

Left-Ventricular Assist Devices as Destination Therapy for End-Stage Heart Failure



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Executive Summary

Left-ventricular assist devices (LVADs) augment the impaired cardiac pumping ability in patients experiencing heart failure. LVADs have previously been assessed as a bridge to transplantation for patients waiting for a donor heart (TEC Assessments, Vol. 11, No. 26). The present TEC Assessment addresses use of LVADs as a permanent implant, or destination therapy, among patients who are not heart transplant candidates. Patients with end-stage heart failure who are ineligible for cardiac transplantation are currently managed with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and inotropic agents. These patients may be excluded from heart transplantation due to advanced age (over 65), insulin-dependent diabetes mellitus or other major comorbidities. Outcomes that may be affected by LVADs or medical management include: survival; function; quality of life; need for hospitalization; and adverse events. This Assessment reviews the available evidence to determine how the efficacy of LVADs compares with optimal medical management among patients with end-stage heart failure who are not candidates for cardiac transplantation.

Based upon the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether left-ventricular assist devices as destination therapy for patients with end-stage heart failure who are not candidates for heart transplantation meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Thoratec Corporation manufactures a vented electric device called the Heartmate® VE Left Ventricular Assist System (LVAS). A pneumatically powered predecessor to this device was originally approved by the U.S. Food and Drug Administration (FDA) in September 1994 as a bridge to transplantation for cardiac transplant candidates. The electrically powered VE version was approved in September 1998 for the same indication. Thoratec submitted a supplemental premarket approval application for use as destination therapy in patients with end-stage left ventricular failure who are ineligible for cardiac transplantation. The FDA approved this application on November 6, 2002. Therefore, the technology meets the first criterion.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The available evidence comes from a single well-designed and rigorously conducted randomized trial (the REMATCH trial). The study was a cooperative effort of Thoratec, Columbia University, and the National Institutes of Health. It included 20 experienced transplantation centers. Enrollment totaled 129 adults with chronic end-stage heart failure (NYHA Class IV) and contraindications for cardiac



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transplantation (e.g., age >65 years; insulin-dependent diabetes mellitus; significant physical or mental comorbidities). LVADs were assigned to 68 patients and 61 received optimal medical management. Committees were established to set guidelines for surgical management, optimal medical management, and review of causes of death and adverse events.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have statistically significantly increased survival on an LVAD compared to treatment with optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this groups better outcomes on function, as assessed by NYHA Class and also by quality of life measures among those living to 12 months. LVAD patients spend a greater relative proportion of time inside the hospital than medical management patients, but the survival advantage would mean a longer absolute time outside the hospital. Device reliability has caused concern: the probability of device failure is 35% at 2 years. End of device life is difficult to predict, based on bench testing performed by the FDA Center for Devices and Radiological Health (CDRH).

5. The improvement must be attainable outside the investigational settings.

Outcomes of use of LVADs as destination therapy similar to those reported in the REMATCH trial should be attainable in specialized centers that are experienced in cardiac transplantation and medical management of end-stage heart failure. Such experienced centers are available outside of the investigational setting.

Therefore, based on the above, left-ventricular assist devices as destination therapy for patients with end-stage heart failure who are ineligible for heart transplantation, and who meet the specific patient inclusion and exclusion criteria in the published REMATCH trial, meets the TEC criteria.

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Assessment Objective

Left-ventricular assist devices (LVADs) augment the impaired cardiac pumping ability in patients experiencing heart failure. LVADs have previously been assessed as a bridge to transplantation for patients waiting for a donor heart (TEC Assessments, Vol. 11, No. 26). The present TEC Assessment addresses use of LVADs as a permanent implant, or destination therapy, among patients who are not heart transplant candidates. Patients with end-stage heart failure who are ineligible for cardiac transplantation are currently managed with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and inotropic agents. These patients may be excluded from heart transplantation due to advanced age (over 65), insulin-dependent diabetes mellitus or other major comorbidities. Outcomes that may be affected by LVADs or medical management include: survival; function; quality of life; need for hospitalization; and adverse events. This Assessment reviews the available evidence to determine how the efficacy of LVADs compares with optimal medical management among patients with end-stage heart failure who are not candidates for cardiac transplantation.

