Optimal timing for heart transplantation in patients bridged with left ventricular assist devices: Is timing of the essence?

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ABSTRACT

Objectives: Due to the scarcity of donor hearts to meet recipient demands, more than 40% of heart transplants are performed in patients bridged to transplant (BTT) with a left ventricular assist device (LVAD). The objective of this study was to determine the effect of BTT duration with an LVAD on posttransplant outcomes.

Methods: From 2009 to 2014, we identified 2639 fee-for-service Medicare patients who underwent a primary heart transplant with 1186 (45%) patients BTT with an LVAD. The LVAD patients were stratified as BTT ≤ 31 days ($n = 28$ [2.4%]), BTT 31-365 days ($n = 748$ [63.1%]), and BTT > 365 days ($n = 409$ [34.5%]). Patients went directly to heart transplantation and were not bridged in 1453 cases (55%). LVAD duration was analyzed dichotomously and as a continuous variable with adjusted overall survival as the primary end point.

Results: All-cause mortality was significantly worse in patients who were BTT < 31 days. Survival at 30 days was 81.5% for BTT < 31 days, 94% for BTT 31 to 365 days, 95% for BTT > 365 days, and 94% for no BTT. At 1 year, survival was 74% for BTT < 31 days, 85% for BTT 31 to 365 days, 88% for BTT > 365 days, and 89% for no BTT ($P = .018$). When LVAD duration was analyzed as a continuous variable, patients BTT with an LVAD < 34 days had significantly increased mortality.

Conclusions: Patients who underwent heart transplantation within the first month of BTT with an LVAD had significantly increased mortality. However, there was no survival difference among patients who were BTT with an LVAD longer than 31 days. (J Thorac Cardiovasc Surg 2019;157:2315-24)

Risk of death after heart transplant based on bridge to transplant duration with an LVAD.

Central Message

The risk of mortality after heart transplantation was greatest when bridge to transplant duration with a left ventricular assist device was < 1 month before transplant.

Perspective

Due to the scarcity of donor hearts, it is critical to determine how BTT duration with an LVAD influences outcomes after transplantation. We found that patients BTT < 1 month have decreased survival, but patients BTT longer than 1 year have increased complications after transplant. This may suggest that earlier transplantation within the first year can improve outcomes.

See Commentaries on page 2325 and 2327.

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The incidence of heart failure is increasing in the United States.¹ Medical therapies for heart failure are limited, and many patients require heart transplant (HTx). Due to

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Abbreviations and Acronyms

BTT	= bridged to transplant
HTx	= heart transplant
ICD-9	= International Classification of Diseases ninth revision
LVAD	= left ventricular assist device

the lack of donor hearts to meet the demands of patients with end-stage heart failure, left ventricular assist devices (LVADs) have been increasingly utilized in this population to prolong survival and bridge patients successfully to transplantation.²⁻⁶ In the United States, approximately 40% of all Htx procedures are completed in patients bridged to transplant (BTT) with an LVAD. Among these patients who are selected for transplantation, recent evidence with continuous flow devices suggests no differences in mortality compared with patients that go directly to HTx.⁷⁻¹⁰ However, very few studies have investigated the influence on the duration of BTT with an LVAD on posttransplant outcomes. The 2 most recent studies demonstrated no survival difference based on the duration of BTT with a LVAD, yet these reports were either limited to short follow-up times or conducted as a small, single-center experience.^{11,12} Older studies that investigated this topic were completed in patients with pulsatile devices and do not reflect current practice patterns.^{13,14}

Due to the scarcity of donor hearts, it is critical to determine how BTT duration with an LVAD influences outcomes after transplantation. This could lead to new policies to help risk-stratify patients on the waiting list and to improve patient selection, with the goal to better allocate limited resources. We performed a cross-sectional analysis among Medicare patients who underwent HTx from 2009 to 2014. Patients were stratified based on BTT duration with an LVAD and compared with patients not bridged with an LVAD to evaluate posttransplant survival and complications.

METHODS

Study Design

We performed a retrospective cross-sectional analysis of fee-for-service Medicare patients from 2009 to 2014 in patients who underwent HTx. Patients were stratified based on the presence and duration of an LVAD before HTx: BTT <31 days, BTT 31 to 365 days, BTT >365 days, and no BTT. Patient groups were compared to determine differences in all-cause mortality, cumulative incidence for postoperative complications, and hospital readmissions.

Study Population and Data

All patients were identified from Medicare Carrier Files using Current Procedural Terminology codes to identify HTx patients (Table E1). Between January 1, 2009, and December 31, 2014, we identified 3187 patients who underwent HTx. Primary HTx occurred in 2639 patients during that time period. Patients were then stratified based on BTT status with an LVAD. We identified 1713 (54%) patients who were BTT with an LVAD

that was explanted on the day of the HTx procedure. We excluded 528 patients who had no date associated with their LVAD implantation because the implant occurred before entering Medicare. We also excluded 21 patients that had missing or incomplete data. Furthermore, patients with right ventricular assist devices, biventricular assist devices, total artificial hearts, and extracorporeal or percutaneous LVADs were not included in the study. Additionally, patients undergoing abdominal transplant concomitantly with the HTx were not included. BTT patients were stratified into the early or late group based on BTT timing with 28 patients (2.4%) BTT ≤31 days, 748 patients (63.1%) BTT 31 to 365 days, and 409 patients (34.5%) BTT >365 days. Patients went directly to HTx and were not bridged in 1453 patients (55%). These time cutoffs were selected based on study design and data presentation of previous manuscripts.^{11,12,14} In addition to dichotomizing duration on LVAD support before transplantation, BTT duration was also analyzed as a continuous variable. Figure 1 presents the flow chart for patient inclusion and exclusion criteria.

