Left ventricular assist devices as destination therapy: A new look at survival

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Objective: The REMATCH trial compared the use of left ventricular assist devices with optimal medical management for patients with end-stage heart failure. When the trial met its primary end point criteria in July 2001, left ventricular assist device therapy was shown to significantly improve survival and quality of life. With extended follow-up, 2 critical questions emerge: (1) Did these benefits persist, and (2) did outcomes improve over the course of the trial, given the evolving nature of the technology?

Methods: We analyzed survival in this randomized trial by using the product-limit method of Kaplan and Meier. Changes in the benefits of therapy were analyzed by examining the effect of the enrollment period.

Results: The survival rates for patients receiving left ventricular assist devices (n = 68) versus patients receiving optimal medical management (n = 61) were 52% versus 28% at 1 year and 29% versus 13% at 2 years ($P = .008$, log-rank test). As of July 2003, 11 patients were alive on left ventricular assist device support out of a total 16 survivors (including 3 patients receiving optimal medical management who crossed over to left ventricular assist device therapy). There was a significant improvement in survival for left ventricular assist device–supported patients who enrolled during the second half of the trial compared with the first half ($P = .03$). The Minnesota Living with Heart Failure scores improved significantly over the course of the trial.

Conclusion: The extended follow-up confirms the initial observation that left ventricular assist device therapy renders significant survival and quality-of-life benefits compared with optimal medical management for patients with end-stage heart failure. Furthermore, we observed an improvement in the survival of patients receiving left ventricular assist devices over the course of the trial, suggesting the effect of greater clinical experience.

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Left ventricular assist devices (LVADs) have been in widespread clinical use for a decade as a temporary device to support patients awaiting cardiac transplantation.[1-9] Successful experience for this bridge-to-transplantation indication, particularly among those with prolonged periods of implantation, justified evaluating these devices as long-term or destination therapies for chronic heart failure. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial recently showed that LVADs could improve both

the survival and quality of life of patients with stage D heart failure who are ineligible for cardiac transplantation.[10,11] This intervention nearly halved (relative risk, 0.52; 95% confidence limit, 0.34-0.78) the mortality seen in the control population, who, despite receiving state-of-the-art medical therapy, succumbed to their disease at a rate of 92% at 2 years. Even with a high frequency of serious adverse events (AEs) from infection, bleeding, and device malfunction, LVAD recipients had an improved survival rate and experienced a superior quality of life than their medical therapy counterparts.[11]

Although the REMATCH trial met its predetermined mortality end point (and, consequently, enrollment discontinued) in July 2001, data collection continues for survivors. We review here the extended survival and AE experience of REMATCH patients, including an additional 125 patient-months of experience for the medical arm (total patient-months, 534) and 375 patient-months for the LVAD arm (total patient-months, 1009). During the enrollment period (1998-2001) in the REMATCH trial, the clinical management of patients receiving LVADs evolved, and device modifications were introduced. Therefore this article also explores how these changes might have affected patient outcomes. Specifically, we examine whether survival in the LVAD arm improved over time and, if so, whether this trend was unique to patients receiving LVADs or seen in medically managed patients as well.

Methods

Trial Organization

The study was conducted in 21 experienced cardiac transplantation centers under a cooperative agreement among Columbia University, Thoratec Inc, and the National Heart, Lung, and Blood Institute of the National Institutes of Health. The trial was supervised by a steering committee and executed by an independent Coordinating Center (International Center for Health Outcomes and Innovation Research, Columbia University). An independent morbidity and mortality committee adjudicated causes of death and AEs. The National Institutes of Health appointed a Data and Safety Monitoring Board to review trial progress. The US Food and Drug Administration (FDA) granted an investigational device exemption as a pivotal phase III trial. Participating institutional review boards approved the protocol, and informed consent was obtained for all patients.

Study Patients

We defined a subset of adults with chronic end-stage heart failure and contraindications to transplantation. Entry criteria included the following: (1) class IV New York Heart Association (NYHA) symptoms for 90 days or greater despite attempted therapy with angiotensin-converting enzyme inhibitors, diuretics, and digoxin (subsequent criteria allowed for patients with class IIIB disease taking inotropes for 14 of 28 days or with intra-aortic balloon pumps); (2) left ventricular ejection fraction of 25% or less; and (3) peak oxygen consumption of 14 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} or less or documented failure to wean intravenous inotropic therapy caused by systolic blood pressure of less than 80 mm Hg, decreasing renal function, or worsening symptoms with objective signs of deterioration. Transplantation was contraindicated for at least one of the following: age greater than 65 years, insulin-dependent diabetes mellitus with end organ damage, chronic renal failure with a sustained serum creatinine level of greater than 2.5 mg/dL for 90 days or more before randomization, or other significant comorbidities. Detailed exclusion criteria were reported previously.[12]

Study Design

We conducted a parallel design study in which patients were randomly assigned to the vented electric Thoratec LVAD or optimal medical management (OMM) in a 1:1 ratio. The randomization was stratified by center and blocked to ensure ongoing equivalence of group size. Eligibility was determined by site investigators and confirmed by the coordinating center gatekeeper. The unethical nature of sham operations and obvious device function precluded double-blind design. However, investigators were masked to overall outcome data throughout enrollment, except for the statisticians. In accordance with FDA requirements, Thoratec received ongoing data for patients receiving LVADs but was masked to all OMM data. The patients were seen monthly until the time of death or up to a period of 24 visits (28 days) from the initial enrollment for the measurement of all secondary end points, including serious AEs and quality of life. After 24 visits, all patients continue to be followed for survival.

