Outcomes of Left Ventricular Assist Device Implantation as Destination Therapy in the Post-REMATCH Era

Implications for Patient Selection

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Background—The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial first demonstrated that implantation of left ventricular assist devices (LVADs) as destination therapy (DT) can provide survival superior to any known medical treatment in patients with end-stage heart failure who are ineligible for transplantation. In the present study, we describe outcomes of DT in the post-REMATCH era in the United States.

Methods and Results—The present study included 280 patients who underwent HeartMate XVE LVAD implantation between November 2001 and December 2005. A preoperative risk score for in-hospital mortality after LVAD implantation was established in 222 patients with complete data. All patients were followed up until death or December 2006. The 1-year survival after LVAD implantation was 56%. The in-hospital mortality after LVAD surgery was 27%. The main causes of death included sepsis, right heart failure, and multiorgan failure. The most important determinants of in-hospital mortality were poor nutrition, hematological abnormalities, markers of end-organ or right ventricular dysfunction, and lack of inotropic support. Stratification of DT candidates into low (n=65), medium (n=111), high (n=28), and very high (n=18) risk on the basis of the risk score calculated from these predictors corresponded with 1-year survival rates of 81%, 62%, 28%, and 11%, respectively.

Conclusions—Appropriate selection of candidates and timing of LVAD implantation are critical for improved outcomes of DT. Patients with advanced heart failure who are referred for DT before major complications of heart failure develop have the best chance of achieving an excellent 1-year survival with LVAD therapy. (***Circulation*. 2007;116:&NA;-.)**

Key Words: heart-assist device ■ heart failure ■ risk factors

It is estimated that 250 000 patients in the United States are in the terminal phase of systolic heart failure and are suffering from severe symptoms that are refractory to maximized medical therapy.[1] To date, heart transplantation has provided the greatest survival benefit, but it is available to only a small fraction of these patients.[2]

Editorial p ●●●
Clinical Perspective p ●●●

The use of implantable left ventricular assist devices (LVADs) in patients with end-stage heart failure as a permanent alternative to heart transplantation, or destination therapy (DT), was first investigated in the landmark Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial.[3] The study randomized 129 patients with New York Heart Association class IV heart failure who were ineligible for transplantation to either mechanical circulatory support or medical therapy. Patients supported with LVAD had significantly improved 1-year survival, from 25% to 52%, providing >2-fold survival benefit over maximal medical therapy. Survival during the first 12 months after LVAD implantation, however, was hindered by high postoperative mortality, raising concerns whether increased operative risk in many DT recipients could minimize the potential benefit of this life-saving therapy and limit its expanded use.

In the present study, we analyzed outcomes of DT in 280 advanced heart failure patients in the United States who

Received January 25, 2007; revision received May 8, 2007.

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The online-only Data Supplement, consisting of an Appendix, is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.691972/DC1.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.107.691972**

underwent LVAD implantation after completion of the REMATCH trial and the US Food and Drug Administration (FDA) approval to use the modified HeartMate XVE LVAD for this indication in November 2002. The aim of the present study was 2-fold: to investigate the impact of the modified HeartMate XVE LVAD on outcomes of DT in the post-REMATCH era and to identify preoperative predictors of in-hospital mortality after pump implantation, which would help physicians to prospectively select DT candidates and to improve long-term success of LVAD therapy.

Methods

Study Population

Three hundred nine patients underwent LVAD implantation as DT in the United States between November 21, 2002, and December 1, 2005, at 66 hospitals after completion of the REMATCH trial and US FDA approval of the modified HeartMate XVE LVAD for this indication in November 2002.

Eligibility Criteria for Destination Therapy

All recipients of DT in the post-REMATCH era met the general criteria for LVAD implantation as published by the Centers for Medicare and Medicaid Services,[4] which were based largely on the criteria used for patient entry into the REMATCH trial,[3] including (1) New York Heart Association class IV symptoms for at least 60 days despite maximized oral therapy or requirement of inotropic support as outlined by the American Heart Association/American College of Cardiology guidelines for heart failure treatment,[5] (2) left ventricular ejection fraction (LVEF) ≤25%, (3) peak oxygen consumption of <12 mL · kg^{-1} · min^{-1} or documented inability to wean intravenous inotropic therapy, and (4) contraindication to heart transplantation because of either age >65 years or comorbidities such as insulin-dependent diabetes mellitus with end-organ damage or chronic renal failure.

Source of Data

Patient data were obtained from the US FDA–mandated DT Registry maintained by the HeartMate LVAD manufacturer, Thoratec Corp (Pleasanton, Calif), which collected information from participating US hospitals at the time of LVAD implantation, as well as adverse events and death. Causes of death were characterized by the attending physician. Autopsy results were not available.