Background

Heart Failure

Chronic heart failure is a common disease responsible for high mortality and morbidity. Heart failure represents a complex clinical syndrome caused by many different etiologies whose clinical manifestations reflect a fundamental abnormality—a decrease in the myocardial contractile state such that cardiac output is insufficient for the metabolic requirements of the tissues and organs. The prevalence of heart failure is estimated at 4 to 5 million cases, with an incidence rate of 400,000 cases per year (Eichorn 2001). The mortality rate is estimated to be as much as 700,000 cases per year. (Zeltsman and Acker 2002).

Medical management is the mainstay of supportive care for patients with chronic heart failure. While medical therapies (e.g., angiotensin-converting enzyme (ACE) inhibitors and beta blockers) have improved survival and quality of life outcomes for patients with mild-to-moderate heart failure (Greenberg 2000; Cohn 2000a), irreversible end-stage cardiac disease

unresponsive to medical therapy continues to occur at an approximate rate of 60,000 patients per year (Oz et al. 1995). Inotropic agents and the intra-aortic balloon pump are the last options for medical management of patients with severe heart failure. Cardiac transplantation is widely accepted as the most effective therapy for the treatment of end-stage cardiac failure, for which survival rates for patients transplanted within the past 5 years are 85.6% and 79.5% after 1 and 5 years (Miniati and Robbins 2002). In contrast, patients with New York Heart Association (NYHA) class IV heart failure not receiving transplantation have achieved 20–30% survival rates (Oz et al. 1995).

Limitations of Cardiac Transplantation

Advances in patient management and immunotherapy, with the introduction of cyclosporine in 1980, have improved clinical outcomes and led to an increasing demand for donor hearts. Registries, such as the United Network for Organ Sharing (UNOS), show ever-longer wait lists, longer wait times, and an increasing percentage of status I patients (the sickest patients) undergoing transplantation (UNOS 2001). The proportion of patients who spent over 2 years waiting for transplantation increased from 7.7% in 1991 to 41.6% in 2000 (UNOS 2001). The percentage of status I patients (the most seriously ill) who undergo transplantation also has increased from 32.9% in 1990 to 74.1% in 2000 (UNOS 2002). As the mix of subjects undergoing transplantation has come to include more seriously ill patients, the median length of time on the waiting list for non-status I patients has increased from 450 days in 1991 to 811 days in 1999 (UNOS 2001).

Despite documented success with long-term survival and improved quality of life, wider use of transplantation is limited. According to UNOS (2001), a total of 4,124 patients were on the waiting list in 2000, 2,286 donor hearts were recovered and 2,198 transplants were performed. While on the waiting list, 592 patients died. The limited supply of donor hearts prevents heart transplantation from being a treatment option for many patients with end-stage heart failure. Patients who have very poor baseline function, advanced age and comorbidities, such as insulin-dependent diabetes mellitus, are less likely to survive the transplantation procedure and would be expected to have poorer long-term survival. Such patients are excluded from transplant eligibility.

Ventricular Assist Devices

Left-ventricular assist devices (LVADs) are intended to augment native left ventricular function in several settings. One setting is to allow short-term recovery in patients with postcardiotomy shock. A second is to serve as a bridge to heart transplantation, helping patients survive long enough on the waiting list to reach a transplant date. The third setting is the focus of this Assessment, comprising a permanent alternative to transplantation, or destination therapy, among patients who are not transplant candidates.