All patients were linked to Medicare Denominator and Beneficiary Summary Files to determine patient demographic characteristics and death status. The Medicare Provider Analysis and Review Files and Carrier Files were used to determine details about the index hospitalization such as length of stay, discharge location after HTx, and posttransplant in-patient hospital readmissions. Patient comorbidities were determined from the previous hospitalizations, outpatient files, or present on admission at the primary hospitalization for heart transplantation within the MedPAR and Carrier Files using International Classification of Diseases ninth revision (ICD-9) codes and categorized with the Elixhauser comorbidity index^{15,16} (Table 1). Tables E2 and E3 present the ICD-9 and Current Procedural Terminology codes used to determine patient comorbidities and preoperative characteristics.

For patients who were BTT, we determined whether they had any LVAD-related complications within 30 days before transplant (Table 1). These data were utilized in the multivariable survival model to analyze whether LVAD complications influenced the need for HTx and postoperative outcomes. LVAD complications were grouped as mechanical complications, pump thrombosis, local/systemic infection, gastrointestinal bleeding, cerebral bleeding, and other major bleeding events.¹⁷ Right heart failure could not be investigated because there is no specific ICD-9 code for this diagnosis.

Outcomes

The primary end point was adjusted all-cause mortality among the BTT <31 days, BTT 31 to 365 days, BTT >365 days, and no BTT. Secondary end points included posttransplant complications at 30 days and 1 year for stroke, pneumonia, respiratory failure, tracheostomy, sepsis, acute kidney injury, hemodialysis, end-stage renal disease, liver failure, extracorporeal membrane oxygenation, reoperative exploration, and bleeding.

Statistical Analysis

Baseline characteristics were summarized by descriptive statistics composed of the mean ± standard deviation and percentages. Differences between patient groups were analyzed using analysis of variance or χ^2 tests. Unadjusted survival was performed using the Kaplan-Meier method with the log-rank test. Adjusted survival was calculated with a multivariable Cox regression adjusted for patient demographic characteristics, preoperative comorbidities, and LVAD complications within the month preceding transplant to determine differences in survival. The Cox proportional hazard tests were assessed the Schoenfeld residuals test. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). We also completed analysis of duration of BTT with an LVAD and the risk of death using LVAD time as a continuous variable. This allowed for analysis of BTT duration without artificially categorizing time points. This was completed using a restricted cubic spline model to analyze the variation of the hazard function on BTT duration compared with the survival of no BTT patients.

FIGURE 1. Flow chart of patient inclusion and exclusion criteria. *BTT*, Bridged to transplant; *LVAD*, left ventricular assist device.

Additionally, we calculated the adjusted cumulative incidence of post-operative complications and hospital readmissions for each patient group, using death as a competing risk. The Fine and Gray method was used to calculate the subdistribution HR and *P* value for all competing risk models. All tests were 2-tailed with an alpha threshold of 0.05. HRs and odds ratios are presented with 95% CIs. Statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, Tex). Data management was performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

We identified 2639 primary Htx procedures from 2009 through 2014, with 1186 patients (45%) BTT with an LVAD. Overall, LVAD patients were bridged for an average of 346.6 ± 288.1 days and a median of 265 days (interquartile range [IQR], 296 days). A histogram of LVAD BTT is presented in Figure E1. The BTT <31 days group had a mean LVAD duration of 15.8 ± 9.3 days, the BTT 31 to 365 days group had a mean LVAD duration of 192.9 ± 86.6 days, and the BTT >365 days group had a mean LVAD duration of 651.2 ± 288.6 days.

Table 1 presents patient characteristics before Htx and LVAD complications within 30-days before transplant for each group. Patients who were BTT with an LVAD had a tendency for increased comorbidities compared with no BTT patients. Patients who were BTT <31 days had the lowest overall LVAD complication rate of 14.3%, followed

by 40.2% for the BTT 31 to 365 days group, and at 44.7% for BTT >365 days group ($P < .005$). For each specific complication, there were no significant differences for mechanical, pump thrombosis, local/systemic infections, or major bleeding among the BTT groups. The median follow-up time was 2.1 years (IQR, 3.8 years) for the BTT <31 days group, 2.3 years (IQR, 3.3 years) for the BTT 31 to 365 days group, 1.7 years (IQR, 2.5 years) for the BTT >365 days group, and 3.1 years (IQR, 1.5-4.5 years) for the no BTT group.

Mortality after Htx

Unadjusted all-cause mortality after Htx was significantly higher for patients BTT <31 days ($P = .018$). Survival at 30 days was 81.5% for patients BTT <31 days, 94% for patients BTT 31 to 365 days, 95% for patients BTT >365 days, and 94% for no BTT. At 1 year, survival was 74% for patients BTT <31 days, 85% for patients BTT 31 to 365 days, 88% for patients BTT >365 days, and 89% for no BTT. At 3 years, survival was 65% for patients BTT <31 days, 78% for patients BTT 31 to 365 days, 81% for patients BTT >365 days, and 82% for no BTT (Figure 2).

