

## CLINICAL RESEARCH

## Clinical Trials

# Chronic Mechanical Circulatory Support for Inotrope-Dependent Heart Failure Patients Who Are Not Transplant Candidates

## Results of the INTrEPID Trial

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- Objectives** This study evaluated the impact of left ventricular assist device (LVAD) support on survival and quality of life in inotrope-dependent heart failure patients ineligible for cardiac transplantation.
- Background** The role for LVADs as a bridge to cardiac transplantation has been established, but data supporting their role as permanent therapy in nontransplant candidates are limited.
- Methods** The INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial was a prospective, nonrandomized clinical trial comparing LVAD with optimal medical therapy (OMT). Fifty-five patients with New York Heart Association functional class IV symptoms who failed weaning from inotropic support were offered a Novacor LVAD. Eighteen of these patients did not receive an LVAD owing to patient preference (n = 14) or unavailability of the device (n = 4) but consented to follow-up and constitute a contemporaneous control group.
- Results** The LVAD and OMT patients were well matched for demographic and disease severity measures, except OMT patients had a lower mean serum sodium (128 mg/dl vs. 134 mg/dl; p = 0.001) and a higher mean blood urea nitrogen concentration (59 vs. 40; p = 0.02). The LVAD-treated patients had superior survival rates at 6 months (46% vs. 22%; p = 0.03) and 12 months (27% vs. 11%; p = 0.02). Adverse event rates were higher in the OMT group. Eighty-five percent of the LVAD-treated patients had minimal or no heart failure symptoms. Five LVAD patients and 1 OMT patient improved sufficiently while on therapy to qualify for cardiac transplantation.
- Conclusions** Inotrope-dependent heart failure patients who are ineligible for transplantation have a high short-term mortality rate and derive a significant survival advantage from “destination” mechanical circulatory support. (J Am Coll Cardiol 2007;50:741–7) © 2007 by the American College of Cardiology Foundation

The role of mechanical circulatory support for patients awaiting cardiac transplantation who develop hemodynamic instability or end-organ dysfunction has been established. In nonrandomized studies, transplant candidates who were sufficiently ill to undergo treatment with a left ventricular

assist device (LVAD) had survival rates comparable with less ill patients managed medically. By the time of trans-

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site payments for enrollment and/or study-related activities. Dr. Butler has received access to the WorldHeart registry database for independent analysis and serves on the Clinical Events Committee for the RELIANT trial. Dr. Portner has been a consultant to WorldHeart and a member of the WorldHeart Advisory Board. Dr. Pasque is a RELIANT trial investigator and has received site payments for enrollment and/or study-related activities. Dr. Pierson is a RELIANT trial investigator and has received site payments for enrollment and/or study-related activities; he has also received honoraria from WorldHeart.

Manuscript received October 10, 2006; revised manuscript received March 22, 2007, accepted March 28, 2007.

**Abbreviations and Acronyms**

- CVA** = cerebrovascular accident
- LVAD** = left ventricular assist device
- NYHA** = New York Heart Association
- OMT** = optimal medical therapy
- TIA** = transient ischemic attack

plant, LVAD-treated patients consistently exhibited improved end-organ function and nutritional status indicative of interim physiologic recovery (1-4). Perioperative morbidity was demonstrated to be lower in patients managed with an LVAD before transplant compared with those treated with intravenous inotropic therapy (5).

The support of several patients for up to 4 years with their original Novacor LVAD (World-

Heart, Oakland, California) provided initial evidence that this mechanical support technology was sufficiently reliable for consideration as “destination therapy” in nontransplant candidates (6,7). The INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial was designed as a feasibility study to evaluate the effectiveness of the Novacor LVAD for long-term mechanical circulatory support of patients who were not cardiac transplant candidates.

