventilation (%)	6.6	7.3	5.6	7.0	6.5	0.13
BMI, mean ± SD kg/m^2	28.6 ± 6.7	28.6 ± 6.9	28.6 ± 6.5	27.9 ± 6.4	28.9 ± 6.6	0.004
BSA, mean ± SD m^2	2.08 ± 0.30	2.07 ± 0.30	2.08 ± 0.30	2.06 ± 0.30	2.09 ± 0.30	0.003
Laboratory values, mean ± SD						
Sodium, mmol/L	134.71 ± 4.85	134.9 ± 4.68	134.8 ± 4.80	134.2 ± 5.15	134.7 ± 4.99	0.004
Creatinine, mg/dl	1.44 ± 0.76	1.4 ± 0.78	1.4 ± 0.73	1.4 ± 0.80	1.4 ± 0.74	0.99
INR	1.34 ± 0.47	1.4 ± 0.50	1.3 ± 0.42	1.4 ± 0.49	1.3 ± 0.43	0.0002
Total bilirubin, mg/dl	1.38 ±1.51	1.4 ± 1.22	1.3 ± 1.17	1.4 ± 2.23	1.4 ± 1.74	0.13
SGOT/AST, U/L	67.51 ± 275.8	72.2 ± 330.7	66.9 ± 242.1	67.6 ± 293.3	60.9 ± 202.8	0.67
SGPT/ALT, U/L	77.02 ± 254.1	75.6 ± 284.3	82.7 ± 251.4	77.8 ± 277.1	71.3 ± 181.6	0.62
Hemoglobin, g/dl	11.38 ± 1.99	11.3 ± 1.99	11.4 ± 1.96	11.6 ± 2.02	11.3 ± 2.02	<0.0001
WBC, µL	8.56 ± 4.22	8.8 ± 4.19	8.4 ± 4.08	8.4 ± 3.68	8.7 ± 4.73	0.005
Device type, %						
LVAD	97.4	96.2	98.4	95.7	99.0	<0.0001
BIVAD	2.60	3.8	1.6	4.3	1.1	<0.0001
INTERMACS level, %						
1. Critical cardiogenic shock	14.9	17.4	14.3	9.9	14.9	<.0001
2. Progressive decline	39.8	42.9	37.4	34.8	41.2	<.0001
3. Stable but inotrope dependent	26.5	25.1	23.2	32.9	29.2	<0.0001
4. Recurrent advanced HF	13.4	10.5	18.3	15.5	10.1	<0.0001
5. Exertion intolerant	3.0	2.2	4.0	3.5	2.5	<0.0001
6. Exertion limited	1.6	1.3	2.1	2.7	1.0	<0.0001
7. Advanced NYHA III	1.0	0.7	0.6	0.7	1.6	0.004
Pre-implant device strategy, %						
BTT (currently listed)	27.1	31.7	25.5	18.5	26.9	<0.0001
BTC						
Listing likely	24.1	21.3	26.7	34.6	18.5	<0.0001
Listing moderately likely	10.2	10.2	8.9	13.3	9.9	0.003
Listing unlikely	3.3	3.0	3.2	5.3	2.5	0.0008
DT (permanent device)	34.1	32.3	34.5	27.3	40.6	<0.0001
Bridge to recovery	1.0	0.7	0.4	0.3	0.7	0.29
Rescue therapy	0.3	0.4	0.2	0.1	0.4	0.38
Other	1.0	0.4	0.7	0.6	0.5	0.54
Patients with LVEF <20%, % (No.)	68.08 (6,665)	67.4 (2,362)	68.7 (1,951)	61.4 (898)	71.9 (1,454)	<0.0001

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Table 1 (*Continued*)

Pre-implant characteristics	Total (n = 7,404)	Northeast (n = 2,605)	Midwest (n = 2,210)	West (n = 973)	South (n = 1,616)	p-value
Severe RVF,%	2.6	3.8	1.6	4.3	1.1	<0.0001
Blood type O, % (No.)	48.5 (7,287)	50.4 (2,528)	44.8 (2,191)	46.1 (969)	51.8 (1,599)	<0.0001
Center characteristics,[a] % (No.)						
Total centers.	134	53	33	23	25	
Transplant center)	90 (120)	87 (46)	91 (30)	91 (21)	92 (23)	
Not a transplant center	10 (14)	13 (7)	9 (3)	9 (2)	8 (2)	
DT certified center	89 (119)	89 (47)	85 (28)	87 (20)	96 (24)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIVAD, biventricular assist device; BMI, body mass index; BSA, body surface area; BTC, bridge to candidacy; BTT, bridge to transplant; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; HF, heart failure; IABP, intraaortic balloon pump; ICD, implantable cardioverter defibrillators; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NYHA, New York Heart Association; RVF, right ventricular failure; SD, standard deviation; SGOT, serum oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase; TIA, transient ischemic attack; WBC, white blood cell.