In an adjusted multivariable Cox regression, survival at 3 years was significantly improved for BTT 31 to

TABLE 1. Preoperative patient characteristics and presence of left ventricular assist device (LVAD) complications within 30-days before heart transplant

Patient characteristic	BTT <31 d (n = 28)	BTT 31-365 d (n = 748)	BTT >365 d (n = 409)	No BTT (n = 1453)	P value
Age (y)	60.5 ± 9.4	58.9 ± 10.4	57.6 ± 11.5	59.3 ± 10.9	.034
Male	20 (71.4)	613 (82.0)	325 (79.5)	1067 (73.4)	<.001
White	21 (75.0)	527 (70.5)	252 (61.6)	1042 (71.7)	<.001
Ischemic cardiomyopathy	23 (82.1)	609 (81.4)	265 (64.8)	969 (66.4)	<.0001
Congenital	7 (25.0)	164 (21.9)	35 (8.6)	206 (14.2)	<.0001
Valvular disease	21 (75)	6262 (83.4)	243 (59.41)	932 (64.14)	<.0001
Hypertension	20 (71.4)	626 (83.7)	303 (74.1)	1025 (70.5)	<.0001
Diabetes	14 (50.0)	398 (53.2)	185 (45.2)	594 (40.9)	<.0001
Hypothyroidism	5 (17.9)	154 (20.6)	90 (22.0)	265 (18.2)	.29
Stroke	8 (28.6)	203 (27.1)	92 (22.5)	219 (15.07)	<.001
Pneumonia	8 (28.6)	311 (41.6)	84 (20.5)	341 (23.5)	<.0001
Chronic obstructive pulmonary disease	8 (28.6)	309 (41.3)	98 (24.0)	423 (29.1)	<.0001
Pulmonary circulation disease	17 (60.7)	525 (70.2)	147 (35.9)	746 (51.34)	<.0001
Chronic kidney disease	3 (10.7)	139 (18.6)	75 (18.3)	235 (16.2)	.37
Hemodialysis pretransplant	0 (0.0)	64 (8.6)	54 (13.2)	76 (5.2)	<.0001
Peripheral vascular disease	18 (64.3)	351 (46.9)	111 (27.1)	560 (38.5)	<.0001
Protein-calorie malnutrition	4 (14.3)	209 (27.9)	43 (10.5)	141 (9.7)	<.001
Obese	3 (10.7)	97 (12.9)	56 (13.7)	113 (7.8)	<.0001
Liver disease	2 (7.1)	108 (14.4)	34 (8.3)	168 (11.6)	.015
Coagulopathy	28 (39.3)	313 (41.8)	108 (26.4)	281 (19.3)	<.0001
Chronic blood loss anemia	2 (7.1)	71 (9.5)	36 (8.8)	35 (2.4)	<.0001
Major bleeding pretransplant	18 (64.3)	504 (67.4)	231 (56.5)	440 (30.3)	<.0001
Deficiency anemia	11 (39.3)	500 (66.8)	206 (50.4)	573 (39.4)	<.0001
Depression	4 (14.3)	160 (21.4)	52 (12.7)	186 (12.8)	<.0001
IABP pretransplant	7 (1.2)	258 (33.7)	129 (31.5)	188 (12.9)	<.0001
ECMO pretransplant	1 (3.5)	20 (2.7)	16 (3.9)	6 (0.4)	<.0001
LVAD complications within 30-d of heart transplant					
Any LVAD complication	4 (14.3)	301 (40.2)	183 (44.7)	NA	.005
Mechanical complications	0 (0)	95 (12.7)	58 (14.2)	NA	.09
Pump thrombosis	0 (0)	39 (5.2)	26 (6.4)	NA	.31
Local/systemic infection	1 (3.6)	69 (9.2)	50 (12.2)	NA	.14
Any major bleeding event	4 (14.3)	177 (23.7)	109 (26.7)	NA	.24
Gastrointestinal bleeding	1 (3.6)	45 (6.0)	24 (6.9)	NA	.86
Cerebral bleeding	0 (0)	10 (1.3)	6 (1.5)	NA	.28
Other major bleeding	3 (10.7)	134 (18.9)	92 (22.5)	NA	.13

Values are presented as mean ± standard deviation or n (%). BTT, Bridged to transplant; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; NA, not available.

365 days (HR, 0.4; 95% CI, 0.21-0.82; $P = .012$), BTT >365 days (HR, 0.39; 95% CI, 0.19-0.80; $P = .010$), and no BTT groups (HR, 0.46; 95% CI, 0.23-0.91; $P = .025$) compared with BTT <31 days. Risk factors for death at 3 years was associated with pretransplant renal insufficiency (HR, 1.25; 95% CI, 1.02-1.56; $P .034$), pneumonia

(HR, 1.64; 95% CI, 1.34-2.01; $P < .001$), and any major bleeding event at 30 days before transplant (HR, 2.07; 95% CI, 1.22-3.53; $P < .007$). Table E4 shows the multivariable Cox regression.

Similarly, risk factors associated with death at 30 days after HTx were significant for renal insufficiency (HR, 1.39;

FIGURE 2. Survival after heart transplantation based on bridge to transplant (BTT) duration with a left ventricular assist device. The 95% confidence intervals for survival can be found in [Table E1](#).

95% CI, 1.08-1.70; $P < .032$), pneumonia (HR, 1.53; 95% CI, 1.07-2.21; $P < .02$), and having any major bleeding event at 30 days before transplant (HR, 3.37; 95% CI, 1.27-8.93; $P < .02$).

The duration of BTT with an LVAD was also analyzed as a continuous variable ([Figure 3](#)). Patients that underwent BTT had statistically increased adjusted mortality when LVAD BTT timing was between 4 and 34 days before HTx. During this early time period, risk of death was up to 50% higher. As seen in [Figure 2](#), this was the only period

when the HR and 95% CIs were all > 1 (shaded area), indicating statistically increased mortality.