Statistical Analysis

The primary end point was all-cause mortality compared by using the log-rank statistic. We used Cox proportional-hazards regression to estimate hazard ratios and 95% confidence intervals and to adjust for differences in baseline outcome predictors. Analyses were both by intention to treat and as treated. We analyzed the trends in survival by year of enrollment, which was not a prespecified analysis. We used the midpoint of LVAD enrollment as the dividing point for comparing the 2 cohorts. AEs were adjudicated as serious if they caused death or permanent disability, threatened life, or required or prolonged hospitalization. Frequency of event occurrence was analyzed by means of Poisson regression. Quality of life and functional status were assessed by using the Minnesota Living with Heart Failure (MLHF) questionnaire and the NYHA classification. The MHLF questionnaire contains 21 questions regarding the patients' perceptions of the effects of heart failure on their daily lives. The best score is 0, and the worst score is 105.[13] Statistical testing was done on a longitudinal data set to account for effect of time on treatment. NYHA scores were compared by using the Fisher exact test. The July 2003 data set was used to compare the survival experience, AEs, and quality of life of the LVAD and OMM treatment groups.

Results

Patient Demographics

A total of 129 patients were enrolled in the study: 68 patients were randomized to ventricular assist device implantation, and 61 patients were randomized to medical management. The baseline characteristics, which capture,

TABLE 1. Baseline characteristics

	Full trial			LVAD			OMM		
	OMM (n = 61)	LVAD (n = 68)	*P* value	Before 2000 (n = 34)	After 2000 (n = 34)	*P* value	Before 2000 (n = 35)	After 2000 (n = 26)	*P* value
Age (y)	68 ± 8.2	66 ± 9.1	.16	64.8 ± 8.5	67.9 ± 9.5	.16	65.8 ± 9.3	71.1 ± 5.3	.01
Male sex (% of patients)	82	78	.66	74	82	.56	80	84.8	.75
Ischemic cause of heart failure (%)	69	78	.32	82	74	.56	57.14	84.62	.03
Left ventricular ejection fraction (%)	17 ± 4.5	17 ± 5.2	.92	18.1 ± 5.1	16.8 ± 5.5	.33	17.1 ± 4.9	17.4 ± 4.2	.86
Blood pressure (mm Hg)									
Systolic	103 ± 17	101 ± 15	.46	102.7 ± 17.2	99.2 ± 13.2	.35	103.3 ± 20.6	102.2 ± 10.9	.78
Diastolic	62 ± 11	61 ± 10	.99	63.1 ± 9	59.9 ± 11.3	.2	61.6 ± 12	61.7	.96
Pulmonary capillary wedge pressure (mm Hg)	24 ± 7.4	25 ± 9.9	.35	24.9 ± 11	25 ± 9.8	.98	23.3 ± 6.7	24.4 ± 8.3	.57
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2 ± 0.6	1.9 ± 1	.36	2 ± 0.6	1.9 ± 0.6	.23	2 ± 0.7	2.1 ± 0.6	.56
Heart rate (beats/min)	84 ± 15	84 ± 16	.8	83.8 ± 17.9	84.3 ± 14.7	.89	84.3 ± 14.3	83.12 ± 16.52	.77
Pulmonary vascular resistance (Wood units)	3.2 ± 1.8	3.4 ± 1.8	.75	3.0 ± 1.8	3.8 ± 2.0	.08	3.2 ± 1.8	3.2 ± 1.7	.93
Quality of life, symptoms of depression and functional status									
MLHF (total score)	75 ± 17	75 ± 18	.63	73.9 ± 21	76.4 ± 14.1	.55	76.5 ± 16.2	71.5 ± 17.9	.26
SF-36 (Physical Functioning)	18 ± 19	19 ± 19	.67	23.1 ± 22.4	14.7 ± 13.7	.07	18.4 ± 19.7	17.7 ± 18.3	.88
SF-36 (Role Emotional)	25 ± 38	33 ± 42	.33	42.2 ± 45.9	24.5 ± 37	.09	21.9 ± 37	29.5 ± 40	.45
BDI	16 ± 8.3	19 ± 9.2	.18	18.9 ± 9.4	18.4 ± 9.2	.8	16.9 ± 8.8	15.8 ± 7.7	.62
NYHA classification IIIb/IV {%/%}	1.6/98.4	2.9/97.1	1	2.9/97.1	2.9/97.1	1	0/100	3.9/96.2	.43

LVAD, Left ventricular assist device; *OMM,* optimal medical management; *MLHF,* Minnesota Living with Heart Failure; *BDI,* Beck Depression Inventory; *NYHA,* New York Heart Association.

among other things, the severity of heart failure, are comparable between the 2 groups in the full trial, as shown in Table 1. The baseline characteristics of the patients receiving LVADs enrolled during the first half of the trial were similar to those enrolled during the second half; for medically managed patients, all characteristics were similar, except for age and the percentage of patients who had ischemic heart disease.

