Improving outcomes with long-term “destination” therapy using left ventricular assist devices

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Objective: Destination therapy experience using long-term left ventricular assist devices was analyzed relative to the benchmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial to evaluate the potential for improving outcomes with this groundbreaking therapy for advanced heart failure.

Methods: The largest single-center experience with destination therapy in the United States (Utah Artificial Heart Program, LDS Hospital, Salt Lake City, UT) was retrospectively analyzed. All destination therapy recipients ($n = 23$) presented with chronic, advanced heart failure, meeting indications for destination therapy adopted from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial. All received HeartMate left ventricular assist devices (Thoratec Corp, Pleasanton, Calif), with 87% receiving an improved XVE model. Advanced practice guidelines were implemented using a multidisciplinary approach. Survivals (Kaplan–Meier, log-rank analyses) and adverse events (Poisson regression) were compared with those of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure left ventricular assist device group ($n = 68$).

Results: Survival in the destination therapy group was significantly increased ($P = .007$), with an overall reduction in mortality of 66%. The 2-year survival was 77% for destination therapy compared with 29% for the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure left ventricular assist device group ($P < .0001$). The 1-year survival was 77% for destination therapy compared with the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure left ventricular assist device rate of 52% ($P = .036$). Adverse events decreased by 38% (3.90 per patient-year in the destination therapy group compared with the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure left ventricular assist device rate of 6.32). Factors related to severity of illness met Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure-like criteria for both groups.

Conclusions: This analysis provides evidence that long-term destination therapy can be improved well beyond the pioneering experience of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial. With continued evolution of devices, management, and patient selection, outcomes approaching those of heart transplantation may be possible.

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Heart failure has become a major public health concern, with an incidence of 4.9 million cases in the United States and 550,000 new cases every year.¹ Heart failure is generally progressive, ultimately reaching an advanced end stage requiring organ replacement or substitution. Heart transplantation is a standard of care, but the availability of donor hearts has leveled at 2100 per year,¹ which is well short of projected needs.

Mechanical circulatory support (MCS) offers hope for the treatment of advanced heart failure. MCS has been used successfully over short to medium-term durations of support for bridging to heart transplantation.^{2,3} As favorable outcomes have been observed over progressively longer durations of support with left ventricular assist devices (LVADs), interest has grown in using these devices for the long-term treatment of heart failure.⁴

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial evaluated the efficacy and safety of long-term support with the HeartMate VE LVAD (Thoratec Corp, Pleasanton, Calif) compared with optimal medical management (OMM) in patients with advanced, chronic heart failure New York Heart Association class IV who were unable to undergo transplantation.

Evidence of superior survival with acceptable safety and quality of life led to the first Food and Drug Administration approval in 2002 of LVADs for long-term destination therapy (DT) with the HeartMate models VE and XVE. The evidence has been compelling enough to justify reimbursement from payers, including the Centers for Medicare and Medicaid Services.

The initial report of the REMATCH trial results identified a significant survival benefit of LVAD therapy compared with OMM.⁵ Survivorship at 1 year of 52% in the LVAD arm compared favorably with 25% in the OMM group. At 2 years, survival was 23% with an LVAD, whereas survival was only 8% with OMM. Overall, there was a 48% reduction in the risk of death from any cause in the LVAD arm compared with the OMM group. In addition, quality of life was better with an LVAD than OMM.

Despite the remarkable impact on survival, the greatest of any heart failure therapy previously studied, LVAD therapy during REMATCH was associated with considerable mortality and morbidity. This is not too surprising given the pioneering initiatives with a new therapy in a high-risk patient population. Nevertheless, for DT with LVADs to succeed, improvements will be necessary with (1) devices, (2) patient management, and (3) patient selection.

The overall experience with DT since the REMATCH trial remains modest. Only a few centers have individual experience beyond 10 patients. To date, there has been only 1 publication reporting DT outcomes outside of the REMATCH trial.⁶ Given the complexities of this therapy with a significant learning curve, information about performance is vital for improvement and responsible dissemination.