Different LVAD designs may be distinguished by whether they are powered electrically or pneumatically and whether a pulsatile pump is used or a rotor mechanism, allowing for continuous blood flow. The model for which its manufacturer has submitted a supplemental premarket approval application (PMA) to the FDA for destination therapy is the Thoratec Heartmate® VE Left Ventricular Assist System (vented electric LVAS). The device consists of a fully implantable pump served by a percutaneous driveline which provides for power and venting. The patient can achieve a high degree of mobility with a wearable battery pack and system controller. An apical anastomosis links the left ventricle with the pump via an inflow cannula. An outflow cannula is anastomosed to the aorta.

Use of LVADs raise important social, economic and ethical issues that are beyond the scope of this Assessment. However, interested readers may wish to examine the report of a Working Group on Mechanical Circulatory Support Systems (Van Critters et al. 1985). The group was appointed by the Director of the National Heart, Lung, and Blood Institute (NHLBI). The report is a comprehensive discussion of the implications of LVAD use.

FDA Status. A pneumatically powered predecessor to the Heartmate® VE LVAS was originally approved by the U.S. Food and Drug Administration (FDA) in September 1994 as a bridge to transplantation for cardiac transplant candidates. The electrically powered VE version was approved in September 1998 for the same indication. Thoratec submitted a supplemental premarket approval (sPMA) application for use as destination therapy in patients with end-stage left ventricular failure who are ineligible for cardiac transplantation. The FDA approved this application on November 6, 2002.

Methods

Search Methods

The MEDLINE database was searched from 1996 through November 2002, using the search term “heart-assist devices.” The search was limited to English-language citations involving human subjects. In addition, *Current Contents* and bibliographies of key articles were reviewed for relevant citations. Also, information was sought from the U.S. Food and Drug Administration Web site.

Study Selection

Studies were sought that provided information about clinical use of LVADs in patients with end-stage heart failure who were not candidates for heart transplantation. One study, a randomized trial (REMATCH Study Group 2001), fit this description.

Medical Advisory Panel Review

Current Assessment. This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on October 10, 2002. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusion of this Assessment.

Formulation of the Assessment

Patient Indications

The patient population of interest consists of adults with end-stage left ventricular failure (New York Heart Association class IV) who have contraindications for cardiac transplantation, such as: age 65 years or older; insulin-dependent diabetes mellitus; chronic renal failure; and other major comorbidities.

Technologies to be Compared

Left-ventricular assist device implantation is the index procedure. LVADs could be proposed for patients receiving suboptimal medical management as a bridge to better medical management. However, when LVADs are given as destination therapy, they are intended for patients who have end-stage left ventricular failure despite receiving optimal medical

management. LVADs are proposed as an alternative to continuation of optimal medical management.

Optimal medical is the only alternative available to this patient population, which can consist of inotropic agents, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and intra-aortic balloon pumps. These patients often spend much of their short life expectancies hospitalized.

Health Outcomes

- Survival
- Function (NYHA class)
- Quality of life
- Time spent hospitalized
- Neurologic dysfunction
- Bleeding
- Embolic events
- Infection/sepsis
- LVAD malfunction/failure

Assessment Question

What is the efficacy of left-ventricular assist device implantation compared with optimal medical management?

Review of Evidence

REMATCH Trial

The only study to meet selection criteria is the “Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure” (REMATCH). This randomized trial compared LVAD implantation with optimal medical management in 129 patients with end-stage heart failure who were not candidates for heart transplantation (Rose et al. 2001; 1999). This trial was published in the *New England Journal of Medicine (NEJM)* and has also been reviewed by the FDA Circulatory System Devices Panel, which met in March 2002. In addition to the *NEJM* article, this Assessment sought information from presentations at the FDA panel meeting, given by Thoratec representatives, REMATCH investigators, and staff of the FDA Center for Devices and Radiologic Health (CDRH).