[a]Region percentages are based on hospitals that contributed data to this cohort. INTERMACS collects information on whether the center is a DT center (based on DT certification posted by Centers for Medicare and Medicaid Services 1/10/2014) and whether the center is or is not a transplant center (includes all organ transplantation).

INTERMACS profile 1 and 2 at the time of device implant,[20,21] we observed that a larger proportion of these sicker patients were from the Northeast and South regions. Possible explanations for this finding include the higher number of LVAD implanting centers in the Northeast, the higher proportion of DT patients in the South, and a higher incidence of RVF in both of these regions. When we compared pre-implant variables between combined regions Midwest/West vs Northeast/South, we found that with few exceptions, no significant differences were present at baseline (Supplementary Table S1, available online).

Advances in device technology and durability, along with improvement in patient management, have led to increased survival of patients on MCS. Since the early results from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial showing 1-year survival of 52% among patients who received first-generation pumps,[6] patient outcomes have remarkably increased, with contemporary estimates of 1-year survival at 86%.[19] Although we noted similar mortality end points in our overall study population, we found important regional differences in outcomes. Notably, patients from the South had a significantly lower survival rate compared with other regions. A number of factors may explain this observation:

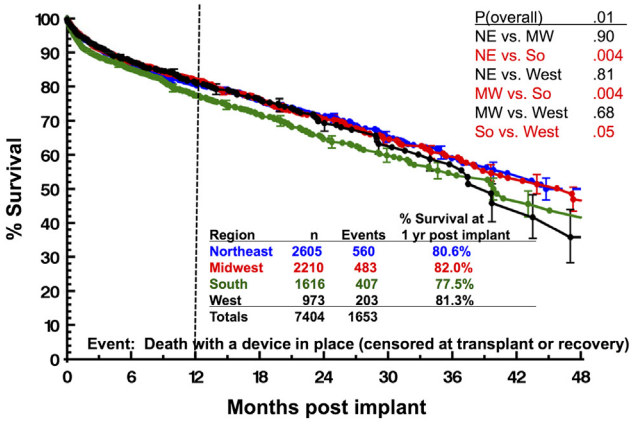

Figure 1 Survival after implant by geographic region. MW, Midwest; NE, Northeast; So, South.

First, the higher mortality observed in the South may be associated with the higher use of DT strategy. Prior data[22,23] support that DT patients are usually sicker and have higher mortality. Several socioeconomic and social factors may potentially affect higher DT rates in this region. For instance, a higher prevalence of tobacco use and obesity may constitute a larger burden of relative contraindications for transplant and BTT listing.[24] In contrast, a number of centers may consider active or recent tobacco use acceptable for DT status. In addition, centers with shorter transplant waiting times (i.e., South region) may choose to place a patient on an initial DT strategy until certain comorbid factors` (e.g., smoking) are resolved.

Second, the relatively higher proportion of patients with INTERMACS profiles 1 and 2 in the South may explain the lower survival rates. This finding is consistent with the established association between INTERMACS profile risk and mortality.[25] Interestingly enough, we found that despite a large number of INTERMACS 1 and 2 patients in the Northeast, mortality in this region did not exceed those of others. This paradoxic finding may be related to the higher proportion of patients who received transplants (i.e., BTT) in this region and the higher proportion of INTERMACS 1 patients receiving short-term MCS before LVAD implant compared with other regions.