Abbreviations and Acronyms

CVA	= cerebrovascular accident
DT	= destination therapy
LVAD	= left ventricular assist device
OMM	= optimal medical management
MCS	= mechanical circulatory support
REMATCH	= Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
VO ₂ max	= maximum oxygen consumption

This study was conducted to evaluate DT outcomes within the largest single-center experience to date to better understand the potential for improving outcomes with this evolving therapy for advanced heart failure.

Materials and Methods

Patient Selection

Patients receiving DT from the Utah Artificial Heart Program at LDS Hospital, Salt Lake City, Utah (LDSH DT cohort) were studied and compared with LVAD recipients from the REMATCH trial. The REMATCH cohort consisted of the 68 patients from the LVAD arm of the REMATCH trial with 89 patient-years of experience. The LDSH DT cohort consisted of all patients in the DT LVAD group not randomized to the LVAD arm of the REMATCH trial and receiving an implant before March 14, 2005: a total of 23 patients with 26.8 patient-years of experience.

The selection of patients receiving DT incorporated REMATCH trial enrollment criteria,⁷ Food and Drug Administration-approved indications, and Centers for Medicare and Medicaid Services qualifications.⁸ Inclusion criteria included (1) New York Heart Association class IV end-stage heart failure during the last 3 months despite OMM, (2) maximum oxygen consumption (VO₂ max) of less than 12 mL/kg⁻¹/min⁻¹ (reduced from REMATCH criteria of 14 mL/kg⁻¹/min⁻¹) or dependence on intravenous inotropes, and (3) left ventricular ejection fraction less than 25%. Exclusion criteria included (1) eligibility for heart transplantation; (2) the presence of comorbid factors, other than those due to heart failure, precluding survival of at least 2 years; and (3) body size too small for the HeartMate VE or XVE LVAD (body surface area < 1.6 m²).

All patients who were in the LDSH DT cohort fit REMATCH qualifications with the exception of 1 patient who would have been excluded from the REMATCH trial by the presence of chronic renal failure requiring dialysis.

Patients from LDSH who were randomized to the LVAD arm of the REMATCH trial remained a part of the REMATCH cohort and were not included in the LDSH DT group.

Appropriate institutional review board approvals were obtained.

Management

DT recipients were guided through the complex management process characteristic of DT in this era by a multidisciplinary team located both at LDSH and in remote locations where the patients lived.

Candidacy was established after conducting reviews from multiple perspectives in consideration of surgical issues, heart failure/

TABLE 1. Baseline characteristics

	REMATCH (n = 68)	LDSH DT (n = 23)	P value
General			
Age (y)	66 ± 9.1	68 ± 8.7	.4360
Male sex (%)	78%	91%	.2204
Heart failure			
Ischemic cause (%)	78%	87%	.5456
NYHA class (IV/IIIb)	66/2	23/0	1.0000
VO ₂ max (mL/kg/min), as obtainable	9.1 ± 2.0 (n = 37)	10.6 ± 1.4 (n = 13)	.0163*
LVEF (%EF)	17 ± 5.2	19 ± 4.4	.4102
Medications			
Digoxin (%)	87%	57%	.0056*
Loop diuretics (%)	96%	91%	.5972
Spironolactone (%)	34%	43%	.4566
ACE inhibitors (%)	62%	39%	.0881
A-II antagonists (%)	10%	22%	.1710
Amiodarone (%)	45%	30%	.2305
Beta-blockers (%)	24%	22%	1.0000
Organ function			
Serum creatinine (mmol/L)	1.7 ± 0.65	1.9 ± 1.2	.3153
Serum sodium (mmol/L)	135 ± 5.4	139 ± 5.8	.0079*
Hemodynamic status			
Systolic BP (mm Hg)	101 ± 15	108 ± 10	.0533
Diastolic BP (mm Hg)	61 ± 10	61 ± 9	1.0000
PCWP (mm Hg)	25 ± 9.9	20 ± 7.8	.0196*
CI (L*min ⁻¹ *m ⁻²)	1.9 ± 0.99	2.2 ± 0.51	.1684
Heart rate (beats/min)	84 ± 16	81 ± 13	.4170
PVR (Wood Units)	3.4 ± 1.8	3.2 ± 1.6	.6382
IABP (%)	10%	13%	1.0000
IV inotropes (%)	65%	61%	.8041