Complications

The cumulative incidences of posttransplant complications are presented at 30 days ([Table 2](#)) and at 1 year ([Table 3](#)). Thirty days after transplant, both the BTT 31 to 365 days and BTT > 365 days groups had a lower incidence of tracheostomy and need for hemodialysis compared with the BTT < 31 days group. Additionally, the BTT 31 to 365 days group had a lower incidence for sepsis, acute kidney injury, and postoperative bleeding compared with BTT < 31 days patients. We found no other differences between the other complications listed in [Table 2](#) at 30 days.

At 1 year posttransplant, the cumulative incidence for hemodialysis and postoperative bleeding were significantly lower in both BTT 31 to 365 days and BTT > 365 days groups, compared with the BTT < 31 days group ([Table 3](#)). Additionally, acute kidney injury was lower in patients BTT 31 to 365 days when compared with BTT < 31 days.

The median length of stay was 42.5 days (IQR, 34.5 days) for BTT < 31 days, 16 days (IQR, 18 days) for BTT 31 to 365 days, and 16 for BTT > 365 days ($P = .002$).

All-cause Hospital Readmissions

We calculated the cumulative incidence for hospitalization readmissions and found that patients BTT > 365 days had the highest greatest incidence of hospital readmissions.

FIGURE 3. Hazard ratio for mortality after heart transplantation based on bridge to transplant duration with a left ventricular assist device (LVAD).

TABLE 2. Cumulative incidence of posttransplant complications at 30 days

Complication	BTT			BTT 31-365 d SHR (95% CI)	P value*	BTT >365 d	
	BTT <31 d	31-365 d	BTT >365 d			SHR (95% CI)	P value*
Stroke	12	7.2	8.1	0.57 (0.21-1.60)	.29	0.62 (0.21-1.85)	.39
Pneumonia	8.3	15	21	2.30 (0.54-9.64)	.26	3.03 (0.72-12.72)	.13
Pulmonary embolism	2.0	1.5	1.9	0.59 (0.06-5.8)	.66	0.81 (0.07-9.35)	.87
Tracheostomy	13	4.8	5.0	0.27 (0.08-0.89)	.03	0.29 (0.1-0.92)	.04
Sepsis	15	4.8	8.2	0.28 (0.10-0.83)	.021	0.51 (0.17-1.47)	.22
Acute kidney injury	58	39	48	0.58 (0.36-0.94)	.018	0.74 (0.46-1.23)	.25
Hemodialysis	29	9.5	13	0.29 (0.13-0.69)	.004	0.35 (0.15-0.85)	.021
Liver failure	4.1	6.5	5.2	1.62 (0.22-12.00)	.63	1.45 (0.18-11.57)	.73
Extracorporeal membrane oxygenation	2.4	1.3	1.8	0.49 (0.05-5.29)	.56	0.73 (0.07-7.68)	.79
Re-exploration	16	7.9	9.2	0.43 (0.15-1.24)	.12	0.51 (0.17-1.54)	.23
Bleeding	36	16	15	0.48 (0.25-0.94)	.031	0.45 (0.22-0.89)	.23

Values are presented as % or subdistribution hazard ratio (95% confidence interval). BTT, Bridged to transplant; SHR, subdistribution hazard ratio; CI, confidence interval.

*Determined by Fine and Gray test.

At 1 year after HTx, the cumulative incidence was 26% for BTT 31 to 365 days group, 33% for BTT >365 days (HR, 1.37; 95% CI, 1.06-1.77; $P = .015$), 14.3% for BTT <31 days (HR, 0.53; 95% CI, 0.17-1.76; $P = .30$), and 17.8% for no BTT patients (HR, 0.67; 95% CI, 0.53-0.83; $P = .001$). Only preoperative pneumonia (HR, 1.43; 95% CI, 1.1-1.71; $P = .005$) and anemia (HR, 1.35; 95% CI, 1.13-1.72; $P = .01$) were associated with increased risk for 1-year hospital readmissions.

DISCUSSION

In our study, we used Medicare data from 2009 to 2014 to investigate outcomes of patients BTT with an LVAD compared with patients who went directly to HTx. The goal of this study was to determine whether there existed an optimal time period during BTT LVAD support when

survival was superior with fewest complications. First, patients BTT with an LVAD had similar all-cause mortality compared with no BTT patients at 3 years' follow-up. Second, when patients are dichotomized based on timing of BTT, patients who underwent transplant within the first month of LVAD implant had a significant increase in all-cause mortality. Patients transplanted during this early time period had up to a 50% increase in the risk for death. However, we found no survival difference between patients who were BTT 31 to 365 days or BTT >365 days. It is important to note that the survival analyses took into consideration if patients had any LVAD-related complications within 30 days preceding transplantation.