Details on study design, patient selection, randomization technique and treatment protocol are included in Table 1. Results are presented in Table 2. The trial was conducted at 20 experienced cardiac transplantation centers under a cooperative agreement between Columbia

University, the National Institutes of Health (NIH), and Thoratec. A power analysis was performed, using survival as the primary study endpoint. Patients were selected primarily for belonging to New York Heart Association (NYHA) Class IV for at least 90 days, despite use of angiotensin-converting enzyme (ACE) inhibitors, diuretics and digoxin. Patients also had left ventricular ejection fraction of 25% or less and a peak oxygen concentration of 12 mL/kg or less, or continued need for intravenous (IV) inotropic therapy for symptomatic hypotension, decreasing renal function or worsening pulmonary congestion. Patients were allowed to continue on beta-blockers if given for at least 60 of the 90 days before randomization. Enrollment criteria were relaxed slightly after 18 months, but only 5 patients were recruited under these modified standards. Cardiac transplantation contraindications included: age over 65 years; insulin-dependent diabetes mellitus with end-organ damage; chronic renal failure and other major physical or mental comorbidities.

Randomization was made at a ratio of 1:1 to either LVAD implantation or optimal medical management, with 68 patients given LVADs and 61 patients assigned to medical management. LVADs were implanted in a preperitoneal pocket or the peritoneal cavity, depending on surgeon preference. Otherwise, surgeons were required to follow a committee’s management guidelines. Optimal medical management guidelines were also developed by a committee and gave specific recommendations on use of ACE inhibitors. Discontinuation of IV inotropic agents was encouraged for medically managed patients. The two groups were found to be comparable on baseline characteristics, which included: age; left-ventricular ejection fraction (LVEF); cardiac index; serum creatinine; use of IV inotropic agents; and Minnesota Living with Heart Failure score. An independent committee was established to review causes of death and evaluate adverse events.

Survival. In the *NEJM* article, 95 deaths had been observed. Comparing Kaplan-Meier survival in the two groups, the relative risk (RR) of all-cause death was significantly reduced among those receiving LVADs (RR: 0.52; 95% confidence interval: 0.34, 0.78). Although the study was not designed to have sufficient power to perform subgroup analyses, this reduction was also significant in the group aged 60 to 69 years (RR: 0.49; 95% CI: 0.25, 0.95). Median survival was 408 days in the LVAD group and

Table 1. REMATCH Trial Methods

Design	Randomized clinical trial conducted at 20 experienced cardiac transplantation centers under cooperative agreement between Columbia University, NIH, and Thoratec. Random 1:1 assignment to either vented electric LVAD or optimal medical therapy. Independent morbidity and mortality committee reviewed causes of death and adverse effects.
Patient Selection	<p>Adults with chronic end-stage heart failure and contraindications to transplantation</p> <ul style="list-style-type: none"> - Symptoms of NYHA class IV heart failure for ≥ 90 days despite ACE inhibitors, diuretics and digoxin; - LVEF $< 25\%$; - Peak O_2 consumption ≤ 12 mL/kg or continued need for IV inotropic therapy for symptomatic hypotension, decreasing renal function or worsening pulmonary congestion; - Patients could continue to receive beta-blockers if administered ≥ 60 of 90 days before randomization. <p>18 months after start, entry criteria expanded to increase enrollment (total 3 LVAD patients, 2 medical therapy patients):</p> <ul style="list-style-type: none"> - NYHA class IV heart failure for ≥ 60 days - Peak O_2 consumption ≤ 14 mL/kg - Patients in NYHA class III/IV for ≥ 28 days, received ≥ 14 days support with intra-aortic balloon pump or dependent on IV inotropic agents, with 2 failed weaning attempts <p>Transplantation contraindications:</p> <ul style="list-style-type: none"> - Age > 65 years; - Insulin-dependent diabetes mellitus with end-organ damage; - Chronic renal failure (serum creatinine > 2.5.mg/dL for > 90 days before randomization); - Presence of other clinically significant conditions.
Randomization Method/Treatment Protocol/Group Size	<p>Block design used to ensure continuously equivalent group size, stratified by center. Coordinating center confirmed eligibility of patients. All investigators except statisticians were unaware of the overall outcome data throughout the enrollment period. LVAD implanted in preperitoneal pocket or peritoneal cavity, based on surgeon preference. Surgical management followed committee guidelines. Medical therapy followed committee guidelines, with specific recommendations on use of ACE inhibitors, encouraged discontinuation of IV inotropic agents. 68 patients received LVADs, 61 assigned to medical therapy.</p>