Values are listed as mean ± standard deviation or as indicated. LDSH DT, LDS Hospital destination therapy group; ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BP, blood pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; VO₂ max, maximum oxygen consumption; IABP, intraaortic balloon pump; EF, ejection fraction; IV, intravenous.

*Statistical significance.

transplant/diagnostic cardiology issues, critical care challenges, medical reserve, physical capacity/conditioning, cognitive capacity, psychosocial support, and factors affecting long-term outpatient support.

Preoperative optimization of the patient was undertaken (with medical therapy, critical care support, and monitoring or intraaortic balloon pump use) when it was possible to do so without introducing additional risk of further decline.

HeartMate LVADs (Thoratec Corp) were used in all patients. Twenty patients (87%) received the improved XVE, and 3 early patients (13%) received the VE.

Field-wide standards of care and guidelines for clinical practice were incorporated whenever available. This included *Infection Control Guidelines* (REMATCH Surgical Committee, available from Thoratec) and *Advanced Practice Guidelines for HeartMate Destination Therapy* (Heart Hope Initiative, Park City Work Group, and Thoratec Corporation).

Analysis

Unpaired *t* tests were used to examine continuous data. Fisher exact tests were performed on discrete data. Probability was

2-tailed in both cases. Survival was analyzed by using the Kaplan–Meier product limit method. Log-rank analysis was used to determine differences in survival distributions. Impact on mortality was analyzed using a Cox proportional hazard model. Poisson regression with 95% confidence intervals was used to analyze adverse event rates.

Definitions for adverse events were the same as for the REMATCH trial.

Results

Patient Characteristics

Patients in the 2 groups had similar baseline characteristics (Table 1). Notably, both REMATCH and LDSH DT groups had very advanced heart failure as manifested by preexisting New York Heart Association class IV status (66/68 patients in the REMATCH group, 23/23 patients in the LDSH DT group), intravenous inotrope requirement (65% in the REMATCH group and 61% in the LDSH DT group), low ejection fractions, and compromised hemodynamics.

Figure 1. LDSH DT versus REMATCH LVAD. One year post-implant: REMATCH, 52% $\pm$ 6%; LDS DT, 77% $\pm$ 10%; $P = .0355$. Two years post-implant: REMATCH, 29% $\pm$ 6%; LDS DT, 77% $\pm$ 10%; $P < .0001$. LDSH, LDS Hospital; LVAD, left ventricular assist device.

The comorbid factor of advanced age is reflected in both groups to a similar degree (average age 66 years in the REMATCH group and 68 years in the LDSH DT group).

Although all patients met REMATCH-like criteria with very advanced heart failure, some preoperative parameters indicate that the LDSH DT group may have been in slightly better condition at the time of implantation than the REMATCH group. Systolic blood pressure was higher (108 vs 101 mm Hg, LDSH DT vs REMATCH), pulmonary capillary wedge pressure was lower (20 vs 25 mm Hg), and serum sodium was higher (139 vs 135 mmol/L) in the LDSH DT group (Table 1). VO_2 max was modestly higher in the LDSH DT group (10.6 ± 1.4 mL/kg/min vs 9.1 ± 2.0 mL/kg/min, LDSH DT vs REMATCH), although the value for both groups was considerably less than 14 mL/kg/min used as the cutoff in the REMATCH trial or 12 mL/kg/min with current selection guidelines.