Survival

Figure 1 depicts the actuarial survival of both REMATCH treatment groups on the basis of an intention-to-treat analysis (ie, based on randomization assignment regardless of treatment crossover; $P = .008$). The 1-year survival was 52% (95% confidence limit [CL], 40%-63%) for patients receiving LVADs versus 28% (95% CL, 17%-39%) for medically managed patients, and the 2-year survival was 29% (95% CL, 19%-40%) versus 13% (95% CL, 5%-22%) for the 2 groups, respectively. The median survival was 408 versus 150 days in the LVAD and OMM groups, respectively, whereas the mean survival was 385 versus 246 days. As of July 2003 (the time of closure of the latest fully adjudicated data set), 11 patients from the original LVAD cohort and 5 from the original OMM cohort were still living. Patients receiving medical therapy were given the option of crossing over to LVAD therapy in June 2001, when the primary end point criteria were reached and LVAD therapy was recognized to offer a survival advantage. Three of the 5 patients elected to do so, 1 patient withdrew from the trial, and 1 patient opted to continue OMM. In an as-treated analysis, in which patients receiving OMM who crossed over to LVAD therapy were censored at the time of crossover, the 2-year survival was 29% (95% CL, 19%-40%) for patients receiving LVADs versus 13% (95% CL, 2%-17%) for patients receiving OMM.

Effect of Enrollment Time on Survival

To analyze whether time of enrollment affected survival in the 2 treatment cohorts, we compared the results of patients enrolled before and after January 1, 2000, the approximate 50% enrollment point of the trial. All but one center had enrolled patients by that point. Figure 2 shows the comparison of the 34 patients receiving LVADs who were enrolled before (20th Century) and the 34 patients with LVADs who were enrolled after (21st Century) January 1, 2000. The 1-year survival in the 21st century subgroup was 59% (95%

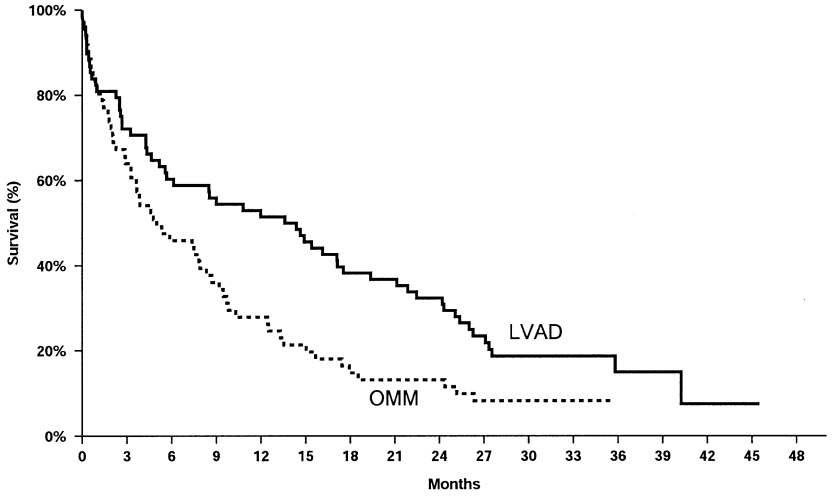

Figure 1. Kaplan-Meier survival curve ($P = .0077$).

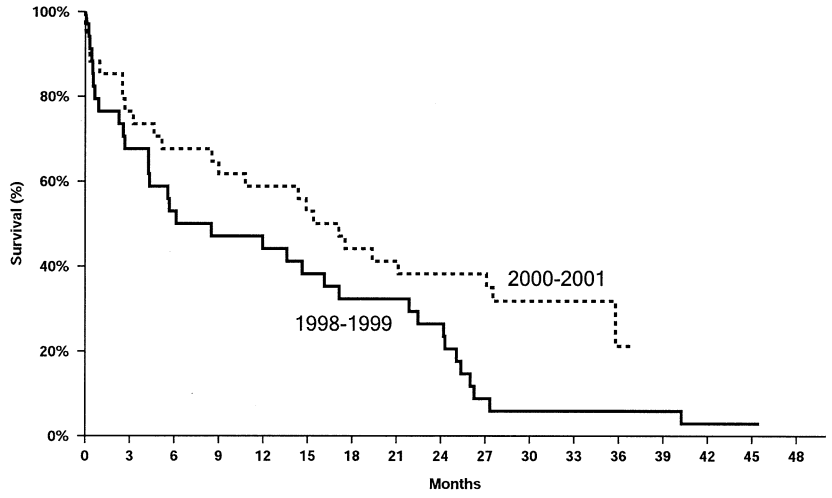

Figure 2. Kaplan-Meier survival curves for patients receiving LVADs enrolled in 1998-1999 and those enrolled in 2000-2001 ($P = .00293$).