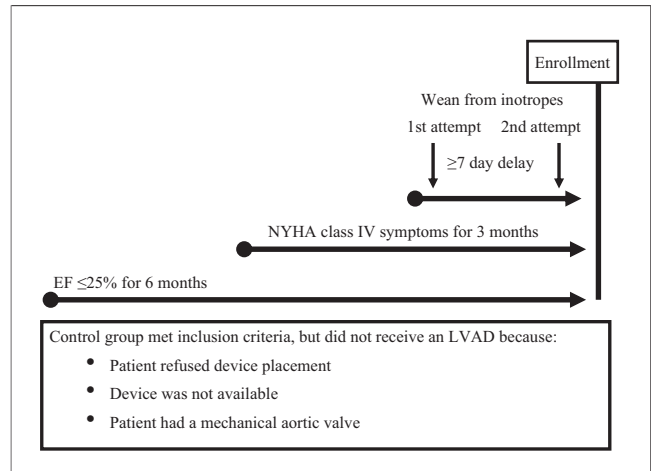
**Methods**

**Trial design and conduct.** The INTrEPID trial was a nonrandomized, 2-arm clinical trial conducted at 13 centers in the U.S. and Canada with experience implanting the Novacor LVAD as a bridge to transplantation (Appendix). The trial was approved by the U.S. Food and Drug Administration (FDA) as a feasibility study. It was hypothesized that the LVAD would improve both survival and quality-of-life measures for patients treated with intravenous inotropic therapy for cardiogenic shock, compared with an optimal medical therapy (OMT) treatment strategy.

Qualifying patients meeting the inclusion and exclusion criteria were enrolled in the LVAD or OMT arms of the trial based primarily upon patient preference or device availability (Fig. 1). In practice, recruitment and study qualification was conducted on hospitalized patients with intermittent or continuous invasive hemodynamic assessments confirming the clinical impressions of disease status.

The primary end point of the INTrEPID trial was all-cause mortality at 6 months. Secondary end points included adverse events, functional capacity, and health-related quality of life.

The costs of data collection were covered by WorldHeart. Patient care costs were shared by the manufacturer and the patients’ public or private insurance as a condition of device availability. An independent Study Steering Committee approved the study design, and a Data and Safety Monitoring Board followed the conduct of the trial and adverse events. Patients provided informed consent before enroll-



**Figure 1** INTrEPID Enrollment Criteria

Enrollment strategy for the INTrEPID trial. Eligible patients had severe left ventricular dysfunction for  $\geq 6$  months, New York Heart Association (NYHA) functional class IV symptoms for  $\geq 3$  months, and were required to fail 2 attempts at weaning from inotropic support separated by at least 7 days. EF = ejection fraction; LVAD = left ventricular assist device.

ment, and the Institutional Review Board at each of the participating institutions approved the trial.

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

**Patients. INCLUSION CRITERIA.** Eligible patients were adults with inotrope-dependent stage D heart failure, an ejection fraction of  $< 25\%$ , and New York Heart Association (NYHA) functional class IV symptoms for  $\geq 3$  months before enrollment and were not candidates for cardiac transplantation based upon site-specific transplant program criteria. Patients had been treated with maximally tolerated doses of angiotensin-converting enzyme inhibitors, beta-blockers, digoxin, diuretics, and/or other vasodilators. All patients were receiving inotropic therapy for clinical and/or hemodynamic evidence of circulatory failure. Before enrollment, the inotropic drugs were weaned on 2 separate occasions separated by at least 7 days. Inability to successfully wean from inotropes was defined by at least 1 of the following: systemic hypotension, exacerbation of heart failure symptoms, worsening end-organ function, a cardiac index of  $\leq 2.2$  l/min/m<sup>2</sup>, or a pulmonary capillary wedge pressure of  $> 20$  mm Hg.

**EXCLUSION CRITERIA.** Patients were excluded from the trial if their body surface area was  $< 1.5$  m<sup>2</sup> or there was a contraindication to chronic anticoagulation. Presence of a mechanical aortic valve constituted an exclusion criterion for LVAD support, because of the thromboembolism risk resulting from leaflet immobility (control patients were exempt from this exclusion criterion). Subjects with a cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months before enrollment, a  $> 70\%$  carotid stenosis, or an ulcerated carotid plaque were excluded. Unresolved drug or alcohol dependency, active systemic infection confirmed by

positive blood culture, a serum creatinine of >5.0 mg/dl, total bilirubin >5.0 mg/dl, mechanical ventilatory support for >48 h at the time of enrollment, or a comorbid medical condition limiting life expectancy to <2 years were also contraindications to enrollment.