On the other hand, intravenous inotrope requirement was comparable (61% use in the LDSH DT group vs 65% in the REMATCH group). The same is true with preoperative intraaortic balloon pump use (13% incidence in the LDSH DT group vs 10% in the REMATCH group).

Comorbidities precluding transplant ineligibility in the LDSH DT group included advanced age (70%), diabetes/atherosclerotic peripheral vascular disease (9%), history of malignancy (9%), renal failure/insufficiency (9%), and obesity (4%). Advanced age accounted for the majority (70%), and most of those were aged 70 years or more. In general,

TABLE 2. Causes of death

	REMATCH (n = 68)	LDSH DT (n = 23)
Sepsis	21	2
LVAD failure	11	2
Cerebrovascular	7	0
Multiple organ failure	7	2
Cardiovascular (RHF, arrhythmia)	6	0
Pulmonary embolism	2	0
Unknown/other	2	0
Malignancy	0	1
Perioperative bleeding	1	0
Total	57	7

LDSH DT, LDS Hospital destination therapy group; LVAD, left ventricular assist device; RHF, right-sided heart failure.

these patients would not likely be considered good transplant candidates anywhere, even in centers in which transplantation with advanced age is being promoted.

Survival

Kaplan-Meier survival curves are displayed in Figure 1. A comparison of survival over the entire 2-year period demonstrated a highly significant improvement of LDSH DT over the REMATCH LVAD group ($P = .007$). Overall, there was a 66% reduction in mortality with LDSH DT compared with REMATCH.

At 1 year, the LDSH DT group had a survival of 77% compared with 52% in the REMATCH LVAD group ($P = .0355$). The 2-year survival of the LDSH DT group was 77% compared with 29% for the REMATCH group ($P = .0006$). At 2 years, this represents a 2.6-fold improvement in survival.

Mortality and Causes of Death

Causes of death for the 2 groups are listed in Table 2. In the REMATCH LVAD group, sepsis was the leading cause of death (37%), followed by LVAD failure (19%).⁹ Perioperative mortality (considered as death before discharge) was 31%. Once discharged, there were 0.48 deaths per patient-year.

Among patients in the LDSH DT group, perioperative mortality was 8.7% (2/23 patients), accounting for approximately one fourth of all deaths. Multiple organ dysfunction was the cause in both cases. Once discharged, death occurred at a rate of 0.19 deaths per patient-year. Causes of death long term (5/23 patients) were related to LVAD failure (n = 2), infection (n = 2), and malignancy (n = 1).

Relative to the REMATCH experience, perioperative mortality in the LDSH DT group was reduced 3.5-fold (from 31% to 8.7%). The rate of death after discharge was decreased by a factor of 2.5 (from 0.48 to 0.19 deaths per patient-year).

TABLE 3. LDSH Hospital destination therapy causes of death in detail

Age and gender	Discharged	Support duration	Cause of death
70 M	No	25 d	Multiple organ failure
73 M	No	82 d	Multiple organ failure
77 M	Yes	229 d/7.6 mo	LVAD infection (causing embolic CVA)
73 M	Yes	297 d/9.9 mo	LVAD infection (resolved, but contributing to inability to recover from HF-related failure to thrive)
74 M	Yes	931 d/2.6 y	Colon cancer
77 M	Yes	1188 d/3.3 y	LVAD failure (on second pump)
76 M	Yes	1677 d/4.6 y	LVAD failure (requiring third pump replacement, complicated by perioperative embolic CVA)

LVAD, Left ventricular assist device; HF, heart failure; CVA, cerebrovascular accident; LDSH DT, LDS Hospital destination therapy group.

More detail about the LDSH DT deaths appears in Table 3. Additional review offers insight useful for improving outcomes.

Perioperative deaths. Both of the LDSH DT perioperative deaths involved acute hemodynamic decompensation preoperatively, superimposed on chronic, advanced heart failure. Before the patients' operations, perfusion and end-organ function had deteriorated requiring heroic attempts to stabilize with intensive care management, hemodynamic monitoring, intubation, and escalating inotropes. Both patients went to the operating room for "salvage" rather than elective placement of an LVAD for DT.