Informed Consent for Data Analysis

Two hundred eighty patients consented to participate in the DT Registry. This accounts for 91% of 309 patients who underwent LVAD implantation in the post-REMATCH era. Patients gave written approval to include their clinical information in the DT Registry either before or after LVAD implantation at the discretion of the attending physician. The DT Registry was approved by the institutional board reviews of all 56 centers where the participating patients received treatment, as listed in the Appendix in the online Data Supplement. Among 29 patients who were not included in the present study, 6 died before consent was obtained, 12 did not receive local Institutional Review Board approval, and data for the remaining 9 patients were not provided to the DT Registry by the participating site.

Patient Follow-Up

All study patients were followed up until death, heart transplantation, reimplantation with pumps other than HeartMate XVE such as Novacor LVAD or axial flow devices (HeartMate II LVAD and DeBakey pump), or day of the last observation on October 1, 2006. The mean follow-up was 10.3 months (range, 1 day to 3.6 years). Patients were followed up for a total of 266.4 patient-years of observation.

Statistical Analysis

Descriptive Statistics

Differences between groups were examined with the χ^2 test. Continuous variables were compared by Student t test if normally distributed; if not, a Wilcoxon rank sum test was used.

Survival Analysis

Survival estimates were based on the Kaplan-Meier method and compared by log-rank statistics.[6] Patient survival was calculated from the day of LVAD implantation until death on mechanical support. In-hospital mortality after LVAD implantation was defined as death before discharge from implanting center to home, hospice, or rehabilitation facility. The durability of the first pump was calculated from the day of implantation until device failure requiring LVAD replacement or resulting in death. All survival analyses on LVAD support were censored at the time of heart transplantation, reimplantation with pumps other than HeartMate XVE, or day of the last observation on October 1, 2006.

Risk Score for In-Hospital Mortality After LVAD Implantation

In a subanalysis of 222 nonselected DT recipients with complete preoperative data, we calculated a risk score for in-hospital mortality after LVAD implantation. Fifty-eight patients were excluded from this subanalysis because of a lack of pertinent data, including serum albumin concentration and/or assessment of pulmonary artery pressures, which were important predictors of LVAD outcomes. Because the majority (79%) of in-hospital deaths occurred during the first 3 months after LVAD implantation, 90-day in-hospital mortality was chosen as the primary binary end point for logistic analysis. Risk factors that correlated with the end point by univariate analysis at a significance level of <0.15 were entered and allowed to stay in a stepwise multiple logistic regression model at a value of $P<0.05$.[7] Continuous variables analyzed in this series were divided into quartiles because they did not linearly correlate with the end point. The cutoff values for continuous variables were selected from the highest quartile, median, or lowest quartile, depending on the cutoff value that by univariate analysis correlated with the end point at a significance level of $P<0.05$. Each variable entered into the multivariable model was assigned a weighted risk score rounded to the nearest integer of the odds ratio. The sum of weighted risk scores was then calculated for each patient.

The goodness-of-fit of the logistic regression model from which the risk score was derived was measured in terms of its discrimination and calibration. Classification system discrimination, which captures the ability of the model to distinguish between patients who die in the hospital and patients who are discharged alive, was assessed by use of the area under the receiver-operating characteristic curve.[8] Calibration, which measures the ability of the model to predict survival for various levels of patient risk, was tested with the Hosmer-Lemeshow[9] statistic. Because of the relatively limited number of patients in the final multivariable model, risk score validation was not performed.

The following clinical data were analyzed: patient demographics; body surface area; cause of heart failure; history of cardiovascular disease (hypertension, coronary artery disease, myocardial infarction, percutaneous revascularizations, previous cardiac surgeries, coronary artery bypass surgery, supraventricular or ventricular arrhythmias, aortic insufficiency); history of comorbidities (diabetes, malignancy, and renal, lung, or thyroid disease); medical and device therapy for heart failure (intravenous inotropes, angiotensin-converting enzyme inhibitors, β-blockers, digoxin, vasodilators, diuretics, resynchronization therapy with biventricular pacing); measures of hemodynamic severity of heart failure (LVEF, blood pressure, right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output and index, pulmonary vascular resistance and index, and systemic vascular resistance and index); laboratory data (white blood count, hematocrit, platelet count, serum sodium concentration, blood urea nitrogen, serum creatinine concentration, total bilirubin concentration, alanine and aspartate aminotransferase activity, albumin concentration, and in-