Patients in the OMT group met all study criteria but did not receive an LVAD because they chose not to undergo LVAD implantation, a mechanical aortic valve was present, or there were inadequate identifiable financial resources to cover the cost of device implantation and follow-up.

**Procedure and follow-up.** The Novacor LVAD is a surgically implanted 1 kg electromagnetically actuated blood pump capable of outputs up to 10 l/min. A conduit placed in the left ventricular apex diverts blood into the pump, and the pump returns blood to the ascending aorta. A driveline tunneled across the abdominal wall is connected to a wearable controller (0.6 kg) that regulates and monitors pump function and a pair of portable batteries (2.7 kg) that provide uninterrupted power for 6 h.

The LVAD recipients were managed with an antithrombotic regimen that included early postoperative heparin (postoperative day 2; target partial thromboplastin time >55 s), coumadin to a target international normalized ratio of 2.5 to 3.5, aspirin 81 to 325 mg/day, and dipyridamole 75 mg 3 times/day. Clopidogrel, 75 mg daily, could be used at the investigator's discretion.

Functional capacity was determined using NYHA functional class assessment. Minnesota Living With Heart Failure Questionnaire and SF-36 Health Survey scores were obtained at 1, 3, 6, and 12 months after enrollment and annually thereafter.

**Statistical analysis.** Categorical variables are presented as percentages and were analyzed using chi-square tests. Continuous variables are presented as means with standard deviation and were analyzed using the unpaired Student *t* test. Adverse events were analyzed as time-dependent variables and statistically compared using Cox *F* test (8). Survival was analyzed as a discrete end point at 6 and 12 months using the log-rank test. Kaplan-Meier survival curves were generated and statistically analyzed using the log-rank test. Patients were censored with respect to subsequent follow-up at the time of transplantation. For all analyses, a *p* value of <0.05 was considered to be statistically significant. All analyses were conducted using SAS statistical software (SAS Institute, Cary, North Carolina).

## Results

Of the 81 patients screened between March 2000 and May 2003, 55 were enrolled in the trial. The presence of exclusion criteria (*n* = 10) and death before enrollment (*n* = 7) were the primary reasons for nonparticipation. Exacerbation of heart failure symptoms constituted the primary reason for inability to wean from inotropic support in 94% of the OMT and 84% of the LVAD cohorts.

Baseline characteristics of the patients are shown in Table 1. Both OMT and LVAD patients had systemic hypotension

**Table 1** Baseline Characteristics of the INTRIPID Population

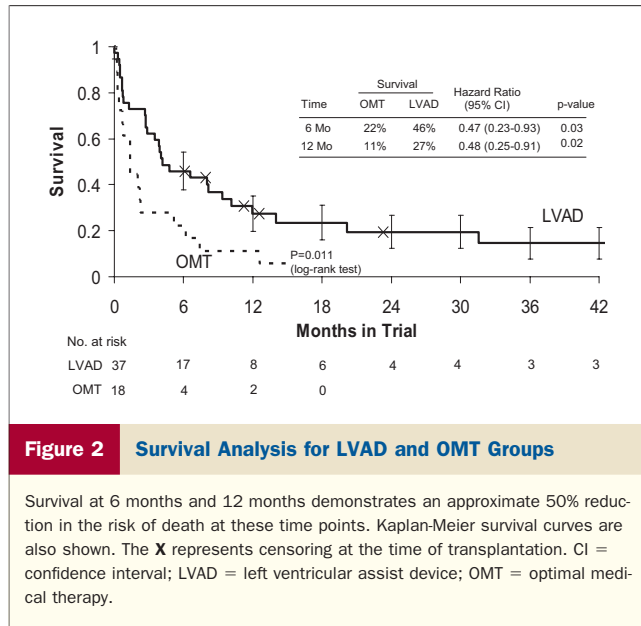
Variable	LVAD (n = 37)	OMT (n = 18)	<i>p</i> Value
Age, yrs	60.0 ± 11.2	58.0 ± 9.9	0.40
Female, %	8	28	0.10
BSA, m <sup>2</sup>	1.96 ± 0.28	1.98 ± 0.18	0.75
Nonischemic, %	43	28	0.38
Prior CABG, %	32	56	0.14
Prior CVA, %	16	11	0.71
ICD, %	46	61	0.39
Albumin, g/dl	3.3 ± 0.5	3.5 ± 0.3	0.25
SGOT, U/l	64 ± 156	62 ± 46	0.73
SGPT, U/l	77.8 ± 182	46.9 ± 46.4	0.55
BUN, mg/dl	40.8 ± 25.9	59.9 ± 34.0	0.02
Creatinine, mg/dl	1.8 ± 0.9	2.1 ± 1.0	0.24
Sodium, mmol/dl	134 ± 4.3	128 ± 8.0	0.001
EF, %	14.2 ± 3.8	13.2 ± 2.0	0.47
MAP, mm Hg	64.4 ± 3.8	63.1 ± 17.0	0.86
RA, mm Hg	13.1 ± 7.5	16.2 ± 6.5	0.15
PAS, mm Hg	55.5 ± 13.5	58.2 ± 13.3	0.53
PCWP, mm Hg	24.7 ± 8.1	29.2 ± 8.0	0.06
PVR, dynes/s/cm <sup>-5</sup>	318.8 ± 199.4	341.1 ± 300.1	0.77