Before the acute events, both patients were chronically compromised enough to meet indications for DT and had been considered "stable." In retrospect, however, they had deceptively limited margins of reserve and were at risk for rapid acute deterioration.

Long-term deaths. Device end-of-life LVAD failure led to 2 of the long-term deaths. One death occurred after 4.6 years of support. At a third pump replacement (all for mechanical failures), this patient experienced a perioperative cerebrovascular accident (CVA), believed to be the result of embolization of fibrous tissue from the left ventricular cannula insertion site, dislodged during LVAD removal. The second death occurred at 3.3 total years support in a patient whose second pump failed. Replacement was not attempted given an unacceptable benefit-to-risk assessment in an 80-year-old patient who was beginning to decline with age-related end-of-life issues.

Infection contributed to the death of 2 patients, the first at 7.6 months. One week after presenting with bacteremia, the patient had a multi-infarct CVA believed to be related to embolization of fibrinous material from his LVAD blood contacting surfaces noted at autopsy.

LVAD infection contributed indirectly to a second death at 10 months. Poor wound healing with delayed breakdown led to an LVAD surface infection after discharge. The "pocket" infection was controlled with high-potency, sustained-release antibiotic beads.¹⁰ However, the patient never regained physical and emotional well-being, and died

with progressive "failure to thrive." Risks for this included preexisting cachexia/malnutrition and severe deconditioning compounded by limited personal and social-support capacity to maintain a strong will to live.

Comorbid disease in the form of colon cancer, not detectable at the time of LVAD implantation, led to a death at 2.6 years of support.

Adverse Events

Adverse events overall, presented in Table 4, were significantly improved in the LDSH DT cohort, reduced to two thirds the rate of the REMATCH LVAD group (rate ratio 0.62, 95% confidence interval: 0.50-0.79).

Among the general adverse events, the 74% lower rate of *sepsis* (rate ratio 0.26, 0.08-0.85) was significantly less in the LDSH DT cohort than in the REMATCH cohort, whereas a 65% lower rate of *local infection* (rate ratio 0.35, 0.11-1.17) trended toward statistical significance. An 85% reduction in the frequency of *late bleeding* (rate ratio 0.15, 0.04-0.62) was noted in the LDSH DT group compared with the REMATCH group. The *neurologic events* in the LDSH DT group (no difference in rate compared with REMATCH) were all reversible, leaving no residual except for 1 patient who had a CVA due to infection-related embolism that resulted in death (as noted above). Thus, seriously compromising strokes occurred at a rate of only 0.04 per patient-year in the LDSH DT group.

In regard to LVAD-related adverse events, *perioperative bleeding* was less in the LDSH DT group (rate ratio 0.22, 0.05-0.92). *Right-sided heart failure* after LVAD placement (0.09 per patient-year for LDSH DT vs 0.16 for REMATCH) was not statistically different. Temporary right ventricular assist devices were used in 10% of all LDSH DT implants, whether initial or replacement.

The rate of *LVAD malfunction* was significantly lower (rate ratio 0.26, 0.11-0.66) with the more recent LDSH DT experience than with REMATCH. There were no catastrophic LVAD failures. It is relevant to note the use of the improved HeartMate XVE in 87% of the patients in the LDSH DT group compared with the REMATCH group,