Another possible factor, not examined in our study, that may explain regional variations in outcomes relates to the LVAD experience of the implanting centers. This is particularly relevant because a significant correlation has been shown between center experience and outcome, particularly in DT patients.[26] Also, our study did not systematically examine variables, such as the use of a pre-operative risk score, and other factors, such as candidate selection bias, which have been shown to be an important determinant of outcome in LVAD patients.[26]

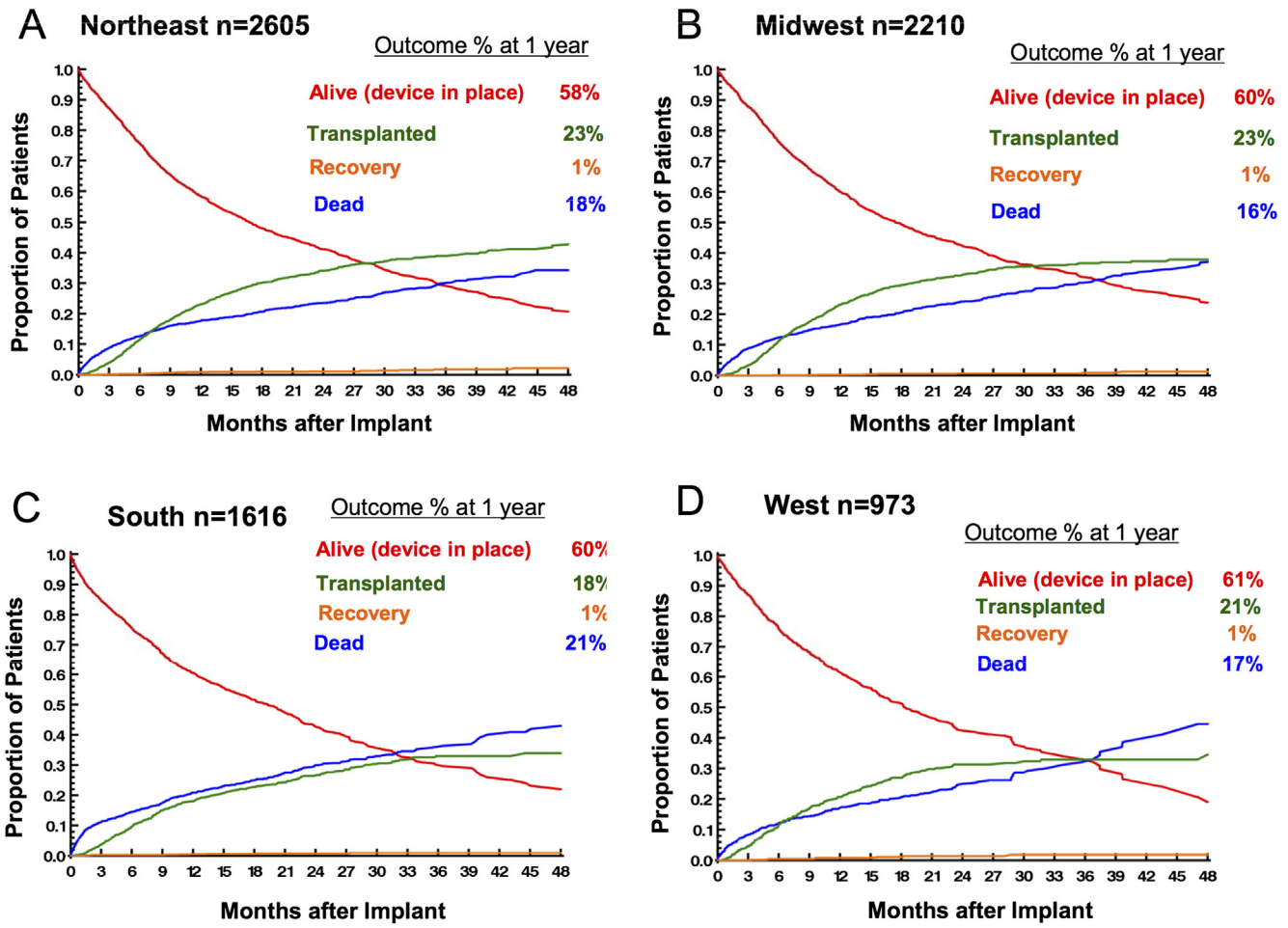

Figure 2 Competing outcomes by region: (A) Northeast, (B) Midwest, (C) South, and (D) West.

Adverse events in the early post-operative period have been linked to nearly 20% of overall mortality among LVAD patients.[7] Consistent with this observation, our study found that regardless of device strategy, regional differences in mortality were only significant in the early phase. Intriguingly, some of these findings persisted even after adjusting for patient characteristics. Among BTT patients, only the Northeast showed better outcome in the early phase compared with the South. Although a lower early mortality was noted in the BTC cohort in all regions compared with the South, DT patients in the Midwest and West but not in the Northeast had lower early mortality compared with the South.