BSA = body surface area; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; CVA = stroke; EF = ejection fraction; ICD = implantable cardiac defibrillator; LVAD = left ventricular assist device; MAP = mean arterial pressure; OMT = optimal medical therapy; PAS = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

(mean arterial pressure: OMT: 63 ± 17 mm Hg; LVAD: 64 ± 3 mm Hg; *p* = 0.86), and a severely reduced left ventricular ejection fraction (OMT: 13.2 ± 2.0; LVAD: 14.2 ± 3.8; *p* = 0.47). Left- and right-sided filling pressures were elevated despite OMT and positive inotropic drugs. Both groups had end-organ hypoperfusion as evidenced by elevated liver function tests, elevated blood urea nitrogen and creatinine, and hyponatremia. The groups were well matched with regard to predictors of adverse outcomes in heart failure, except that OMT patients had lower serum sodium than the LVAD patients (128 ± 8.0 mmol/dl vs. 134 ± 4.3 mmol/dl; *p* < 0.001), and a higher blood urea nitrogen (60 ± 34.0 mg/dl vs. 41 ± 25.9 mg/dl; *p* = 0.02).

Patients treated with an LVAD had superior survival rates at 6 months (46% vs. 22%; *p* = 0.03) and 12 months (27% vs. 11%; *p* = 0.02) compared with patients treated with OMT (Fig. 2). The hazard ratio for mortality associated with LVAD support was 0.46 (95% confidence interval 0.25 to 0.85). Causes of death are shown in Table 2. In the OMT group, all of the patients died of cardiovascular dysfunction (primarily heart failure), whereas stroke (34%) and infection (24%) accounted for the majority of deaths in the LVAD group. A total of 5 patients (13.5%, time from enrollment 6 to 23 months) in the LVAD group and 1 patient (6%, time from enrollment 16 months) in the OMT group became eligible for and received a cardiac transplant.

The rates of nonfatal adverse events are shown in Figure 3. Bleeding was more frequently seen in the LVAD group and was most common during the perioperative period. Cardio-



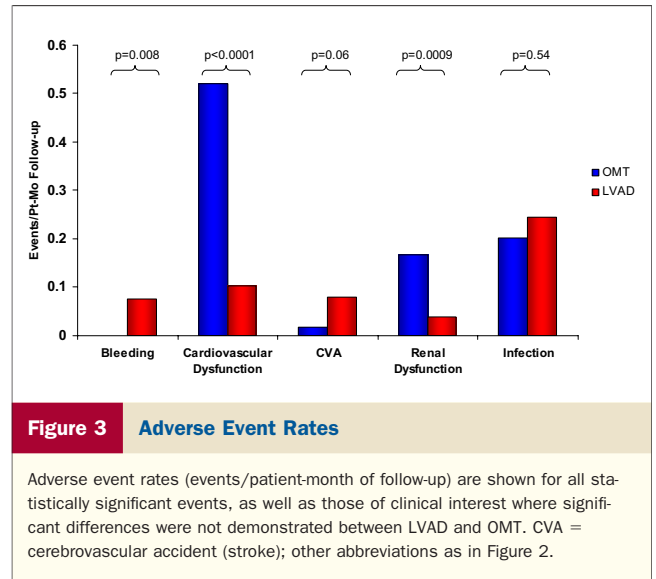
**Figure 2** Survival Analysis for LVAD and OMT Groups