TABLE 4. Adverse events

	REMATCH (n = 68) events/patient-y	LDSH DT (n = 23) events/patient-y	Rate ratio (95% CI)
Any adverse event	6.32	3.90	0.62 (0.50-0.79)*
General AEs			
Sepsis	0.51	0.13	0.26 (0.08-0.85)*
Local infection	0.38	0.13	0.35 (0.11-1.17)
Bleeding, non-neurologic	0.6	0.09	0.15 (0.04-0.62)*
Neurologic dysfunction	0.44	0.44	1.02 (0.5-2.09)
Renal failure	0.22	0.22	1.02 (0.37-2.81)
Hepatic failure	0.03	0.00	—
Serious psychiatric disease	0.03	0.00	—
Other AE	1.35	1.73	1.30 (0.89-1.89)
Supraventricular arrhythmia	0.12	0.04	0.38 (0.05-3.06)
Ventricular arrhythmia	0.23	0.09	0.38 (0.09-1.66)
Syncope	0.09	0.04	0.51 (0.06-4.23)
Cardiac arrest	0.09	0.00	—
Nonperioperative MI	0.02	0.00	—
Peripheral thrombosis or TE	0.09	0.18	2.04 (0.58-7.23)
AEs associated with LVAD			
Perioperative bleeding	0.41	0.09	0.22 (0.05-0.92)*
Right-sided heart failure after LVAD	0.16	0.09	0.56 (0.12-2.51)
Perioperative MI	0	0.00	—
Malfunction of LVAD	0.85	0.22	0.26 (0.11-0.66)*
Catastrophic failure of LVAD	0.1	0.00	—
Infection of drive-line tract or pocket	0.35	0.44	1.27 (0.61-2.67)
Infection of pump interior, inflow tract, or outflow tract	0.19	0.00	—
Thrombosis in LVAD	0.04	0.00	—

AE, Adverse event; MI, myocardial infarction; TE, thromboembolism; LVAD, left ventricular assist device; LDSH DT, LDS Hospital destination therapy group; CI, confidence interval. *Statistical significance.

during which the earlier model, the HeartMate VE, was used exclusively. It is not possible, given limited numbers, to determine how this has translated into greater durability.

Still, LVAD replacement was required in the LDSH DT group 7 times, in 5 patients, all as a result of mechanical failure (0.26 LVAD replacements per patient-year of support). No devices failed until after the first 12 months. By 24 months, 50% of LVADs had failed. Perioperative mortality with replacement was 14%.

Discussion

Historical Context

The REMATCH trial initiated a new era in the field of MCS. REMATCH was a groundbreaking, innovative trial yielding results that have served as a benchmark for long-term, so-called DT with LVADs. The results are remarkable, considering the revolutionary nature of this initial experience with long-term LVADs in the population with the highest risk of heart failure studied up to that time.

It is important that DT outcomes be improved beyond the original performance of REMATCH. Although the REMATCH trial demonstrated a greater impact of LVADs on survival than any previously evaluated therapy, the mortality and

morbidity were substantial. The mortality (77% at 2 years when first reported), resulting mainly from infection and device failure, became a clear target for improvement, as was the morbidity of adverse events.

Much was learned during the REMATCH trial about patient selection,¹¹ surgical technique,¹² and patient management.^{13,14} This knowledge has been coalesced into advanced practice guidelines. In addition, changes to the HeartMate LVAD have been made to improve reliability.^{6,9,15}

Although, in general, outcomes with MCS have improved with experience,¹⁶ it is important to establish that DT can be improved. The first indication of such was the finding of improved survival in the LVAD arm over the course of the REMATCH trial.⁹ Two-year survival with LVADs in the last half of the trial was 38% compared with 21% in the first half of the trial, whereas there was no change in survival with medical management. It was suggested that advances in patient management and LVAD technology led to this improvement.

The only other report to date of experience beyond REMATCH confirms an ongoing trend toward improved outcomes in experienced centers.⁶

Importance of the Present Study

The results reported in this study provide strong affirmation of the potential for improving outcomes with long-term LVAD DT. Further, the magnitude of improvement sets new standards on which to create realistic goals for the future of DT as essential processes of care mature.

Three major contributors to improving DT outcomes include (1) patient management, (2) LVAD device improvements, and (3) patient selection. Although all 3 of these are likely to have played some role in the present experience, we believe the importance of patient management and patient selection cannot be underemphasized. This is consistent with the present state of the art, in which the “steep learning curve” must be addressed by a more rapid evolution of DT management and more immediate refinement of patient selection (even within the overall constraint of a REMATCH-like population with very advanced heart failure), whereas improvements in devices will be slower to materialize.