CL, 42%-75%), and in the 20th century group it was 44% (95% CL, 27%-61%). At 2 years, the survival was 38% (95% CL, 22%-55%) and 21% (95% CL, 7%-34%) in the 21st and 20th century subgroups, respectively. The overall survival curves were significantly different, as determined by using the log-rank test ($P = .029$). This difference was not concentrated in the perioperative period; the 30-day survival curves between the 2 cohorts were similar ($P = .539$).

Figure 3 compares the survival of the 35 patients receiving OMM enrolled before the millennium with the 26 patients enrolled after the millennium. The 1-year survival in the late enrollment subgroup (21st century) was 35% (95% CL, 16%-53%) compared with 23% (95% CL, 9%-37%) in the early enrollment subgroup (20th century). At 2 years, the survival was 29% (95% CL, 19%-40%) and 9% (95% CL, 0%-16%) in the late and early subgroups, respectively. The overall survival curves were not significantly different ($P = .255$).

Causes of Death and AEs

Major causes of death in the LVAD arm were sepsis and device failure, whereas in the medical arm by far the majority of patients die from progression of their ventricular failure (Table 2). Patients receiving LVADs were a little more than twice as likely to experience a serious AE as their medical counterparts (Table 3). The most common AEs among patients receiving OMM were ventricular arrhythmia, sepsis, local infection, and neurologic dysfunction. The

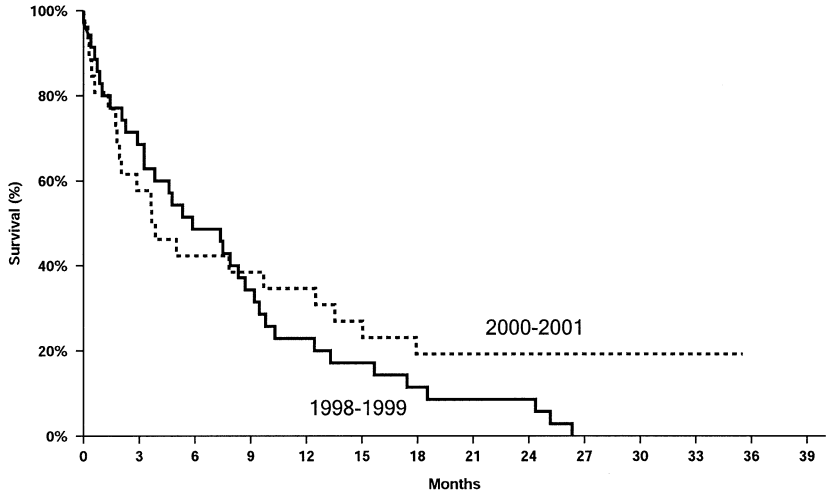

Figure 3. Kaplan-Meier curves of OMM survival in patients enrolled in 1998-1999 and those enrolled in 2000-2001 ($P = .2551$).

most common AEs in the LVAD arm were sepsis, bleeding, and neurologic dysfunction. Neurologic dysfunction subsumes stroke, transient ischemic attacks, and metabolic encephalopathy. The majority of neurologic events were transient in nature.

Table 4 stratifies the AE rates for patients receiving LVADs in the early (20th century) versus the late (21st century) enrollment subgroup. The overall AE rate for the late enrollment subgroup was significantly lower than for the early subgroup. In particular, the rates per patient-year of sepsis, renal failure, and pump housing, inflow, or outflow graft infections were significantly lower for those patients enrolled during the second half of the trial.

Quality of Life

At baseline, nearly all patients (97%) were in NYHA class IV. At 1 year, only 17% of surviving medically managed patients improved to class I/II, whereas 71% of surviving patients receiving LVADs improved to this level ($P = .0017$). The MLHF score was significantly better for the patients receiving LVADs over the course of the study ($P = .007$). The magnitude of difference at 1 year was 11 points on the MLHF scale: 53 for medically managed patients and 42 for patients receiving LVADs (Figure 4).