TABLE 1. Baseline Patient Characteristics

Patient Characteristics	
Age, y*	60.7±12
Male, %	82%
Body mass index, kg/m^2*	29.5±7
Ischemic cause of heart failure, %*	65%
LVEF, %*	17.6±6
Blood pressure, mm Hg*	
Systolic	103.3±17
Diastolic	60.9±10
Pulmonary capillary wedge pressure, mm Hg‡	23.5±8.9
Cardiac index, L · min^{-1} · m^{-2}*	2.07±0.7
Pulmonary vascular resistance, dynes · s^{-1} · cm^{-5}‡	233±158
Serum sodium, mmol/L*	135±5
Serum creatinine, mg/dL	1.7±0.7
Estimated glomerular filtration rate, mL · min^{-1} · 1.73 m^{-2}	51.1±22
Serum albumin, g/dL†	3.3±0.6
Concomitant medications, %	
Digoxin	59
Diuretics	91
ACE inhibitors or A-II antagonists	62
β-Blockers	49
Vasodilators	30
Antiarrhythmics	45
Intravenous inotropic agents	70
NYHA class	IV

Values are mean±SD when appropriate. ACE indicates angiotensin-converting enzyme; A-II, angiotensin II receptor; and NYHA, New York Heart Association.

*Data are missing for <5% of patients.

†Data are missing for 15% of patients.

‡Data are missing for 23% of patients.

ternational normalization ratio); year of implantation (2002 through 2005); and center experience, defined as the number of DT implantations performed at the time of LVAD surgery. Because of the high prevalence of older and morbidly obese patients in the studied cohort, in addition to the estimated glomerular filtration rate obtained with the Modification of Diet in Renal Disease equation,[10] we estimated creatinine clearance from the Salazar-Corcoran equation, which has been shown to better estimate renal function in obese patients.[11] All data were analyzed with the SAS System software version 9.0 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Patient Characteristics

The demographic characteristics of DT recipients in the post-REMATCH era are listed in Table 1. Most patients were white men >60 years with ischemic cardiomyopathy. All patients had New York Heart Association class IV symptoms and hemodynamic parameters consistent with severe heart failure, as evidenced by mean LVEF of 17.6±6%, systolic blood pressure of 103.3±17 mm Hg, and cardiac index of 2.07±0.7 L · min^{-1} · m^{-2}. Seventy percent required inotropic support at the time of LVAD implantation. Cardiopulmonary exercise testing was performed in only 18.6% of patients because most patients were too sick to undergo exercise testing. All patients had at least one contraindication to heart transplantation, including advanced age, pulmonary hypertension, renal insufficiency, diabetes mellitus with end-organ damage, active malignancy, and morbid obesity.

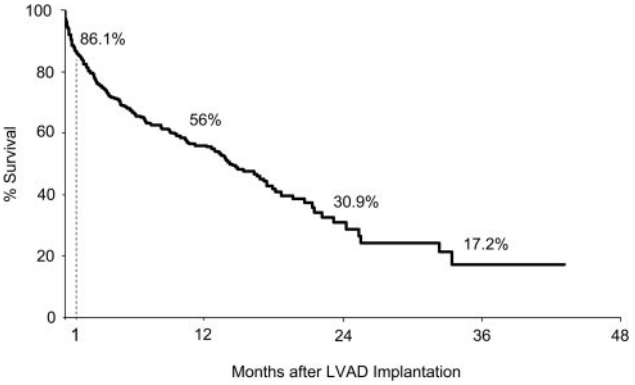

Figure 1. Survival after LVAD implantation as DT in the post-REMATCH era.

Patient Survival

The overall survival on LVAD support was 86.1%, 56.0%, and 30.9% at 30 days, 1 year, and 2 years after LVAD implantation, respectively, as shown in Figure 1. A total of 155 of 280 patients (55%) died during the mean support time of 10.4 months (range, 1 day to 3.6 years).

Survival to Hospital Discharge

Seventy-six patients died before hospital discharge after LVAD implantation (27.1% in-hospital mortality). In-hospital deaths accounted for two thirds of all deaths (76 of

TABLE 2. Causes of Death After LVAD Implantation as DT

	Total Deaths (n=155)	In-Hospital Deaths (n=76)
Sepsis	46 (29.5)	25 (32.9)
Multiorgan failure	20 (12.8)	15 (19.7)
Stroke	14 (9.0)	2 (2.6)
Right heart failure	12 (8.4)	11 (14.5)
LVAD failure	10 (6.4)	4 (5.2)
Respiratory failure	7 (4.5)	5 (6.6)
Technical	5 (3.2)	4 (5.3)
Hemorrhage	5 (3.2)	2 (2.6)
Cancer	4 (2.6)	1 (1.3)
Arrhythmia	4 (2.6)	1 (1.3)
Accident	3 (1.9)	0
Pulmonary embolism	2 (1.3)	1 (1.3)
Sudden death	2 (1.3)	0
Left ventricular failure	2 (1.3)	0
Other causes	12 (7.7)	4 (5.2)
Not reported	7 (4.5)	1 (1.3)

Values are expressed as n (%).