The question of optimal BTT duration has been previously examined. Most recently, Grimm and colleagues¹¹ investigated 1332 patients BTT with an LVAD using United

TABLE 3. Cumulative incidence of posttransplant complications at 1 year

Complication	BTT			BTT 31-365 d SHR (95% CI)	P value*	BTT >365 d	
	BTT <31 d	BTT 31-365 d	BTT >365 d			SHR (95% CI)	P value*
Stroke	23	14	15	0.57 (0.21-1.60)	.29	0.62 (0.21-1.85)	.39
Pneumonia	29	32	36	2.30 (0.54-9.64)	.26	3.03 (0.72-12.72)	.13
Pulmonary embolism	8.2	4.2	5.8	0.59 (0.06-5.8)	.66	0.81 (0.07-9.35)	.87
Tracheostomy	13	4.8	6.3	0.27 (0.08-0.89)	.03	0.29 (0.1-0.92)	.04
Sepsis	18	16	20	0.28 (0.10-0.83)	.021	0.51 (0.17-1.47)	.22
Acute kidney injury	76	54	60	0.58 (0.36-0.94)	.018	0.74 (0.46-1.23)	.25
Hemodialysis	32	13	15	0.29 (0.13-0.69)	.004	0.35 (0.15-0.85)	.021
Liver failure	7.2	11	9%	1.62 (0.22-12.00)	.63	1.45 (0.18-11.57)	.73
Extracorporeal membrane oxygenation	2.6	2.1	3.7	0.49 (0.05-5.29)	.56	0.73 (0.07-7.68)	.79
Re-exploration	17	9.1	10	0.43 (0.15-1.24)	.12	0.51 (0.17-1.54)	.23
Bleeding	49	31	29	0.48 (0.25-0.94)	.031	0.45 (0.22-0.89)	.23

Values are presented as % or subdistribution hazard ratio (95% confidence interval). BTT, Bridge to transplant; SHR, subdistribution hazard ratio; CI, confidence interval. *Determined by Fine and Gray test.

Network for Organ Sharing data from 2011 to 2012.¹¹ BTT patients were grouped into <90 days, 90 to 365 days, and >365 days groups. No survival difference was detected among any of the groups at 30 days or 1 year posttransplant. Although postoperative complications were not present in the United Network for Organ Sharing database and could not be evaluated, the investigators analyzed functional outcomes of patients using the Karnofsky performance scale. They found that patients with increased BTT length (>90 days) had the greatest increase in functional performance while on the waiting list. However, if a patient had BTT length >90 days but poor functional performance at the time of HTx, posttransplant mortality was increased in this subgroup. In another study, John and colleagues¹² evaluated data from the HeartMate II trial from 2005 to 2008 and presented BTT data for 250 patients who eventually underwent transplant. At 1 year posttransplant, no survival differences were detected in groups BTT <30 days, 30 to 90 days, 90 to 179 days, or 180 days or longer. At 1 year after transplantation, survival was 94% for BTT duration <30 days, 93% for BTT duration 30 to 89 days, and 84% for BTT duration 90 to 179 days ($P = .18$). Due to the small sample size in each group and limited follow-up data, survival was only analyzed at 1 year after transplant. Other studies that have investigated BTT timing are not generalizable to the modern era because patients were transplanted from 1999 to 2006 and were primarily bridged with pulsatile devices.^{13,14,18,19}

Our study is complementary to these investigations but provides new insights. First, we have 6 years of recent data (to 2014). Because there is longer follow-up than in previous studies, we have presented survival up to 3 years posttransplant and have shown no differences among groups. Second, because Medicare data were used, we were able to analyze perioperative complications and hospital readmissions. These outcomes have never been evaluated in recent reports. Third, we have compared BTT patients with nonbridged patients. We believe that due to the scarcity of donor hearts, it is critical to also determine whether timing of BTT has a deleterious influence on survival compared with no BTT. And finally, we evaluated BTT duration as a continuous variable and confirmed that survival is only worse if BTT duration is less than approximately 1 month. The benefit of this approach is that duration of BTT is not categorized into artificial groups.

We discovered that patients BTT <31 days had very poor survival. Among patients transplanted within 31 days of BTT, only 81.5% were alive at 30 days and only 74.1% were alive at 1 year. When BTT time was analyzed as a continuous variable, patients transplanted between 4 and 34 days after LVAD insertion had up to 50% greater risk of death than other patients. However, there were only 28 out of 1186 patients (2.4%) who underwent transplant

during this early time period. It appears that practice patterns have changed significantly over the past decade because we found that few patients undergo transplant immediately after LVAD implantation in the current era.

Smedira and colleagues¹⁴ evaluated outcomes in patients from 1991 to 2006, using single institution data on 375 patients who were BTT with an LVAD. Forty-four patients (17%) were transplanted with BTT times <30 days. Exact survival percentages in this early group were not provided, but predicted survival among all BTT patients revealed no mortality increase during the first 30 days. However, almost all patients had pulsatile pumps during this study. Only in the study by John and colleagues that was discussed previously,¹² is BTT timing <30 days presented among patients with continuous flow devices. They investigators found no detriment in survival among patients BTT <30 days. However, the data they analyzed were from the HeartMate II pivotal trial, and all patients had advanced heart failure but without evidence of multi-organ failure. These patients were all carefully selected and possibly not reflective of real-world practice. We specifically investigated <31 days on LVAD as a time point in our study because we expected these patients to undergo HTx due to early LVAD complications and would likely have increased perioperative mortality. However, we found that this early group had the lowest proportion of LVAD complications within the month preceding HTx. Regardless, using more recent data, we determined that very few patients are undergoing transplantation within the first 30 days of bridging with an LVAD. Although we cannot determine the Interagency Registry for Mechanically Assisted Circulatory Support profile of the patients who underwent early transplantation, the poor survival in this group suggests caution is necessary before proceeding. In the study by Attisani and colleagues,⁹ LVAD therapy is a successful bridge to temporize critically ill patients with multiorgan failure so that HTx can be completed electively. During this early period, patients who are recovering from cardiogenic shock and multiorgan injury after LVAD implantation should recover before transplant procedures are undertaken.