Discussion

The REMATCH trial results, first reported in 2001, established LVAD implantation as a viable option for patients with end-stage heart failure.[11] The 2 years of additional observation on REMATCH patients reported here substantiates the continuing survival benefit conferred by LVAD support. LVAD treatment more than doubled the survival seen at 2 years with OMM. Accounting for crossover among patients receiving OMM through an as-treated analysis only increases the survival benefit further. As of July 24, 2003, the closure date for the data set analyzed here, 14 patients were alive on LVAD support, including 3 crossover patients from the medical therapy group, compared with only 2 survivors with native hearts (1 of whom was enrolled in another heart-failure trial). The additional follow-up time of the study established that the quality of life and functional status of patients in the LVAD arm remained significantly better than those of their medical counterparts. The differences in quality-of-life measurements observed here translate into significant differences in activities of daily living and emotional well-being. These improvements occurred despite the fact that patients receiving LVADs were more than twice as likely to experience AEs than medically managed patients.

TABLE 2. Causes of death

	LVAD	OMM
LV dysfunction	1	52
Sepsis	21	1
LVAD failure	11	0
Other noncardiac cause	7	0
Cerebrovascular disease	7	0
Other cardiovascular	5	1
Pulmonary embolism	2	0
Acute myocardial infarction	0	1
Cardiac procedure	0	1
Perioperative bleeding	1	0
Unknown	2	0
Total	57	56

LVAD, Left ventricular assist device; *OMM,* optimal medical management; *LV,* left ventricular.

TABLE 3. Adverse events (AE)

	No.		Rate				
	OMM	LVAD	OMM	LVAD	Ratio	Lower CI	Upper CI
AE							
Any AE	108	431	2.85	6.32	2.21	1.79	2.73
Neurodysfunction	5	30	0.13	0.44	3.33	1.29	8.57
Bleeding	3	41	0.08	0.60	7.58	2.35	24.47
Localized infection	10	26	0.26	0.38	1.44	0.70	2.99
Sepsis	10	35	0.26	0.51	1.94	0.96	3.92
Thromboembolism	3	6	0.08	0.09	1.11	0.28	4.43
Cardiac arrest	6	6	0.16	0.09	0.55	0.18	1.72
Ventricular arrhythmia	22	16	0.58	0.23	0.40	0.21	0.77
Supraventricular arrhythmia	1	8	0.03	0.12	4.44	0.55	35.47
Syncope	0	6	0.00	0.09			
Nonperioperative MI	0	1	0.00	0.02			
Renal failure	7	15	0.19	0.22	1.19	0.48	2.91
Chronic renal dysfunction	0	0	0.00	0.00			
Hepatic failure	0	2	0.00	0.03			
Psychiatric episode	0	2	0.00	0.03			
Other	41	92	1.08	1.35	1.24	0.86	1.80
Perioperative MI	0	0	0.00	0.00			
LVAD-specific AE							
LVAD-related RVH		11		0.16			
Perioperative bleeding		28		0.41			
Percutaneous site infection		24		0.35			
Pump housing infection		13		0.19			
Device thrombosis		3		0.04			
LVAD system failure		7		0.10			
Suspected device malfunction		58		0.85			

OMM, Optimal medical management; *LVAD,* left ventricular assist device; *CI,* confidence interval; *MI,* myocardial infarction; *RVH,* right ventricular hypertrophy.

Whereas LVADs have been widely used for bridge to transplantation, destination therapy is an entirely new use.[14] In fact, the FDA only allowed bridging patients to be discharged to their home environment as of 1996. Thus the ambulatory experience with these patients was still rather new when the REMATCH trial started, and the extended experience led to changes in patient management, as well as device modifications. During the trial, for example, locking screw ring connectors were added to the inflow and outflow grafts to avert disconnections, and outflow graft bend relief was introduced to prevent kinking and the resultant inflow valve incompetence. At the same time, changes in patient management took effect, such as infection management guidelines, which defined the choice of antimicrobial prophylaxis and the use of abdominal binders to stabilize the driveline exit site. Therefore we questioned whether these changes had an effect on survival over the course of this trial.

We found that the time of enrollment was a significant factor in determining survival. In fact, there was about a 15% improvement in survival rate both at 1 and 2 years between the patients receiving LVADs who were enrolled during the second half of the trial compared with those enrolled during the first half. This finding is unlikely to be a result of clinical center participation in the trial because all but one clinical site was enrolling patients before January 1, 2000. It is also unlikely that these differences came from better patient selection in the second half of the trial. The 2 LVAD cohorts were similar in all their baseline characteristics. However, these groups did manifest differences in overall AE rates, with the later enrolled cohort experiencing significantly fewer overall AEs than the cohort enrolled during the first half of the trial. These differences were concentrated in the areas of sepsis, pump housing inflow and outflow graft infections, and renal failure. Moreover, bleeding, which is an important AE in this group of patients, shows a trend toward improvement over the course of the trial. Although we are limited by the small numbers of patients, these data suggest that changes in patient management (as, for instance, codified in the infection management guidelines) had an effect during the REMATCH trial. More generally, these data suggest that AE rates and survival outcomes can be improved as we mature in our experience

TABLE 4. Adverse events (AE)