TABLE 3. Univariate Analysis for Risk Factors for 90-Day In-Hospital Mortality After LVAD Implantation as DT (n=222)*

Patient Characteristics	Odds Ratio (CI)	*P*
Platelet count $\leq 148\times10^3/\mu$L§	7.2 (3.5 to 14.6)	<0.001
International normalization ratio >1.1§	5.0 (1.7 to 14.7)	0.001
Serum albumin ≤3.3 g/dL†	3.8 (1.8 to 8.0)	<0.001
Aspartate aminotransferase >45 U/mL†	3.8 (1.9 to 7.6)	<0.001
Ventilatory support	3.7 (1.3 to 10.9)	0.01
Hematocrit ≤34%‡	3.4 (1.6 to 7.0)	<0.001
Serum creatinine clearance ≤41 mL/min§	3.0 (1.5 to 5.9)	0.002
Age 64 to 70 y	2.8 (1.4 to 5.5)	0.003
Serum creatinine >2.1 mg/dL,†	2.7 (1.3 to 5.6)	0.006
Total bilirubin >1.8 mg/dL†	2.7 (1.3 to 5.4)	0.006
Alanine aminotransferase >52 U/mL†	2.6 (1.3 to 5.2)	0.008
Body surface area ≤1.9 m^2§	2.5 (1.3 to 4.9)	0.006
Blood urea nitrogen >51 U/dL†	2.4 (1.2 to 4.8)	0.01
Mean pulmonary artery pressure ≤25 mm Hg§	2.3 (1.2 to 4.7)	0.02
Glomerular filtration rate ≤34 mL · min^{-1} · 1.73 m^{-2}§	2.1 (1.0 to 4.2)	0.002
White blood count $>10.5\times10^3/\mu$L†	1.9 (0.9 to 2.8)	0.08
Digoxin	1.8 (0.9 to 3.5)	0.07
No intravenous inotropes	1.7 (0.9 to 3.5)	0.11
Diastolic pulmonary artery pressure ≤19 mm Hg§	1.7 (0.9 to 3.5)	0.10
Vasodilator therapy	1.6 (0.8 to 3.2)	0.14
Year of implantation, 2005 vs 2002 to 2004	0.5 (0.2 to 1.0)	0.06

*Glomerular filtration rate was calculated with the Modification of Diet in Renal Disease equation[7]; serum creatinine clearance, with the Salazary-Corcoran equation.[8,9]

The cutoff values for continuous variable used in the univariate analysis was selected either from the †highest quartile, ‡median, or §lowest quartile, depending on the value that correlated at significance level of $P<0.05$ with the end point.

118) in the first year after LVAD implantation. Seventy-nine percent of in-hospital deaths (60 of 76) occurred within 3 months after LVAD placement (range, 1 day to 10.6 months). Among surviving patients, 200 DT recipients (71%) lived to hospital discharge to home or a nursing facility, 3 patients were transplanted before hospital discharge, and 1 patient was still hospitalized at the time of study closure (median discharge time, 36 days; range, 8 days to 12 months).

Causes of Death

Among 76 patients who died before hospital discharge, the main causes of death included sepsis, multiorgan failure, and right heart failure. These were also the leading causes of overall mortality in this population (Table 2). LVAD failure accounted for 10 deaths (6%). Two patients died of heart failure.

LVAD Durability

The median time of LVAD support on the first pump was 18.6 months (range, 1 day to 3.6 years). During the follow-up period, 69 patients (24.6%) either required LVAD replacement because of device end of life or died as a result of pump failure or complications. The probability of device exchange or fatal device failure was 17.9% and 72.9% at 1 and 2 years, respectively.

Change of Transplant Eligibility Criteria

Forty-seven DT recipients (17%) underwent heart transplantation after a mean mechanical support time of 10.2 months (range, 1.8 to 28.4 months). Change in transplant eligibility criteria was due to reversal of pulmonary hypertension (n=12), recovery of renal function (n=4), 5-year cancer-free survival (n=5), weight loss (n=3), infection (n=4), and other (n=16).