This study was conducted in the modern era of continuous flow devices. The durability of continuous flow LVADs have dramatically improved durability compared with the early pulsatile devices, and this has allowed patients to remain for longer duration on LVAD support. In our study, 34% of all BTT patients were transplanted after 365 days of support without an increase in all-cause mortality or complications. However, this group had an increased incidence of hospital readmissions compared with BTT duration of 31 to 365 days. Reasons for this increase in hospital readmissions are not explainable with this dataset.

VIDEO 1. Video contribution from authors explaining significance of study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30539-2/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30539-2/fulltext).

This study has several limitations. First, Medicare fee-for-service patients were analyzed and represent an older cohort of patients requiring HTx. Although longitudinal analysis of these patients is robust, it comprises <50% of all patients undergoing HTx in the United States and may not be generalizable to all patients undergoing HTx. Additionally, analyses using administrative claims data are subject to coding errors and lack important clinical variables such as listing status (United Network for Organ Sharing 1A or 1B status), laboratory data, LVAD device model information, and operative characteristics. Medicare data lack donor details, and we were unable to incorporate this into the multivariate analysis. It is possible that this could influence outcomes across groups. Another limitation is the inability to determine whether Medicare patients with an LVAD are BTT or destination therapy at time of LVAD implant. For this reason, BTT candidates could only be identified as LVAD patients who eventually underwent HTx. Thus, we were unable to analyze the mortality of LVAD BTT patients before transplantation. This has likely produced selection bias among the BTT groups because the people who underwent transplant were highly selected and survived to transplantation. Lastly, this study examined patients who underwent a surgical LVAD implantation, and should not be generalized to patients who are placed on extracorporeal membrane oxygenation or a temporary, percutaneous LVAD.

CONCLUSIONS

BTT with an LVAD is a suitable strategy to temporize patients with end-stage heart failure. We have found that patients who are BTT with an LVAD and then undergo transplant within the first month have an increased risk for mortality and perioperative complications. Additional caution is necessary before scheduling patients for transplant within this early time period. However, there were no survival differences among patients who were BTT with an LVAD >31 days before transplant (Video 1).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18May01/23BC%203.MCS%20Transplant/S96_1_webcast_040407381.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: LVAD, survival, heart transplant, bridge to transplant, outcomes research, health policy research

Discussion

Dr Manuel Antunes (Coimbra, Portugal). I would like to thank the Association for the privilege of discussing this interesting paper. Dr Brown, I enjoyed your short presentation and thank you for sending me the manuscript in advance.

You and your colleagues wanted to determine the effect of duration—not timing, timing is the word that you use in the manuscript—of left ventricular device bridging to transplantation on postoperative heart transplant outcomes, reviewing the available data of more than 2500 Medicare patients who underwent heart transplant using a primary end point of overall survival and dividing into <1 year and >1 year of assistance compared with patients who did not have assistance before transplantation.

I suggest 2 or 3 aspects because they will generate my questions. Early mortality was equal amongst the groups, and you found that at 3 years adjusted survival was similar between groups, so no difference with regard to survival. All your patients who underwent transplant within 34 days of bridging were at a significantly increased risk of death, but patients bridged beyond 1 year had an increased risk of postoperative complications and a significantly increased risk for hospital readmission at 1 year. Those are the main conclusions as I see them.

I think this is an important study with similar data from other reports, although yours used a longer follow-up, which is really important. In an area where there is an increasing shortage of donors, bridging is the only salvation for many patients.

Although Medicare patients who at present are an older cohort of heart transplantation patients, I believe that your sample still represents the whole population. However, because of the administrative data, you acknowledge that

there were a lot of missing data that would be important, especially the clinical. There were a lot of difference among these 3 groups, and this may confuse a little bit the conclusions. Therefore, one must be careful about deriving conclusions on these otherwise excellent results.

One comment I want to make is that unfortunately left ventricular assist device is not available elsewhere in the world as easily as it appears to be in the United States judging from the number of patients, and I noticed that you excluded from this study patients who were bridged with other devices such as extracorporeal circulation and so on, and those are the devices that the common people in the real world use more frequently. It would have been important to know if there was any influence between the different types of devices, and you say these administrative data did not have sufficient information.

However, and this is my question, did you or could you have access to any data that would allow you to say what type of devices was better in this type, having in mind that in the 6 years' duration of this study there have been a lot of changes in this respect. You did not put it in the article, but do you have any feeling about it?

Dr Chase R. Brown (Philadelphia, Pa). In terms of the types of devices that were actually used, like a circulatory versus pulsatile type devices?

Dr Antunes. Yes.

Dr Brown. Unfortunately, the way that Medicare is coded out, these procedural codes are not specific enough to actually tell you the type of device that is actually used, and that's another limitation of the study. Because a lot of the studies that looked at this previously looked at studies that were mixed with pulsatile devices and circulatory devices, I think that because they were mixed, some of the outcomes weren't as applicable to the time frame now, when the majority of the devices are nonpulsatile. But that's really the only granular information that you can get out of a Medicare database, unless you could do it within the United Network for Organ Sharing database, but we didn't have access to that.

Dr Antunes. I can't understand why the short-term assisted patients had worse outcomes, in fact in the early days, because those patients were very unstable and had organ failure, and that is easy to understand. Why would patients who have been on bridging for more than a year have so many more complications than those who were less than a year? And of course if you are at 364 days, you end up in 1 group; if you are 366 days, you end up in the other group. Was there a continuum or was there a difference, and what are the causes for that?