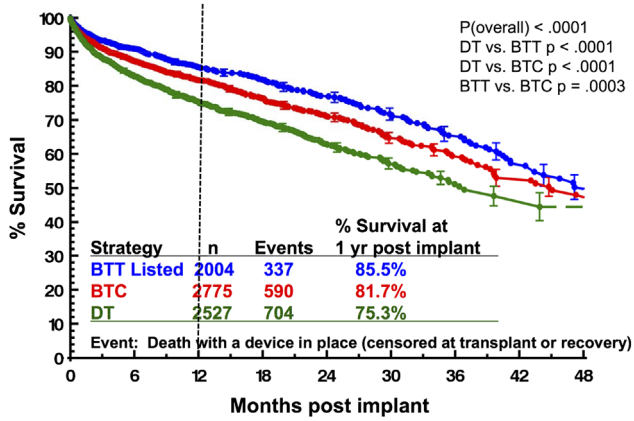

Figure 3 Overall survival by device strategy. BTC, bridge to candidacy; BTT, bridge to transplant; DT, destination therapy.

With the exception of RVF, our study showed no significant differences in causes of death among regions. Examining RVF-related deaths is challenging due to hospital-level variability on how to manage LVAD-associated RVF. To illustrate, certain centers may have lower thresholds of placing an RVAD intraoperatively rather than implanting an RVAD as a rescue strategy for post-operative RVF. This mode of management may correlate with improved mortality. Other centers, in contrast, may favor medical therapy over RVAD surgery and consequently experience poorer outcomes. This strategy is particularly relevant among centers with high DT volumes because they do not have an option of transplant should RVF be unrecoverable.

Some limitations inherent to registry-based studies need to be mentioned. First, because of the retrospective nature of our study, there is potential for bias. Data were collected using a medical record review and dependent on the accuracy and completeness of documentation, abstraction, and reporting to INTERMACS.

Second, residual unmeasured confounding variables may also explain some of these findings.