Risk Score for In-Hospital Mortality After LVAD Implantation

Risk Factors

The results of univariate and multivariable analyses are shown in Tables 3 and 4, respectively. The following predictors of 90-day in-hospital mortality after LVAD implantation were identified by multivariable analysis: platelet count $\leq 148\times10^3/\mu$L, serum albumin ≤3.3 g/dL, international normalization ratio >1.1, vasodilator therapy at time of implantation, mean pulmonary artery pressure ≤25.3 mm Hg, aspartate aminotransferase >45 U/dL, hematocrit ≤34%, blood urea nitrogen >51 U/dL, and lack of intravenous inotropic support. Because of redundancy of serum creatinine and serum creatinine clearance with blood urea nitrogen, these variables were not entered into the multivariable model. Patient age range of 64 to 70 years was removed from the

TABLE 4. Multivariable Analysis of Risk Factors for 90-Day In-Hospital Mortality After LVAD as DT (n=222)

Patient Characteristics	Odds Ratio (CI)	*P*	Weighted Risk Score
Platelet count $\leq 148\times10^3/\mu L$	7.7 (3.0 to 19.4)	<0.001	7
Serum albumin ≤3.3 g/dL	5.7 (1.7 to 13.1)	<0.001	5
International normalization ratio >1.1	5.4 (1.4 to 21.8)	0.01	4
Vasodilator therapy	5.2 (1.9 to 14.0)	0.008	4
Mean pulmonary artery pressures ≤25 mm Hg	4.1 (1.5 to 11.2)	0.009	3
Aspartate aminotransferase >45 U/mL	2.6 (1.0 to 6.9)	0.002	2
Hematocrit ≤34 %	3.0 (1.1 to 7.6)	0.02	2
Blood urea nitrogen >51 U/dL	2.9 (1.1 to 8.0)	0.03	2
No intravenous inotropes	2.9 (1.1 to 7.7)	0.03	2

final model because of correlation with other predictors in the model. A subsequent multicollinearity analysis revealed a maximal variance inflation factor of 1.14 with a mean variance inflation factor of 1.09. Hence, the final parameter estimates were not unduly influenced by collinearity between predictors.

Risk Score

Each of the 9 variables entered into the multivariable model was assigned a weighted risk score, as shown in Table 4. The cumulative risk score was calculated for each patient and ranged from 0 to 27 in this database. The risk score demonstrated good discrimination C statistic (C-statistic value, 0.89; sensitivity, 82.6%; and specificity, 80.0% at $P=0.24$) and good calibration by the Hosmer-Lemeshow statistic (χ^2 value, 4.5; $P=0.81$).

Operative Risk Categories

The probability of 90-day in-hospital mortality, including predicted and observed 90-day in-hospital mortality after LVAD implantation, was calculated for each of the deciles of the cumulative risk score in Table 5. Patients were divided into 4 operative risk categories based on the probability of 90-day in-hospital mortality: low (probability <0.10; n=65), medium (probability, 0.01 to 0.50; n=111), high (probability, 0.50 to 0.70; n=28), and very high (probability >0.70; n=18) risk. The corresponding predicted and observed 90-day mortality rates for each of the 4 operative categories are shown in Table 6. The observed survival to hospital discharge in low-, medium-, high-, and very high-risk operative candidates was 87.5%, 70.5%, 26%, and 13.7%, and 1-year survival was 81.2%, 62.4%, 27.8%, and 10.7%, as illustrated in Table 6 and Figure 2. The survival of 176 lower-risk candidates (median- and low-risk category, 79% of the studied 222 patients) was 69% and 40% at 1 and 2 years compared with the survival rates of 46 higher-risk candidates (high- and very high-risk category, 21% of the studied 222 patients), which were 13% and 13% at 1 and 2 years, respectively ($P<0.001$).

Characteristics of Lower- Versus Higher-Risk Candidates

The preoperative characteristics of low-risk (low and medium operative risk) and high-risk (high and very high operative risk) DT candidates are shown in Table 7. The cause and severity of heart failure were similar between the 2 groups, as

TABLE 5. Operative Risk Categories With Corresponding Cumulative Risk Score for 90-Day In-Hospital Mortality after LVAD Implantation as DT and Survival to Hospital Discharge and 1-Year Survival Depicted by Deciles of Cumulative Risk Score*

			In-Hospital Mortality Within 90 Days		
Operative Risk Categories	Risk Score	No.	Observed	Predicted	% Probability (CI)
Low	0 to 4	19	0	0.2	0.2 (0.03 to 1.2)
	5 to 6	22	1	0.4	0.4 (0.1 to 2.1)
	7 to 8	24	1	0.4	0.9 (0.3 to 3.5)
Medium to high	9	19	0	0.7	2.1 (0.7 to 6.0)
	10	17	1	0.9	4.5 (1.9 to 10.1)
	11 to 12	28	1	1.6	9.4 (5.1 to 16.7)
	13 to 14	19	3	2.9	18.5 (12.2 to 27.0)
	15 to 16	28	3	5.0	33.1 (24.8 to 42.7)
	17 to 19	18	11	10.1	52.0 (40.6 to 63.2)
Very high	>19	28	25	23.7	70.3 (56.2 to 81.4)

*Analysis was limited to 208 patients with available measures of pulmonary artery pressure and serum albumin level.