Survival at 6 months and 12 months demonstrates an approximate 50% reduction in the risk of death at these time points. Kaplan-Meier survival curves are also shown. The X represents censoring at the time of transplantation. CI = confidence interval; LVAD = left ventricular assist device; OMT = optimal medical therapy.

vascular dysfunction and renal dysfunction were more common in the OMT group. There was a strong trend toward a higher stroke rate in LVAD patients ( $p = 0.06$ ). The infection rate was similar between groups. When evaluated as time-dependent variables, the highest risk for an adverse event was seen during the first month after implant and declined thereafter.

The CVA and TIA rates are shown in Figure 4. Twenty LVAD patients experienced 30 strokes, and 10 patients experienced 15 TIAs. Overall, 62% of LVAD patients and 11% of OMT patients experienced a stroke or TIA during the study. The risk of stroke was highest during the first month after device implant and subsequently decreased over time to a rate of  $<0.1$  events/patient-month. The TIA rate was low and remained constant throughout the trial.

Patients in the OMT group experienced no improvement in NYHA functional class (Fig. 5). In contrast, 85% of the LVAD patients had either no symptoms or minimal heart failure symptoms at the last assessment. Minnesota Living With Heart Failure Questionnaire scores and SF-36 Health Survey physical and mental functioning scores improved



**Figure 3** Adverse Event Rates

Adverse event rates (events/patient-month of follow-up) are shown for all statistically significant events, as well as those of clinical interest where significant differences were not demonstrated between LVAD and OMT. CVA = cerebrovascular accident (stroke); other abbreviations as in Figure 2.

throughout the observation period in the LVAD group (data not shown). The small number of OMT patients in this trial did not permit a meaningful comparison of the quality-of-life measures.

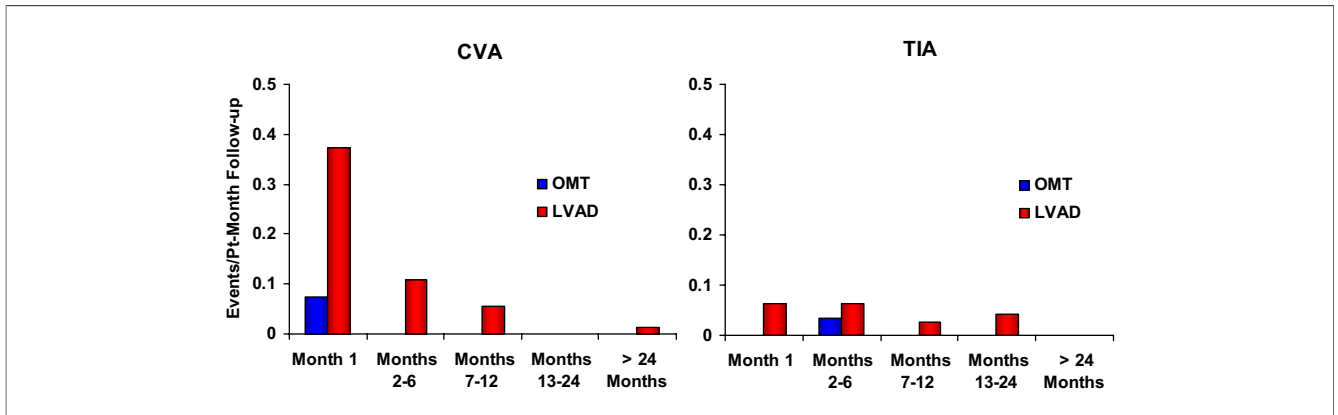
**Discussion**

Outcomes in the INTrEPID trial highlight several important issues for patients with advanced/end-stage heart failure and their caregivers. Medically managed patients who are dependent upon inotropic therapy to maintain end-organ perfusion, reasonable hemodynamics, and modest residual congestion had a mortality rate of nearly 90% at 1 year. In a similar group of patients, LVAD support resulted in a significant survival advantage associated with functional and quality-of-life improvements. This suggests that the benefits of restoring a relatively normal hemodynamic profile outweigh the surgical risk and subsequent device-related complications.