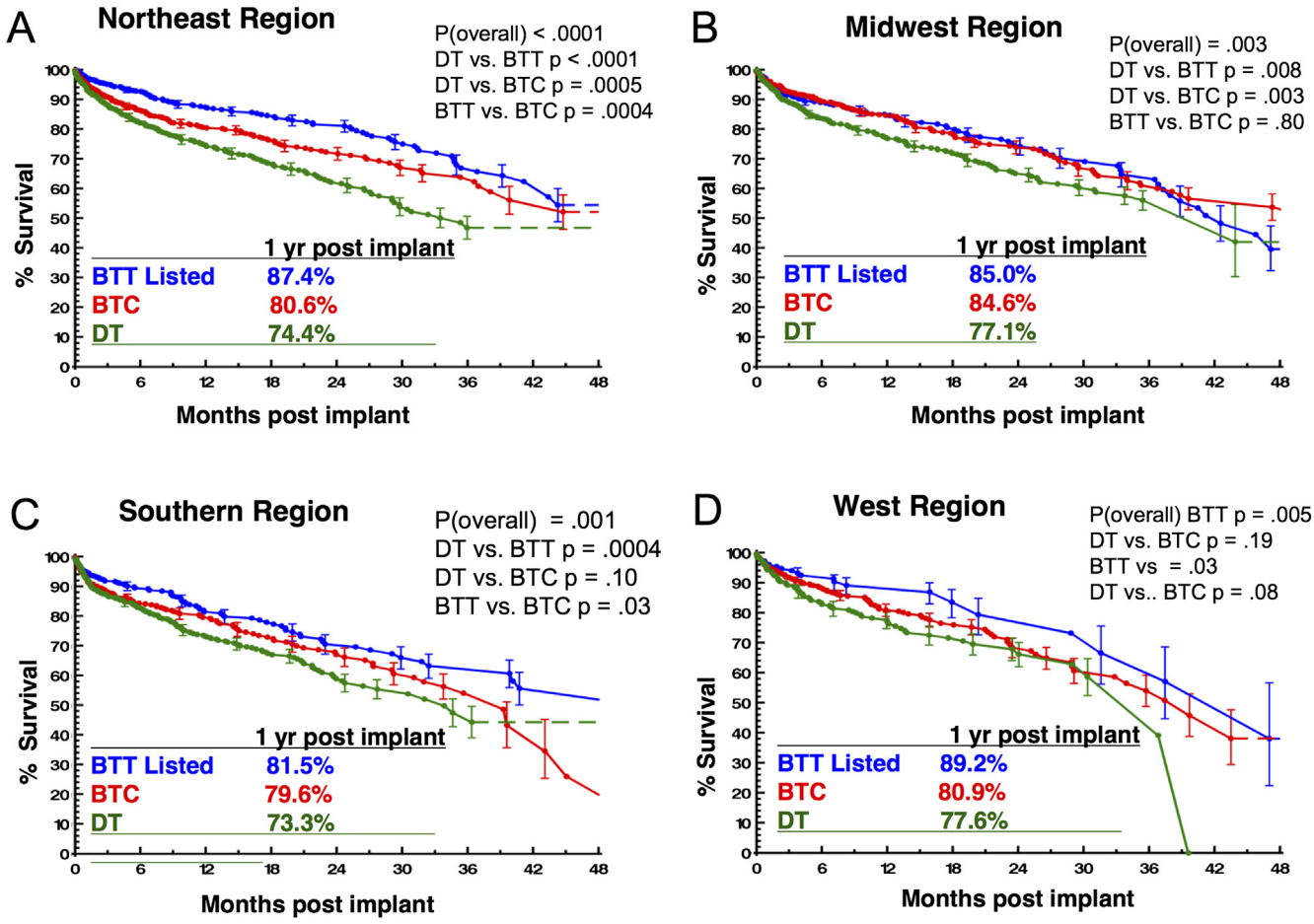

Figure 4 Overall regional survival by device strategy: (A) Northeast, (B) Midwest, (C) South, and (D) West. BTC, bridge to candidacy; BTT, bridge to transplant; DT, destination therapy.

Table 2 Unadjusted and Adjusted[a] Hazard Ratios With 95% Confidence Intervals for Bridge to Transplant and Destination Therapy by Geographic Region (Using South as Reference Group)

	Bridge to transplant: patient listed				Destination therapy			
	Early		Constant		Early		Constant	
Geographic regions	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Northeast vs South								
Unadjusted	0.28 (0.12–0.67)	0.004	0.74 (0.51–1.05)	0.1	0.87 (0.56–1.35)	0.55	0.97 (0.74–1.25)	0.82
Adjusted	0.37 (0.17–0.83)	0.02	0.81 (0.57–1.15)	0.26	0.65 (0.41–1.03)	0.07	0.97 (0.75–1.26)	0.87
Midwest vs South								
Unadjusted	0.89 (0.45–1.74)	0.74	1.01 (0.69–1.46)	0.97	0.69 (0.43–1.09)	0.12	0.81 (0.61–1.06)	0.13
Adjusted	0.60 (0.29–1.22)	0.16	1.06 (0.73–1.51)	0.76	0.51 (0.31–0.83)	0.01	0.82 (0.63–1.07)	0.16
West vs South								
Unadjusted	0.59 (0.23–1.51)	0.28	0.76 (0.42–1.35)	0.35	0.73 (0.40–1.32)	0.30	0.82 (0.57–1.18)	0.30
Adjusted	0.52 (0.19–1.39)	0.19	0.85 (0.49–1.49)	0.59	0.43 (0.22–0.83)	0.01	0.71 (0.50–1.00)	0.05

CI, confidence interval; HR, hazard ratio.

[a]Variables in the model: age, sex, race/ethnicity, college education, body mass index, smoking, alcohol use, Interagency Registry for Mechanically Assisted Circulatory Support profile, previous cancer, chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, peripheral vascular disease, coronary artery disease, history of coronary artery bypass graft, history of valve surgery, ascites, implantable cardiac defibrillator, serum sodium, albumin, total bilirubin, blood urea nitrogen, creatinine, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, cholesterol, white blood cell count, use of intraaortic balloon pump, left ventricular ejection fraction $<20\%$, left ventricular end-diastolic diameter, severe right ventricular dysfunction, biventricular assist device use, concomitant surgery, inotrope use, and pre-implant invasive hemodynamics, including cardiac output, cardiac index, right atrial pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance.