	Before 2000*		After 2000†		Comparison		
	No.	Rate	No.	Rate	Ratio	Lower CI	Upper CI
Any	232	7.65	199	5.25	1.46	1.21	1.76
Neurodysfunction	14	0.46	16	0.42	1.09	0.53	2.24
Bleeding	22	0.73	19	0.50	1.45	0.95	2.20
Localized infection	13	0.43	13	0.34	1.25	0.58	2.70
Sepsis	24	0.79	11	0.29	2.73	1.34	5.57
Thromboembolism	3	0.10	4	0.11	0.94	0.21	4.19
Cardiac arrest	6	0.20	0	0.00			
Ventricular arrhythmia	6	0.20	10	0.26	0.75	0.27	2.06
Supraventricular arrhythmia	4	0.13	4	0.11	1.25	0.31	5.00
Syncope	1	0.03	5	0.13	0.25	0.03	2.14
Nonperioperative bleeding	0	0.00	1	0.03	0.00		
Renal failure	12	0.40	3	0.08	5.00	1.41	17.72
Chronic renal	0	0.00	0	0.00			
Hepatic failure	1	0.03	1	0.03	1.25	0.08	19.99
Psychiatric episode	1	0.03	1	0.03	1.25	0.08	19.99
Other AE	48	1.58	44	1.16	1.36	0.91	2.05
Perioperative MI	0	0.00	0	0.00			
LVAD-related RHF	4	0.13	7	0.18	0.71	0.21	2.44
Perioperative bleeding	17	0.56	11	0.29	1.93	0.91	4.13
Percutaneous site infection	13	0.43	11	0.29	1.48	0.66	3.30
Pump housing infection	11	0.36	2	0.05	6.88	1.52	31.03
Device thrombosis	0	0.00	3	0.08	0.00		
LVAD system failure	4	0.13	3	0.08	1.67	0.37	7.45
Suspected LVAD failure	28	0.92	30	0.79	1.17	0.70	1.95

CI, Confidence interval; *MI,* myocardial infarction; *LVAD,* left ventricular assist device; *RHF,* right heart failure.
*11,078 follow-up days.
†13851 follow-up days.

with LVAD as a destination therapy. By contrast to the LVAD experience, the time-stratified survival curves in the medically managed arm were not significantly different. Although there were some important medical therapeutic advances for patients with heart failure during the REMATCH trial period, such as the confirmation of the value of β-blockers and spironolactone, these interventions do not address patients with the severity of heart failure seen in the REMATCH population.[15] Despite differences in 2 of the baseline characteristics (age and cause of heart failure) in time-stratified medical cohorts, it is unlikely that these differences would mask a true survival difference of the magnitude seen in the LVAD arm. However, one must keep in mind the limitations of this study. In particular, this comparison is a post hoc analysis of changes in survival over time. In addition, the limited sample size in this subgroup analysis affects our ability to make adequately powered comparisons for each of the AE types.

The results of the REMATCH trial have led to FDA approval of the Heartmate VE for destination therapy in November 2002, and in October 2003, the Center for Medicare and Medicaid Services decided to cover and reimburse LVADs for this indication. With these regulatory decisions, the stage is set for wider dissemination of these devices. We anticipate significant and steady improvement in survival

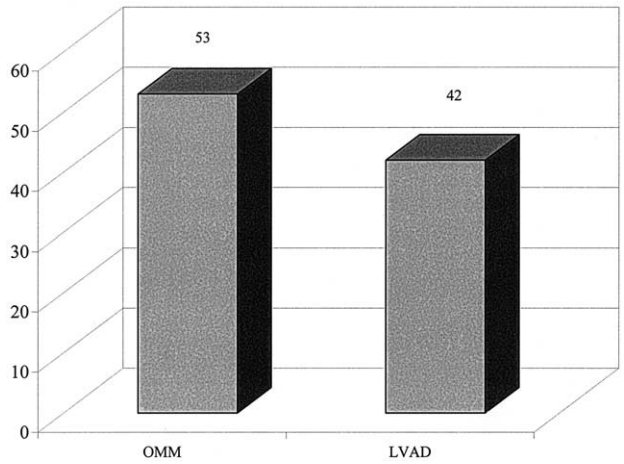

Figure 4. Disease-specific quality of life at 12 months. The MLHF scale range is 0 (best) to 105 (worst). The MLHF score was significantly better for the patients receiving LVADs over the course of the study ($P = .007$). The magnitude of difference at 1 year was 11 points on the MLHF scale: 53 for medically managed patients and 42 for patients receiving LVADs.

and quality of life over time as we continue to learn to take care of these patients and as device modifications are introduced into practice. An important factor in such learning will be our ability to track changes in patient management and device modifications and how they affect patient outcomes. Furthermore, as new LVADs emerge as potential destination therapy devices, our ability to collect data concerning improved device design and patient outcome would be imperative for a long-term success of destination therapy. This argues for international participation of LVAD clinical centers and device manufacturers in a clinical registry.