TABLE 6. Operative Risk Categories With Corresponding Cumulative Risk Score for 90-Day In-Hospital Mortality After LVAD Implantation as DT and Survival to Hospital Discharge and 1-Year Survival Depicted by the Operative Risk Categories*

			In-Hospital Mortality Within 90 Days			Survival, %		
Operative Risk Categories	Risk Score	No.	Observed, n	Predicted, n	% Probability (CI)	To Discharge, %	90 d	1 y
Low	0 to 8	65	2	1.6	2 (1.1 to 5.4)	87.5	93.7	81.2
Medium	9 to 16	111	12	13.7	12 (8.0 to 18.5)	70.5	86.5	62.4
High	17 to 19	28	10	7.9	44 (32.8 to 55.9)	26	38.9	27.8
Very High	>19	18	22	22.8	81 (66.0 to 90.9)	13.7	17.9	10.7

* Analysis limited to 208 patients with available measures of pulmonary artery pressure and serum albumin level.

evidenced by the percentage of LVEF, serum sodium concentration, and hemodynamics. Higher-risk patients were less often supported with intravenous inotropes and were more frequently treated with digoxin and antiarrhythmic agents. Risk factors that defined the higher-risk category were more common among higher-risk patients such as the markers of liver and renal dysfunction, hematological and coagulation abnormalities, and lower serum albumin level.

Discussion

Three hundred nine patients underwent LVAD implantation as an alternative to heart transplantation, or destination therapy (DT), since the completion of the landmark REMATCH trial, which first demonstrated the superiority of mechanical circulatory support over medical therapy for end-stage heart failure in patients who were not eligible for heart transplantation.[3] In this series, we analyzed outcomes of 280 of these patients who had institution approval for use of the clinical data.

The 1- and 2-year survival rates after LVAD implantation in the post-REMATCH era were 56% and 33%, respectively. In addition, as many as 17% of DT recipients were able to undergo heart transplantation after their relative contraindications improved on mechanical support. Although the long-term survival has not substantially improved since the REMATCH trial (reported 1- and 2-year survival rates, 52% and 23%, respectively),[3] the benefit of LVAD implantation continued to markedly exceed the 1- and 2-year survival rates of 25% and 8% reported in the medical arm of the REMATCH trial.[3]

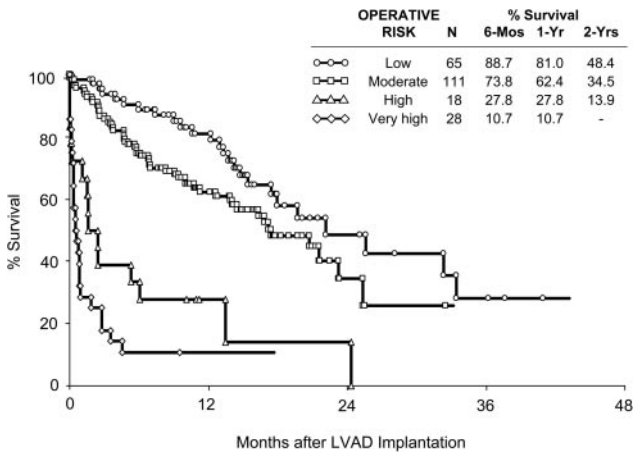

Figure 2. Survival after LVAD implantation as DT by the candidate's operative risk.

Despite several modifications of the HeartMate XVE design, improved safety and reliability of the new device,[12] and growing overall experience with mechanical support,[13] the 1-year outcomes of LVAD therapy continued to be hindered by high rates of serious postoperative complications. Sepsis, right heart failure, and multiorgan failure were the main causes of postoperative death and were the main contributors to the relatively high in-hospital mortality (26.8%) after device implantation. The vast majority of these deaths occurred within the first 3 months after LVAD surgery. Because these complications were unrelated to device malfunction, this finding suggests that selection of candidates and timing of LVAD implantation are the most likely determinants of the operative success.

The tremendous impact of patient selection on the outcomes of LVAD surgery has been recognized since the first devices were used as a "bridge" to transplantation. Regardless of the type of device, implantations performed in patients with severe functional impairment, end-organ dysfunction and right ventricular failure, malnutrition, or infection had been consistently associated with adverse outcomes.[14–18] Although no one variable may predict survival, nearly every composite risk score describing clinical status and severity of multiorgan impairment, including classic risk scores used in critically ill patients such as the APACHE (Acute Physiology and Chronic Health Evaluation) score, closely correlated with outcomes of LVAD surgery.[18]

In a subanalysis of 222 patients in the post-REMATCH era with available preoperative data, we reconfirmed many of the risk factors that had been previously described to adversely affect operative outcomes of LVAD implantation as a "bridge" to transplantation. We found that regardless of recipient age, hemodynamic severity of left ventricular failure, era of implantation, and center experience, candidates for DT with severe deterioration of general medical condition, as evidenced by poor nutritional status with low serum albumin level, impaired renal function, markers of right heart failure such as low pulmonary artery pressures, or congestive elevation of liver enzymes, were at the highest risk of in-hospital mortality after LVAD surgery. Probable infection, as evidenced by leukocytosis, and coagulation abnormalities such as declining platelet count or prolonged international normalized ratio, anemia, and small body size further worsened the chance of operative survival.