Patient selection. The demographics of the LDSH DT group clearly meet REMATCH-like indications of a population with advanced heart failure. Thus, we have not evolved beyond REMATCH-like indications. The experience within this study may indicate a small trend toward selecting slightly less-compromised patients within this group of candidates with advanced heart failure.

All of the perioperative mortalities occurred in patients in whom we tried to intervene too late in their course. We now consider urgent use of DT, in a salvage-like manner, to be highly lethal or to lead to serious perioperative morbidity. Our patient selection has subsequently evolved to extreme caution and even exclusion with such patients. It will be important, as further experience accrues, to improve the criteria for selecting patients to undergo DT with formal risk analysis tools, as has been described for bridging to transplantation,¹⁷ to avoid DT when likely to be futile.

We believe timing is critical to outcomes. Judging from the steep mortality in the early stages of the REMATCH control medical arm (~5% mortality per week), it takes only a few weeks beyond the first diagnosis as a REMATCH-like candidate to subject the patient-in-waiting to an undesirable 15% to 20% additional risk of mortality while waiting.

Beyond those risk factors previously identified for bridging to transplantation, we consider important *perioperative* risk factors relevant to this patient population to include ravages of chronic decline, deconditioning, and malnutrition. Factors particularly prevalent in the DT population that we believe affect *long-term* outcomes include age-related issues (cognition, dexterity, comorbid diseases) and social support.

Left ventricular assist device improvements. The HeartMate technology used in this study is good technology¹⁸

and continues to undergo important improvements. Although the full impact of the modifications incorporated into the XVE model cannot be determined by this study, we continue to experience end-of-life device failures requiring replacement on average between 18 and 24 months. The apparent reduction in LVAD failure-related mortality in our experience compared with the REMATCH trial is largely due to improved management with a reduction of mortality with device replacement from 30% to 40% to approximately 15%. Improved durability beyond that of the present HeartMate XVE is essential to further reduce the risks associated with device failure. It is hoped that trials of other devices using the HeartMate as a control will provide further knowledge.

Management. We approach DT with the perspective that, in its current pioneering status, DT may be among the most complex therapies in medicine, mostly because it involves complex decision-making across multiple disciplines, often requiring the creation of new knowledge, and numerous steps in a spectrum of care from before the operation through the end of life. We believe that team organization and operation contribute immensely and allow these challenging patients to survive through implantation, who would otherwise fail were it not for such a support system.

Limitations

Study design, sample size, and uncertainties of applicability are limitations, none of which are believed likely to undo the major contributions of the study.

A study design using a historical control is not the quality of a randomized, controlled trial. However, we sought to limit as many disparities between the historical and present study as possible, save those that represent advancements by applying the same quality of decision-making and data collection, as well as applying similar inclusion and exclusion criteria. Facilitating that is the conduct of the present study by the same experienced research group who were also major contributors to the historical data.

Sample size is certainly a limitation. A small number of added mortalities or adverse events has a greater impact on a small sample size than a large one. However, it would take an unusually large deviation from current experience to modify the data so significantly that it compromises the important findings of this study. To put this into perspective, this remains the largest single-center experience with DT in a field in which the numbers remain modest.

Applicability of this study to other centers is certainly a limitation of any single-center study. However, we use practices that have been reduced to advanced guidelines available to others and believe that our processes are reproducible by others.

Conclusions

Although many challenges in the evolution of long-term DT with LVADs for advanced heart failure have been addressed, many hurdles remain.

It will be necessary for outcomes to improve beyond REMATCH to transfer the sense of great potential held by those with pioneering spirit to those who are waiting for evidence of substantial benefit to choose DT as a standard of care from among the growing number of alternative therapies. A field-wide goal of 50% 2-year survival seems reasonable at this stage.