Table 3 Unadjusted and Adjusted[a] Hazard Ratios With 95% Confidence Intervals for Bridge to Candidacy by Geographic Region (Using South as the Reference Group)

	Bridge to candidacy			
	Early		Constant	
Geographic regions	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Northeast vs South				
Unadjusted	0.66 (0.40–1.08)	0.1	0.78 (0.56–1.09)	0.15
Adjusted	0.54 (0.33–0.89)	0.02	0.79 (0.56–1.11)	0.18
Midwest vs South				
Unadjusted	0.37 (0.20–0.67)	0.001	0.72 (0.52–1.00)	0.06
Adjusted	0.48 (0.27–0.84)	0.01	0.76 (0.55–1.05)	0.1
West vs South				
Unadjusted	0.54 (0.30–0.97)	0.04	0.90 (0.64–1.27)	0.58
Adjusted	0.41 (0.22–0.76)	0.005	0.95 (0.67–0.95)	0.79

CI, confidence interval; HR, hazard ratio.

[a]Variables in the model: age, gender, race/ethnicity, college education, body mass index, smoking, alcohol use, Interagency Registry for Mechanically Assisted Circulatory Support profile, previous cancer, chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, peripheral vascular disease, coronary artery disease, history of coronary artery bypass graft, history of valve surgery, ascites, implantable cardiac defibrillator, serum sodium, albumin, total bilirubin, blood urea nitrogen, creatinine, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, cholesterol, white blood cell count, use of intra-aortic balloon pump, left ventricular ejection fraction $<20\%$, left ventricular end-diastolic diameter, severe right ventricular dysfunction, biventricular assist device use, concomitant surgery, inotrope use, and pre-implant invasive hemodynamics including cardiac output, cardiac index, right atrial pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance.

Third, although this study demonstrates regional variation in use and outcomes of LVAD patients, causes of these important regional differences remain unclear and need to be further elucidated in future studies.

Fourth, our analysis did not adjust for LVAD volume and experience of implanting centers. However, analysis of center volume in a voluntary registry such as INTERMACS is fraught with inherent confounders. For example, centers that joined the registry at a later date may be underrepresented. Also, patients who do not consent for enrollment will not be included, which decreases the perceived center volume. Moreover, large-volume centers that enroll a large number of patients in clinical trials (not represented in the registry) will be falsely identified as low-volume centers. Data on center experience are not available in the INTERMACS registry. Importantly, the data presented highlight a significant deficit in the current knowledge regarding the frequency, duration, and type of short-term MCS (e.g., intraaortic balloon pump, Impella, Tandem Heart) used as a bridge-to-bridge at the national level. The use of temporary short-term devices and their effects on post-LVAD outcome remains unclear.

Finally, at the local level, surgeon-specific data are paramount to better understand these observed differences in outcomes among regions to potentially improve overall patient outcome. As we move forward, perhaps combining INTERMACS data with other MCS databases, such as The Society of Thoracic Surgeons (STS) database, which for instance, includes data on surgeon-specific volumes and data on Food and Drug Administration-approved commercially

Table 4 Causes of Death by Geographic Region[a]

Causes of death	Total ($n = 1653$) (%)	Northeast ($n = 560$) (%)	Midwest ($n = 483$) (%)	West ($n = 203$) (%)	South ($n = 407$) (%)	*p*-value[b]
Right heart failure	5.3	6.1	3.5	2.5	7.9	0.01
Major bleeding	4.2	5.0	3.7	5.4	3.	0.32
Cardiac arrhythmia	3.0	3.0	2.5	3.9	3.2	0.78
Hemolysis	0.5	0.7	0.6	0.5	0.3	0.76
End-stage cardiomyopathy	1.8	1.6	1.2	3.0	2.2	0.41
Major infection	10.4	11.8	11.4	7.4	8.9	0.2
Device malfunction	3.2	2.9	3.7	4.9	2.2	0.28
Hepatic dysfunction	1.2	0.9	1.7	0.5	1.2	0.53
Renal dysfunction	1.6	1.1	1.9	0.5	2.7	0.12
Neurologic dysfunction	18.3	16.8	18.6	19.2	19.4	0.72
Other	47.7	47.7	47.6	49.8	46.9	0.93
Unknown	2.7	2.5	3.5	2.5	2.2	0.63

[a]Data (%) are shown as total deaths/total patients
[b]Overall *p*-value = .23.

available devices and also investigational devices, may fill this important knowledge gap.

In summary, regional differences in clinical profile and LVAD strategy exist in the U.S. Despite an overall high survival rate at 1 year, important regional differences in overall mortality were noted. Although the lower survival rate in the South may be attributed to patient characteristics and higher use of LVADs as DT, it is important to note that further research is needed because some other potential factors not included in this analysis may also explain these observed regional differences in outcome.

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Supplementary data

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

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