Table 2. REMATCH Trial Results

Results (Cox proportional hazards regression used to adjust for differences in baseline predictors; analyses conducted by intention-to-treat)	2 patients in medical therapy group withdrew at 1 mo., 6 mos.; none crossed over; none underwent cardiac transplantation.		Survival, LVAD			Survival, Med Ther		
	RR	95% CI	Med	1 yr.	2 yrs.	Med	1 yr.	2 yrs.
Death, any cause, all	0.52	0.34, 0.78	408 d	52%	23%	150 d	25%	8%
18-59 years	0.47	0.17, 1.28		74%				33%
60-69 years	0.49	0.25, 0.95		47%				15%
≥ 70 years	0.59	0.31, 1.15						
			LVAD		Med Ther		p value	
			Assessed	Score	Assessed	Score		
SF-36 physical function			23/24	46±19	6/11	21±21		0.01
SF-36 emotional role			23/24	64±45	6/11	17±28		0.03
Minnesota Living with HF			23/24	41±22	6/11	58±21		0.11
Beck depression			22/24	8±7	5/11	13±7		0.04
Median NYHA class			24/24	II	7/11	IV		<0.001
Adverse events rate per patient year			LVAD	Med Ther	Rate Ratio (95% CI)			
All			6.45	2.75	2.35 (1.86, 2.95)			
Non-neurologic bleeding			0.56	0.06	9.47 (2.30, 38.90)			
Neurologic dysfunction			0.39	0.09	4.35 (1.31, 14.50)			
Supraventricular arrhythmia			0.12	0.03	3.92 (0.47, 32.40)			
Peripheral embolic event			0.14	0.06	2.29 (0.48, 10.80)			
Sepsis			0.60	0.30	2.03 (0.99, 4.13)			
Local infection			0.39	0.24	1.63 (0.72, 3.70)			
Renal failure			0.25	0.18	1.42 (0.54, 3.71)			
Miscellaneous adverse events			1.37	0.98	1.41 (0.93, 2.12)			
Syncope			0.04	0.03	1.31 (0.12, 14.40)			
Serious psychiatric disease			0.04	0.03	1.31 (0.12, 14.3)			
Cardiac arrest			0.12	0.18	0.65 (0.21, 2.00)			
Non-perioperative myocardial infarction			0.02	0.03	0.65 (0.04, 10.30)			
Ventricular arrhythmia			0.25	0.56	0.45 (0.22, 0.90)			
Hepatic failure			0.02	0.00				
Event related to the LVAD								
Suspected malfunction of the LVAD			0.75					
Perioperative bleeding			0.46					
Infection of the drive-line tract/pocket			0.41					
Infection of pump interior, inflow tract, or outflow tract			0.23					
Right heart failure			0.17					
Failure of LVAD system			0.08					
Thrombosis in LVAD			0.06					
Perioperative myocardial infarction			0.00					
Hospitalization								
Days spent out of the hospital			340	106				
Days spent in the hospital			88	24				
Days spent in the hospital for medical management or implantation of LVAD			29	5				

150 days in the medical therapy group. One- and two-year survival rates were 52% and 23% in the LVAD group, compared with 25% and 8% in the medical management group. Follow-up through February 2002 presented by Dr. Eric Rose at the FDA advisory panel meeting showed that Log-rank test results were still highly significant ($p=0.001$).