References

1. Goldstein D, Oz M, Rose E. Implantable left ventricular assist devices. *N Engl J Med.* 1998;339(21):1522-33.
2. Frazier O, Rose E, Macmanus Q, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. *Ann Thorac Surg.* 1992;53:1080-90.
3. Pennington D, McBride L, Peigh P, et al. Eight years' experience with bridging to cardiac transplantation. *J Thorac Cardiovasc Surg.* 1994; 107:472-81.
4. Korfer R, El-Banayosy A, Arusoglu L, et al. Single-center experience with the thoratec ventricular assist device. *J Thorac Cardiovasc Surg.* 2000;119(3):596-600.
5. McBride LR, Naunheim KS, Fiore AC, et al. Clinical experience with 111 Thoratec ventricular assist devices. *Ann Thorac Surg.* 1999;67(5): 1233-9.
6. Portner P, Oyer P, Pennington D, et al. Implantable electrical left ventricular assist system: bridge to transplantation and the future. *Ann Thorac Surg.* 1989;47:142-50.
7. Moskowitz A, Weinberg A, Oz M, Williams D. Quality of life with an implanted left ventricular assist device. *Ann Thorac Surg.* 1997;64: 1764-9.
8. Catanese K, Goldstein D, Williams D, et al. Outpatient left ventricular assist device support: a destination rather than a bridge. *Ann Thorac Surg.* 1996;61:646-53.
9. Mehta S, Aufiero T, Pae W, et al. Combined registry for the clinical use of mechanical ventricular assist pumps and the total artificial heart in conjunction with heart transplantation: sixth official report. *J Heart Lung Transplant.* 1994;14:585-93.
10. AHCPR. Clinical practice guideline #11. Heart Failure: Evaluation and care of patients with left-ventricular systolic dysfunction. Washington (DC): US Department of Health and Human Services; 1994.
11. Rose E, Gelijns A, Moskowitz A, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med.* 2001;345:1435-43.
12. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. *Ann Thorac Surg.* 1999;67(3):723-30.
13. Rector T, Cohn J, Pimobendan Multicenter Research Group. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, controlled trial of pimodbendan. *Am Heart J.* 1992;124(4):1017-25.
14. Oz MC, Argenziano M, Catanese KA, et al. Bridge experience with long-term implantable left ventricular assist devices. Are they an alternative to transplantation? *Circulation.* 1997;95(7):1844-52.
15. Braunwald E. Expanding indications for beta-blockers in heart failure. *N Engl J Med.* 2001;344(22):1711-2.

Discussion

Dr Stephen Westaby *(Oxford, United Kingdom)*. REMATCH is a landmark clinical trial. The clear survival advantage for patients receiving LVADs now justifies the use of circulatory support well beyond the transplant setting. By means of randomization, REMATCH also served to define the dismal natural history of advanced heart failure and to provide reliable outcome data for a first-generation blood pump. Patient enrollment was clearly difficult. The patients had to be nontransplant eligible, but 20 different centers had different eligibility criteria. One patient underwent transplantation at the end of this trial. The initial recruitment was around 2 patients per center per year, and I would suggest that a subsequent relaxation of entry criteria might explain some of the findings in this presentation.

The majority of patients were already receiving inotropes, balloon pump support, or both. The trial was analogous to randomizing Titanic patients to a lifeboat or the sea. Apart from the primary end point, some of the outcomes were disappointing.

Only half of the patients receiving LVADs survived for 1 year. On the Minnesota Scale, the quality of life was not greatly improved by the LVAD. It takes 3 months to recover from a major heart operation, and as anticipated, many experienced chronic infection or neurologic events. Ten of 68 LVADs were replaced, and at last follow-up, 2 of the survivors had actually had a third LVAD. Patients receiving LVADs spent one fifth of their survival period in the hospital, and lifetime use will only prove economically viable if this strategy keeps patients out of the hospital.

The current presentation does not add substantially to the outstanding *New England Journal of Medicine* article. The argument that LVAD survival improved by 6 weeks during the course of the trial is not compelling. I think adjusted entry criteria and progressively more careful patient selection might have accounted for the improvement.

My first question is as follows: Could you elaborate on improvements in the LVAD itself and in postoperative management? Why did these not affect the 30-day mortality? Would you also comment on the durability of the HeartMate LVAD? I think the main question now, is whether, after REMATCH, we move forward with mechanical circulatory support. I would say that at present there are at least 10 continuous flow pumps under development or in clinical practice. These LVADs are much smaller and can be implanted with less perioperative morbidity, fewer complications, and earlier hospital discharge. Infection in these new pumps is uncommon.

Our first patient receiving a lifetime axial flow pump is now 3 years after implantation, in NYHA class I, and fully employed. Others are following in this course. He travels internationally, visits Washington, and talks to the FDA about permanent support.

The other aspect is that the partially unloaded native heart continues to function and often improves with this type of LVAD, and therefore the patient is not entirely dependent on either his own heart or the pump.