The present OMT patient outcomes and reports from other researchers consistently demonstrate that end-stage heart failure patients who are clinically failing standard therapies have limited therapeutic options and a poor prognosis. The 6- and 12-month mortality rates in patients treated with medical therapy in this trial were 78% and 89%, respectively. In a similar study population in whom inotropic therapy was not required for enrollment, the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) investigators demonstrated mortality rates of 75% at 1 year and 92% at 2 years in patients treated with evidence-based pharmacotherapeutic regimens (9). The survival of OMT patients in the present report is even less favorable and is similar to the Hershberger et al. (10) series of patients treated with ambulatory inotropic therapy, who experienced a 90% mortality rate at 12 months.

Cause of Death	LVAD	OMT
	(n = 29/37)	(n = 17/18)
Cardiac dysfunction	5	17
CVA	10	0
Infection	7	0
Respiratory failure	2	0
Arrhythmia	1	0
Bleeding	1	0
Multisystem organ failure	1	0
Nonembolic colon ischemia	1	0
Renal failure	1	0

Abbreviations as in Table 1.



**Figure 4** Rates of Adverse Neurologic Events

The risk of stroke was greatest during the first month following device implantation, then it decreased to <0.1 strokes/patient (pt)-month on the device. Two patients in the OMT group had neurologic events (1 CVA, 1 TIA). TIA = transient ischemic attack; other abbreviations as in Figures 2 and 3.

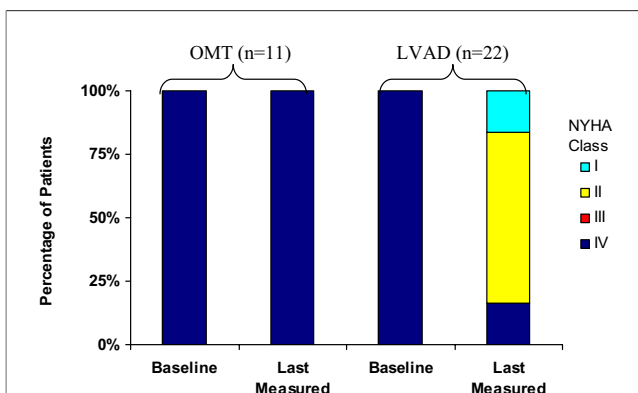
To date, only the REMATCH trial, which used the Thoratec HeartMate XVE LVAD (Pleasanton, California), has examined the role of mechanical circulatory support in nontransplant candidates (9). The results of the INTrEPID trial reinforce the REMATCH data by demonstrating clinically significant short- and intermediate-term survival benefits in LVAD-treated patients associated with quality-of-life improvements. These trials also illustrate the challenges of obtaining good results with LVAD therapy in this critically ill patient population.

The nonrandomized INTrEPID study design was selected as the best compromise to manage the ethical quandary faced by inotrope-dependent patients excluded from transplantation. Multiple nonrandomized bridge-to-transplant analyses have demonstrated superior morbidity and mortality outcomes in LVAD-treated patients compared with medically treated patients. Therefore, the precondition of equipoise between two treatment strategies for a randomized clinical trial was contentious within the heart

failure community. At the time that the INTrEPID trial was designed, REMATCH enrollment was slow, partially related to patient reluctance to accept assignment to the medical therapy arm. In response, the INTrEPID steering committee and the FDA reviewers did not feel that randomization of patients to medical therapy represented a feasible study design. Supported by the highly concordant REMATCH results, we conclude that it would no longer be ethical or appropriate to randomize patients to medical therapy in an LVAD trial for inotrope-dependent patients, based on the significant survival advantage experienced by patients who received an LVAD (11).