Function. NYHA Classes may be distinguished as follows: I is defined as no symptoms produced by ordinary daily activity; II is symptoms present during normal daily activities; III is symptoms with less than normal activity; and IV is symptoms at rest (Cohn 2000b). At baseline, 65 of 68 LVAD patients were in NYHA Class IV and 60 of 61 medical management patients were similarly classified. At 1-year follow-up, 24 of 24 living LVAD patients had been reassessed, compared with 7 of 11 patients who received medical management. The median follow-up NYHA Class was II in the LVAD group and IV in the medical management group. The March 2002 presentation by CDRH staff at the FDA advisory panel meeting showed p values for statistical tests of NYHA Class at 3 months, 6 months, and 12 months. At each follow-up interval, the LVAD group had better outcomes, significant at $p<0.001$. Dr. Rose's presentation at the FDA advisory panel meeting revealed that approximately 30% of LVAD patients were in NYHA Class III or IV at 12 months, compared with 100% of medical management patients.

Adverse Events. Due to differences between groups in survival, the *NEJM* article reported adverse events as rates per patient-year. Considering all serious adverse events, the LVAD group was more than twice as likely to experience them, compared with the group receiving medical management: a rate ratio of 2.35 was obtained with a 95% CI of 1.86 to 2.95. Specific serious adverse events that were significantly more likely in the LVAD group included non-neurologic bleeding (rate ratio: 9.47; 95% CI: 2.30, 38.90) and neurologic dysfunction (rate ratio: 4.35; 95% CI: 1.31, 14.50). A higher rate of sepsis was nearly significant, with a rate ratio of 2.03 and 95% CI from 0.99 to 4.13. Rate ratios exceeded 2.0 for supraventricular arrhythmia and peripheral embolic events, but 95% confidence intervals overlapped 1.0.

Events related to the LVAD were also reported as rates per patient year. The rates for specific types of events are: suspected malfunction of the LVAD (0.75); perioperative bleeding (0.46);

infection of the drive-line tract or pocket (0.41); other pump component infections (0.23); right heart failure (0.17); failure of the LVAD system (0.08); and thrombosis in the LVAD (0.06).

The CDRH presentation noted the number of patients who withdrew from treatment in each group, based on data reported through June 2001. Among patients managed medically, 4 patients withdrew from treatment within 1 month of randomization, while 8 withdrew later. In the LVAD group, 7 patients (or family members) chose to have the device turned off or did not agree to replacement; 6 others elected to have treatment withdrawn.

Device Failure/Reliability. In the *NEJM* article, the probability of device failure was reported as 35% at 2 years. The LVAD was replaced in 10 patients. In the CDRH presentation at the FDA advisory panel meeting, implant element replacement was reported to be required for 20 elements in 19 patients. Among these cases, 12 pumps were removed and 8 were replaced. Seven of these 8 patients died and all 4 patients who did not get replacement devices died. External element replacement was required for 50 elements in 38 patients. There were 156 reported malfunctions in 25 patients.

The CDRH presentation also described the results of bench testing, in which 15 LVAD units performed a mock circulatory loop, immersed in water. Ten units failed, 8 due to main bearing malfunction, while 5 remained on test as of August 3, 2001. Reliability was estimated to be 86% at 2 years, at 60% confidence and 76% at 2 years, at 90% confidence. Mean time to pump failure was estimated at 4 years at 60% confidence and 3 years at 90% confidence. Key comments from CDRH staff included: observed pump end-of-life events were at low end of reliability prediction, and no objective device end of life indicator has been established.

Hospitalization. The *NEJM* article stated that the median number of days spent in the hospital was 88 for the LVAD group and 24 for the medical management group. Median time spent out of the hospital was 340 days for LVAD patients and 106 days for patients managed medically. The CDRH presentation cited different values for these outcomes, with smaller differences between groups. It is unclear which source represents more complete follow-up. However, the CDRH presentation identified the total amount of time spent in and out of the

hospital and expressed these as a percentage of total time. Number of days in the hospital was 24% of the total in the LVAD group, versus 15% in the medical management group. Number of days out of the hospital was 76% of the total for LVAD patients and 85% for medical management patients. No statistical test results were provided. Although LVAD patients appeared to spend a lower relative proportion of their remaining days outside the hospital, their longer overall survival would translate into a greater absolute number of days outside the hospital.