Dr Brown. That's why we originally wanted to do it as a continuous variable like we did with showing the hazard of time. We did not do that with complications, but I think it would be a good idea, because I think, again, it's an artificial

cutoff at 365 days. So to do that and to look at the rate of complications with a hazard, I think it probably would be more appropriate to see if there is an inflection point.

To be honest, I don't have a good explanation, a mechanistic explanation, of why patients who were bridged the longest had more complications, because they were also the patients who looked, at least on the comorbidities, that they were not the sickest. They were actually less sick than people who were bridged younger.

When I was talking to cardiologists about this, their thinking whether or not having a nonpulsatile device, how that influences end-organ outcomes, I don't know. Those are completely hypothesizing to explore.

Dr Antunes. Because these causes for readmission were not really directly related to the device.

Dr Brown. No, because that is all after the transplant. These were readmissions after transplantation.

Dr Antunes. Okay, thank you. Once again, congratulations on good work and a nice presentation.

Dr Valluvan Jeevanandam (*Chicago, Ill*). Perhaps the answer to that question is how did those patients who were there for more than a year actually get transplanted? A lot of them end up getting transplanted because they get urgent status as 1A because they actually have a complication. So they might have had infection, stroke, device malfunction, or gastrointestinal bleeding, which could cause issues, stuff like that. So maybe that may answer that question.

Dr Brown. Some of that information we could get from the Medicare database.

Dr Jeevanandam. I don't know if it is in the Medicare database, like were they transplanted as United Network for Organ Sharing status 1A or 1B.

Dr Brown. Yes, that wouldn't be, but we could see the timing of their transplantation after maybe a readmission for a diagnosis code. So if they came in for sepsis or for stroke, we would be able to then see their time from that hospitalization until transplantation.

Dr Scott C. Silvestry (*Orlando, Fla*). I have a comment. To echo Dr Jeevanandam's statement, I think the trouble with this type of analysis in addition to the artificiality of 1 year is that we don't code very well why that patient was transplanted at that moment, and device-related complications are prob-

ably the bigger driver, or social things. We have many patients who are bridged to transplant but they are waiting for them to quit smoking or do other things like that, or they are raising funds, and it is so difficult to figure out why they were listed at that moment or got transplanted at that moment.

Some of it is coded in the United Network for Organ Sharing data set that you can look that they had device malfunction at the time of transplant, but it's a difficult thing to tease out from that. I am curious, this is Medicare data?

Dr Brown. Yes.

Dr Silvestry. And yet the average age of your recipients was in the 50s. That's pretty young for a Medicare population.

Dr Brown. The way you can get on Medicare is being older than age 65 years, but you can also get into Medicare by having a disability for 2 years and then get put on Medicare.

Dr Silvestry. It's an interesting social statement for US health care that that's how we are getting these people on Medicare.

FIGURE E1. A histogram of patients bridged to transplant with a left ventricular assist device.

TABLE E1. Overall survival of patients at each time point with 95% confidence intervals for heart transplant patients stratified by the presence of a bridge to transplant (BTT) left ventricular assist device

	30 d	1 y	3 y
BTT <31 d	0.81 (0.61-0.91)	0.74 (0.53-0.86)	0.65 (0.44-0.80)
BTT 31-365 d	0.94 (0.92-0.96)	0.85 (0.83-0.88)	0.78 (0.76-0.82)
BTT >365 d	0.95 (0.93-0.97)	0.88 (0.85-0.92)	0.81 (0.76-0.85)
No BTT	0.94 (0.93-0.96)	0.89 (0.86-0.90)	0.82 (0.79-0.84)

BTT, Bridge to transplant.

TABLE E2. International Classification of Diseases ninth revision (ICD-9) and Current Procedural Terminology (CPT) codes for patient characteristics and comorbidities

Comorbidity	ICD-9 diagnosis codes	ICD-9 procedure code	CPT codes
Left ventricular assist device insertion	V4321	3766	33979 33975
Left ventricular assist device removal			33977 33980
Hypertension	4010 4011 4019 40200 40201 40210 40211 40290 40291 40300 40301 40310 40311 40390 40391 40400-40403 40410-40413 40490 40491 40492 40493 40501 40509 40511 40519 40591 40599 4372 64200-64204 64210-64214 64220- 64224 64270-64274 64290-64294		
Congestive heart failure	39891 4280-4289		
Peripheral vascular disease	4400-4409 44100-4419 4420-4429 4431 -4439 44421-44422 4471 449 5571 5579 V434		
Chronic obstructive pulmonary disease	490 4910 4911 4912 49120 49121 49122 4918 4919 4920 4928 494 4940 4941 496		
Renal failure	5853 5854 5855 5856 5859 586 V420 V451 V560 -V5632 V568 V4511-V4512		
Chronic kidney disease	585 5859 5851 5852 5853 5854 5855		
Hemodialysis	40301 40311 40391 40402 40403 40412 40413 40492 40493 5856 V451 V4511 V4512 V560 V561 V5631	3995	90925 90935 90937 90945 90947 90999
Liver disease	07022 07023 07032 07033 07044 07054 4560 4561 45620 45621 5710 5712 5713 57140-57149 5715-5719 5723 5728 5735 V427		
Diabetes	24900-24931 24940-24991 25000-25033 25040-25093 64800-64804 7751		
Metastatic cancer	1960-1991 20970-20975 20979 78951		
Dementia	2900 29010 29011 29012 29013 29020 29021 2903 29040 29041 29042 29043 940 2941 29410 29411 29420 29421 33119 33182		
Protein-calorie malnutrition	2638 2639		
Pulmonary Hypertension	4160 4168		
Ischemic cardiomyopathy	4149 4148 4100 41000 41001 41002 4101 41010 41011 41012 4102 41020 41021 41022 4103 41030 41031 41032 4104 41040 41041 41042 4105 41050 41051 41052 4106 41060 41061 41062 4107 41070 41071 41072 4108 41080 41081 41082 4109 41090 41091 41092		
Congenital	7450 74510 74511 74512 74519 7452 7453 7454 7455 74560 74561 74569 7457 7458 7459 74600 74601 74602 74609 7461 7462 7463 7464 7465 7466 7467 74681 74682 74683 74684 74685 74686 74687 74689 7469 7470 74710 74711 74720		