TABLE 7. Characteristics of Low-Risk (Low or Medium Operative Risk Category) and High-Risk (High or Very High Operative Risk Category) Candidates for DT (n=208)

Patient Characteristics	High-Risk DT Candidates (n=46)	Low-Risk DT Candidates (n=176)	*P*
Age, y	63.4±12	60.0±13	0.09
Male, %	15%	14%	0.78
Body surface area, m^2	2.0±0.3	2.1±0.3	0.09
Ischemic cause of heart failure, %	70%	64%	0.43
LVEF, %	17.9±7	17.6±6	0.83
Systolic blood pressure, mm Hg	102.1±15	104.4±17	0.41
Pulmonary capillary wedge pressure, mm Hg	22.6±8	23.6±9	0.58
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.10±0.7	2.08±0.7	0.76
Mean pulmonary artery pressure, mm Hg	32.4±11	34.8±11	0.61
Pulmonary vascular resistance, dynes $\cdot s^{-1} \cdot cm^{-5}$	264±189	230±152	0.30
Systemic vascular resistance, dynes $\cdot s^{-1} \cdot cm^{-5}$	2000±908	1967±720	0.32
Serum sodium, mmol/L	135±6	135±5	0.92
Blood urea nitrogen >51 U/dL, %*	43	20	0.001
Serum creatinine >2.1 mg/dL, %*	46	14	<0.001
Glomerular filtration rate ≤34 mL $\cdot min^{-1} \cdot 1.73\ m^{-2}$, %*	54	17	<0.001
Serum albumin concentration ≤3.3 g/dL, %†	80	44	<0.001
Alanine aminotransferase >52 U/mL, %*	40	20	0.02
Aspartate aminotransferase >45 U/mL, %*	48	18	<0.001
Total bilirubin >1.8 mg/dL, %*	43	18	<0.001
Hematocrit ≤34%, %†	78	44	<0.001
White blood count $>10.5\times10^3/\mu L$, %*	28	24	0.54
International normalization ratio >1.1, %*	37	20	0.01
Platelet count $\leq148\times10^3/\mu L$, %*	80	11	<0.001
Concomitant medications, %			
Digoxin	50	65	0.07
Diuretics	87	93	0.22
ACE inhibitors or A-II antagonists	54	63	0.28
β-Blockers	48	49	0.90
Vasodilators	39	31	0.28
Antiarrhythmics	56	45	0.16
Intravenous inotropic agents	59	76	0.02
LVADs placed as DT at given center at time of LVAD implantation, n	7.9±8	8.5±8	0.64
Era of implantation, 2005 vs 2002-2005, %	30	43	0.12

Values are mean±SD when appropriate. ACE indicates angiotensin-converting enzyme; A-II, angiotensin II receptor. Cutoff values for continuous variables were derived from *quartiles or †medians as described in Methods.

The cumulative risk score, calculated for each patient from hazard ratios of the most significant of the above predictors for in-hospital mortality after LVAD surgery, closely correlated with long-term outcomes of DT. An example of this is shown in Figure 2, in which the 1-year survival after DT depicted by the cumulative risk for in-hospital mortality after LVAD surgery ranged from >81% in the lowest-risk candidates to imminent postoperative death and only 11% 1-year survival in the highest-risk candidates.

It is important to note that the hemodynamic severity of heart failure as assessed by blood pressure, LVEF, cardiac index, or pulmonary capillary wedge pressure did not correlate with the risk of LVAD surgery. Intolerance of angiotensin-converting enzyme inhibitors or β-blockers despite nearly significant association did not enter either the univariate or multivariable model (data not shown). Because the operative risk is determined primarily by the presence of comorbidities, it may be important to address correctable factors that may lead to postoperative complications such as coagulation abnormalities- (low platelet count, international normalized ratio, anemia), active infection, or poor nutrition. Thus, the initially high operative risk should not dissuade physicians from considering LVAD therapy because these patients may become acceptable candidates with intensive medical treatment.

The severity of left ventricular failure in patients referred for DT in the post-REMATCH era described in the present

study was nearly identical to that in patients enrolled in the REMATCH trial, historically considered to be the sickest heart failure patients ever studied. Thus, in the post-REMATCH era, nearly one fifth of the studied patients demonstrated high operative risk at the time of device implantation associated with only 18% survival rate to hospital discharge and 11% 1-year survival. With the patients with predicted futile outcomes excluded, the vast majority of DT candidates (79% of cohort) were able to achieve 1- and 2-year survival rates of 69% and 40%, respectively.