Quality of Life. In the *NEJM* article, quality of life was assessed among patients who survived to 12 months and were assessable. Dr. Rose presented on quality of life at 1, 3, 6 and 12 months in his presentation at the FDA advisory panel meeting. Of 24 LVAD survivors at 12 months, 22 or 23 patients were assessed on various quality of life measures. Of 11 medical management survivors at 12 months, 5 or 6 patients were assessed. According to the *NEJM* article, at 12 months, the LVAD group had significantly better mean scores on the SF-36 physical function scale ($p=0.01$) and the SF-36 emotional role scale ($p=0.03$). Graphs of these two scales show apparently smaller advantages for the LVAD group at 3 and 6 months, and the smallest difference occurs at 1 month, favoring medical management. A similar pattern was observed on the Minnesota Living with Heart Failure Scale, but the difference between groups was not significant at 12 months. The Beck Depression Inventory scores favored the LVAD group at every interval and was significant at 12 months ($p=0.04$).

Quality of life data presented by CDRH staff at the advisory panel meeting conflicts somewhat with the *NEJM* article, but it is unclear which source provides more complete follow-up. While the article reported a significant difference between groups in the SF-36 physical scale at 12 months, the CDRH presentation stated there was no significant difference at 12 months and 6 months, while a borderline significant difference ($p=0.052$) was observed at 3 months. CDRH stated that the SF-36 mental scale saw no significant differences at 3, 6 and 12 months. CDRH reported a significant difference in the Beck Depression Inventory at 6 months, and borderline significance at 3 and 12 months.

The quality of life data clearly show that, with the exception of the first postoperative month,

LVAD patients clearly do not measure as worse than patients who receive optimal medical management. At 12 months, LVAD patients on average have significantly better quality of life, but it could not be considered as good as that for healthy people in the general population. The *NEJM* article notes that SF-36 physical function scores for the LVAD patients are similar to those for patients undergoing long-term hemodialysis or ambulatory patients with heart failure. Despite the considerable adverse events associated with LVAD implantation, the improved survival, function and quality of life make this an option that many patients would prefer over optimal medical management.

Summary of Application of the Technology Evaluation Criteria

Based upon the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether left-ventricular assist devices as destination therapy for patients with end-stage heart failure who are not candidates for heart transplantation meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The available evidence comes from a single well-designed and rigorously conducted

randomized trial (the REMATCH trial). The study was a cooperative effort of Thoratec, Columbia University, and the National Institutes of Health. It included 20 experienced transplantation centers. Enrollment totaled 129 adults with chronic end-stage heart failure (NYHA Class IV) and contraindications for cardiac transplantation (e.g., age ≥ 65 years; insulin-dependent diabetes mellitus; significant physical or mental comorbidities). LVADs were assigned to 68 patients and 61 received optimal medical management. Committees were established to set guidelines for surgical management, optimal medical management, and review of causes of death and adverse events.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have statistically significantly increased survival on an LVAD compared to treatment with optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this groups better outcomes on function, as assessed by NYHA Class and also by quality

of life measures among those living to 12 months. LVAD patients spend a greater relative proportion of time inside the hospital than medical management patients, but the survival advantage would mean a longer absolute time outside the hospital. Device reliability has caused concern: the probability of device failure is 35% at 2 years. End of device life is difficult to predict, based on bench testing performed by the FDA Center for Devices and Radiological Health (CDRH).

5. The improvement must be attainable outside the investigational settings.

Outcomes of use of LVADs as destination therapy similar to those reported in the REMATCH trial should be attainable in specialized centers that are experienced in cardiac transplantation and medical management of end-stage heart failure. Such experienced centers are available outside of the investigational setting.

Therefore, based on the above, left-ventricular assist devices as destination therapy for patients with end-stage heart failure who are ineligible for heart transplantation, and who meet the specific patient inclusion and exclusion criteria in the published REMATCH trial, meets the TEC criteria.

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