I think improved safety justifies implantation before inotrope dependency, and new adjuvant therapies might promote and sustain myocardial recovery.

With the conclusion of REMATCH, it is probably time to plan REMATCH II with second-generation devices and begin implanting them before terminal decline.

I would like to congratulate Dr Park, Dr Rose, and all the colleagues associated with the REMATCH trial.

Dr Park. Thank you, Dr Westaby, for your wonderful comments. I concur with many of the things that you said, and I think

you have a good insight into this study. I would like to respond to your comments. I might differ in some aspects.

This was a prospective randomized trial. The entry criteria were changed during the course of the trial because we had a less-than-anticipated enrollment initially; the number of patients who actually qualified under the new criteria was small. Unlike the surgical cohort, we did not see any survival change during the course of the trial within the medical group. Had we influenced patients' outcome by changing enrollment criteria, we would expect that it would have affected both groups and not just the surgical group, as observed in this randomized trial. Furthermore, the 2-year survival outcome has improved from 0% (PREMATCH) to 21% (first half of REMATCH) and then to 37% (second half of REMATCH) with the same LVAD system. This seems to reflect the benefit of improved management of these patients. Device modifications, such as locking screw and outflow bend relief, are minor changes in my mind to affect survival outcome in any meaningful way.

The REMATCH investigators participating in the surgical group came up with the infection prevention protocols, and we also had conferences about how to manage their nutritional needs. I would say that those are some of the things that we learned as a community caring for these patients. This is the first time this type of device has been tried as a destination therapy in very sick persons, and I think we will continue to learn over time.

Durability is a major problem, and in fact, every patient at our institution who is currently alive had to undergo device change-outs. I am convinced that device change-out is a doable task with acceptable risk. Nevertheless, I do concur with you that we need to have a more reliable and durable device to have long-term success in destination therapy. Perhaps the next-generation axial flow pumps and other things might be the answer, and I agree that is where we should be headed.

I am delighted to hear that you have a patient who has been supported on an axial flow pump over 3 years. Perhaps that is the right technology to adopt. But right now, for many people who are dying from advanced heart failure, the REMATCH trial has for the first time evaluated a new technology in a scientific format in which we have evidence-based medicine that we could practice until the next trial and new devices come along.

In terms of myocardial recovery, it is hard to speculate that a particular device is more effective over another. We are just learning about myocardial recovery. Last year, I had 5 patients in whom I was able to explant devices. We do not know whether an axial flow pump or another pump would be better, but we should be open minded about that.

Dr O. Howard Frazier *(Houston, Tex).* The REMATCH trial was a colossal endeavor by Dr Rose and his team to correlate a group of patients that we could earmark for the future of these studies. I think the miraculous thing was that any of them survived. It was interesting that the first 3 months' survival was the same for both the medical and the surgical group, and the surgical group underwent surgical intervention. I have implanted over 200 HeartMates, and I had 3 early deaths with one 2-year survival. Therefore I think what should be stressed by the REMATCH trial is that this medical group should no longer be subjected to a rather hopeless future.

As to the quality-of-life data, I would like for you to comment on how many of the LVAD survivors are now currently outpatients and how many of the medically treated group are currently outpatients.

As to the patients receiving axial flow pumps, not a one of them would survive this type of randomization. It is a tremendous tour de force of surgery of the groups, particularly in Minnesota and Utah, that were able to achieve very good survival with this.

Dr Park. Thanks, Dr Frazier, for your comments. I think you are right. There were some concerns about the trial initially because we were dealing with such a sick group of patients. Often, we did not have enough time to evaluate them properly, and that might have resulted in early deaths.

The first 2 patients I implanted the device in at the University of Minnesota died. One patient ended up having a massive pulmonary emboli, which was misinterpreted as worsening chronic heart failure. The second patient did well with the operation, but she died of cerebral hyperperfusion. I was very happy to see that her cardiac index went from somewhere around 1.6, I suppose, to 2.5 and 3, and I thought the patient was doing very well. It turned out that she was having too much acute change in cerebral perfusion, which resulted in profound cerebral edema. Those problems have been dealt with in subsequent patients. We have reported this phenomenon of hyperperfusion-related problems in the literature.

When you deal with such a sick group of patients with high baseline mortality, therapeutic efficacy of VAD therapy might not be demonstrable until some time beyond 3 months.

One of the problems as a presenter dealing with a multicenter trial is that you do not really have hands-on experience with every patient. Therefore I will tell you only about my experience at the University of Minnesota, about patients receiving optimal medical management versus those receiving devices and how they are doing with quality of life and survival.

We have one survivor in the optimal medical management group, and he is currently living with the ventricular assist device as a crossover patient. Five other patients have all died within about 6 months of enrollment. Of 8 device implantations, including one crossover, the first 2 died. The subsequent 6 all went home healthy with devices. All 6 patients have required device change-outs, and 2 patients died after device change-out. The remaining 4 patients are currently alive with devices and are all at home in NYHA functional class I.