(Continued)

TABLE E2. Continued

Comorbidity	ICD-9 diagnosis codes	ICD-9 procedure code	CPT codes
	74721 74722 74729 7473 74731 74732 74739 74740 74741 74742 74749 7475 7476 74760 74761 74762 74763 74764 74769 74781 74782 74783 74789 7479		
End-stage renal disease	40301 40311 40391 40402 40401 40403 40412 40492 40493 5856		
Bleeding	99811 430 431 4320 4321 4329 4230 4233 4560 45620 4590 53021 5310 53100 53101 5312 53120 53121 5320 53200 53201 5322 53220 53221 5330 53300 53301 5332 53320 53321 5340 53400 53401 5342 53420 53421 5693 578 5780 5781 5789 5314 53140 53141 5316 53160 53161 5324 53240 53241 5326 53260 53261 5330 53300 53301 5334 53340 533401 5336 53360 53361 5344 53440 53441 5346 53460 5346 53501 53511 53521 53531 53541 53551 53561 53571 5997 59970 59971 7191 71910 71911 71912 71913 71914 71915 71916 71917 71918 71919 7848 7863 78630 78639 7847 36281 36243 36361 36362		

ICD-9, International Classification of Diseases ninth revision; CPT, Current Procedural Terminology.

TABLE E3. International Classification of Diseases ninth revision (ICD-9) and Current Procedural Terminology (CPT) codes for posttransplant complications

Complication	ICD-9 diagnosis codes	CPT codes
Stroke	34660 34661 34662 34663 430 431 4320 4321 4329 43301 43311 43321 43331 43381 43391 4340 43400 43401 4341 43410 43411 4349 43490 43491 436 99702	
Acute renal failure	5845 5846 5847 5848 5849	
Pneumonia	00322 0203 0204 0205 0212 0221 0310 0391 0521 0551 0730 0830 1124 1140 1144 1145 11505 11515 11595 1304 1363 4800 4801 4802 4803 4808 4809 481 4820 4821 4822 4823 48230 48231 48232 48239 4824 48240 48241 48242 48249 4828 48281 48282 48283 48284 48289 4829 483 4830 4831 4838 4841 4843 4845 4846 4847 4848 485 486 5130 5171	
Sepsis	99591 99592	
Respiratory failure	5173 5185 51851 51852 51853 51881 51882 51883 51884 V461 V4611 V4612 V4613 V4614 V462	
Acute kidney injury	5849	
Embolization	4449 44422 44421 5570 36230 44489 4332 4338 59381	
Acute heart failure	42821 42823 42831 42840 42841 42843 4280	
Re-exploration		35820
Intra-aortic balloon pump		33967
Extracorporeal membrane oxygenation		33960 33961 36822
Tracheostomy		31600 31601

ICD-9, International Classification of Diseases ninth revision; CPT, Current Procedural Terminology.

TABLE E4. Multivariable analysis for all-cause mortality at 3 years*

Preoperative patient characteristic	Hazard ratio (95% confidence interval)	P value
Bridge to transplant		
31-365 d	0.41 (0.21-0.82)	.01
>365 d	0.39 (0.19-0.80)	.01
No bridge to transplant	0.46 (0.23-0.91)	.03
Age (y)	1.00 (0.99-1.01)	.84
Male	1.04 (0.82-1.32)	.74
Chronic kidney disease	1.25 (1.02-1.53)	.03
Hemodialysis	1.06 (0.75-1.50)	.74
Pneumonia	1.64 (1.34-2.01)	.00
Congestive heart failure	0.49 (0.23-1.05)	.07
Peripheral vascular disease	1.00 (0.82-1.23)	.98
Pulmonary circulatory disease	0.98 (0.80-1.19)	.82
Stroke	1.08 (0.84-1.39)	.54
Chronic obstructive pulmonary disease	0.85 (0.69-1.05)	.14
Diabetes	1.15 (0.94-1.40)	.18
Liver failure	1.11 (0.84-1.48)	.46
Coagulopathy	1.00 (0.80-1.24)	.97
Obesity	1.31 (0.97-1.76)	.08
Weight loss	0.88 (0.63-1.22)	.45
Anemia	1.10 (0.89-1.36)	.37
Hypertension	1.17 (0.91-1.50)	.22
LVAD complications within 30 d of heart transplant		
Mechanical complications	0.95 (0.57-1.57)	.83
Pump thrombosis	0.89 (0.44-1.80)	.74
Local/systemic infection	1.24 (0.74-2.10)	.42
Any major bleeding event	2.07 (1.22-3.53)	.01
Any LVAD complication	0.86 (0.47-1.59)	.64

LVAD, Left ventricular assist device. *Reference of hazard ratio for bridge to transplant is bridge to transplant duration <31 d.