Because DT is intended to be an elective surgical treatment and the progression of heart failure and comorbidities inevitably leads to deterioration of the patient's condition, defining the time when the survival benefit of LVAD implantation would be the greatest and risk of surgery would be the lowest is of paramount importance. It is clear from the post hoc analysis of the REMATCH trial[19] and experience with patients bridged with LVAD to transplantation[20] that the sickest heart failure patients requiring inotropic support would derive the greatest survival benefit from device therapy (49% versus 24% 1-year survival on LVAD support versus optimal medical therapy; $P<0.001$[19]). Results of the present study indicate, however, that deferring implantations until patients progress to biventricular and end-organ failure may significantly increase the risk of adverse operative outcomes. In this regard, risk scores such as the Seattle Heart Failure model, which has recently been reported in patients with less severe heart failure, may aid physicians in estimating the time of referral in the future.[21] It remains unproven, however, whether LVAD implantation in patients with less severe heart failure would surpass outcomes achievable with optimal medical therapy.

Study Limitations

It is important to note that because of the relatively small sample of analyzed DT recipients and small number of events, the risk score for in-hospital mortality after LVAD implantation demonstrated wide CIs, thus suggesting limited precision of the model. Additionally, because of the small size of the studied cohort, many potentially important risk factors for adverse outcomes of LVAD surgery did not enter into the multivariable analysis model. Prospective studies in much larger cohorts of patients that would include relevant preoperative information in all patients (such as nutritional state or estimates of right ventricular function) are needed to validate the presented risk score. The presented risk score may not apply to the new generation of axial flow pumps, which are much smaller than the HeartMate pusher-plate pumps and require more intensive perioperative anticoagulation. In addition, analyses that take into account LVAD-related morbidity and quality of life are necessary.

Results of the present study should be interpreted with caution because they were based on a retrospective analysis of the registry database, which carries limitations associated with the quality of the source data. Information on how many of the studied patients received DT as "bridge to decision" and were listed for heart transplantation after their condition improved on mechanical support or died before being evaluated for transplant was not available. The main causes of death were not adjudicated, and it is possible that these conditions could have coexisted in patients who were assigned sepsis, multiorgan failure, or right heart failure as the primary cause of death. The reported preoperative hemodynamics reflect the most recent measures before LVAD implantation, and the exact time when these were obtained may vary between centers. Because of the high prevalence of obese patients in the present study, the degree of renal dysfunction and its impact on the operative risk may be underestimated in this series.

Conclusions

The vast majority of patients treated with DT are able to achieve an excellent 69% 1-year survival. Patient selection, however, is critical to successful operative outcomes. Because worsening of the general medical condition and development of end-organ or biventricular failure can increase the operative risk or even render the LVAD surgery futile, advanced heart failure patients should be referred to LVAD centers earlier in the disease course. High operative risk should not dissuade physicians from considering patients for DT because it may be potentially reduced with intensive medical treatment. Patients who require inotropic support appear to derive the greatest benefit from mechanical circulatory support. It remains to be investigated, however, whether LVAD implantation in less severely ill patients, particularly those not requiring intravenous inotropes, provides justifiable survival benefit over medical treatment.

Acknowledgments

The authors would like to thank the Thoratec Corp (Pleasanton, Calif), particularly David Farrar and Jerry Heatley, for coordinating data collection from participating centers; Tyson B. Rogers from the Department of Medicine at the University of Minnesota for statistical assistance and critical review of the manuscript; the site coordinators for their support during the study; and all the patients and participants in the study for their interest and cooperation.

Disclosures

None.

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CLINICAL PERSPECTIVE

The use of implantable left ventricular assist devices (LVADs) in patients with end-stage heart failure as a permanent alternative to heart transplantation, or destination therapy, was first investigated in the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial, which showed significant superiority of mechanical circulatory support over maximal medical therapy. In the present study, we show sustained improvement of survival in 280 destination therapy recipients who underwent LVAD implantation after completion of the REMATCH trial and the US Food and Drug Administration approval to use the modified HeartMate XVE LVAD for this indication in November 2002. Because destination therapy is intended to be an elective surgical treatment and the progression of heart failure and comorbidities inevitably leads to deterioration of the patient's condition, defining the time when the survival benefit of LVAD implantation would be the greatest and the risk of surgery would be the lowest appears of paramount importance to the future wide application of this technology. The present study presents an operative risk score for in-hospital mortality after pump implantation. This score may help clinicians prospectively identify candidates for destination therapy and further improve long-term success of LVAD therapy.