In the future, DT will become less demanding as (1) devices evolve,^{19,20} (2) management becomes standardized, and (3) patient selection improves first within current advanced, REMATCH-like indications then followed by less-advanced heart failure as justified by outcomes. Until then, dissemination must be responsibly done among centers willing to approach this with the necessary commitment, resources, and patience.

It is not unreasonable to expect that DT may eventually reach outcomes on par with heart transplantation, especially when 10% to 15% mortality on the waiting list is added to current posttransplant survival curves. It is worth remembering that when heart transplantation was started, outcomes were not too different than the early pioneering experiences with DT and that approximately 2 decades were required to evolve transplantation into the standard of care of today.^{1,21}

This experience of improving outcomes with DT should encourage continued pioneering with ventricular assist devices for the treatment of advanced heart failure. For many patients at or nearing end-stage heart failure, there is no other alternative at the present time that is equally promising.

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Discussion

Dr Cleveland (Denver, Colo). Jim, I congratulate you and your coauthors at the Utah artificial heart program for achieving exemplary outcomes with a complex and challenging group of patients undergoing LVAD therapy as sole therapy for advanced heart failure. Again, Jim did a good job emphasizing and placing this group of patients and the results of the study in the context of the fact that these are critically ill patients. All had class IV congestive heart failure for at least 90 days. All had an ejection fraction less than 25%. All had a VO_2 max less than 12 mL/kg/min, and most important all had no other therapy (ie, heart transplantation). The principle finding of the present study in this cohort of 23 patients undergoing DT in Utah is a 1-year survival of 77% versus 52% in the surgically implanted destination group in the REMATCH trial. Particularly noteworthy is the subsequent 2-year survival of 77% in Dr Long's cohort versus only 30% in the REMATCH cohort.

If one considers the nature of this therapy for heart failure, there are 3 main mechanisms that could be offered to explain the

improved outcomes seen in your study. First is earlier patient implant. Obviously these are sick but not moribund patients, and you alluded to that, perhaps if their sodium was a little higher, perhaps if their blood pressure was a little higher. Second is improvement in the HeartMate or LVAD technology itself. Third is improvement in patient management. Which of these 3 do you believe is most operant in providing for these results?

Dr Long. In this era I think patient management is the most critical step by which we can improve this field. Certainly as devices improve we are going to see added reliability and durability, but we have not yet been able to identify that in the limited numbers we've seen. Reduction in mortality because of device failure is largely the result of managing patients better through the perioperative period. We think the reduction in infection, the first leading cause of mortality in the REMATCH trial, is also largely the result of infection, but clearly as devices improve, get smaller with percutaneous leads that are smaller, it will be much easier to reduce infections, much easier to implant these, and have a more durable device, moving beyond 2-year devices into the 4+ range. Patient selection is critical. Now we are constrained to the REMATCH-like patients largely because of Centers for Medicare and Medicaid Services constraints and the regulatory approval process. I think if we are going to do this effectively we have to move beyond that, but we really can't move beyond that until we

get some good results with those kinds of patients. I think it is important for centers across this country to set targets of 50% 2-year survivorship, and if we do achieve that across this field I think we earn the right to move to a less ill patient population analogous to those who were in the REMATCH trial.

Dr Cleveland. Second, as discussed in your article, and it's really a well-written and clear article, DT has been offered only to a small number of patients. I think a reason for this is cost. Eric Rose and colleagues published subsequent cost data from the REMATCH trial suggesting that with DT if the patient incurs complications perioperatively, particularly that of sepsis or bleeding, the cost of this therapy increases to near-prohibitive levels. Do you have associated data? I know you didn't present here today, but do you have data suggesting that with your improved outcomes the cost of the therapy is less and therefore it may make this more approachable by many centers?

Dr Long. Your observation is right on. The destination field really didn't begin picking up post-REMATCH until Centers for Medicare and Medicaid Services approval was in place, so that gives you some indication how important reimbursement is to this. In more recent studies yet to be released, we're finding that we can decrease this to the \$140,000 range and to the \$130,000 range in those without complications.