The survival rate for both the LVAD and OMT treatment groups in the INTrEPID trial was lower than that observed in the REMATCH trial, highlighting the severity of illness of patients enrolled in this trial. Although the majority of baseline characteristics that predict heart failure mortality were similar between the LVAD arms of both trials, statistically robust comparisons are not feasible, because of fundamental differences in the patient populations. It is clear that study selection criteria in both trials identified patients with a very high 30-day operative mortality risk. The REMATCH investigators reported superior outcomes in LVAD recipients enrolled during the second half of the trial, suggesting that refinement of patient selection, surgical technique, and postoperative management may have favorably influenced the trial outcomes for the LVAD patients (12). The small size and short duration of the INTrEPID trial did not permit a similar analysis. Finally, intrinsic differences in pump design may have influenced survival in the LVAD-treated patients in the INTrEPID trial.

An important concern about the use of mechanical devices for the long-term definitive treatment of heart failure is the risk of adverse events. The INTrEPID and REMATCH trials demonstrated that LVAD recipients are exposed to an incremental risk of neurologic events, infections, and bleeding complications, whereas the medically



**Figure 5** NYHA Functional Class

At the last measurement of functional class, 85% of LVAD recipients were asymptomatic or had minimal heart failure symptoms. Abbreviations as in Figures 1 and 2.

treated patients were at greater risk for heart and renal failure as well as increased early mortality. In contrast to the REMATCH trial, the risk of significant device malfunction in the INTrEPID trial was very low. Only 1 INTrEPID patient experienced failure of an implanted component (fracture of a pump-drive decoupling spring), which did not result in an appreciable change in pump performance. No pump replacements were required during the conduct of this trial, and there was no mortality attributable to LVAD malfunction.

Neurologic adverse events continue to represent a significant cause of morbidity and mortality in LVAD trials (13). We believe that the major contributor to stroke risk in the INTrEPID trial was the inflow conduit vascular graft material previously used in the Novacor LVAD. Examination of both DeBakey and Vascutek inflow conduits recovered from devices used in this trial revealed a lining of friable pannus. We postulate that a substantial proportion of the neurologic events were particuloembolic, caused by material originating on the pannus (14). Since completion of the INTrEPID trial, the Novacor LVAD inflow conduit material has been changed to ePTFE, eliminating pannus formation. This modification reduced the stroke rate to 5.3% in a series of 57 LVAD recipients supported for a cumulative duration of 53.5 years (15).

Five LVAD recipients (13.3%) with transplant contraindications at enrollment successfully underwent transplantation after a period of support. Bridging patients to transplant candidacy is increasingly recognized as a viable and appropriate management strategy based upon physiologic improvements commonly observed after a period of LVAD support. Young et al. (16) recently reported a retrospective analysis of the original Novacor bridge-to-transplant clinical trial, and found that 37% of LVAD-treated patients had  $\geq 1$  contraindication to transplantation that would have precluded listing by at least 1 of 10 high-volume U.S. transplant centers. These LVAD-treated patients had a 6-fold improvement in survival compared with medically treated patients and a similar survival to patients without transplant contraindications. The International Society for Heart and Lung Transplantation Mechanical Circulatory Support Registry has reported that 11% of patients who had an LVAD inserted as destination therapy have subsequently undergone transplantation (17). The present findings support the long-term use of LVADs as a viable option for selected patients with medical, social, or financial obstacles to transplant candidacy at the time of transplant evaluation. **Study limitations.** The INTrEPID trial is the second study to demonstrate the value of mechanical circulatory support in nontransplant candidates with advanced heart failure. Because the trial design was nonrandomized, it is possible that institutional or investigator bias contributed to patients' decisions to continue medical therapy rather than receive a LVAD. Although patient characteristics of the study populations were similar, there were differences

in baseline BUN and serum sodium. We cannot exclude the possibility that these differences biased study findings against medical therapy in ways that are difficult to measure.

On the other hand, stringent enrollment criteria identified a population of patients with extremely poor prognosis and end-organ dysfunction that may have limited device efficacy. These enrollment criteria define critically ill and unstable patients with short- and intermediate-term morbidity and mortality (both medical and surgical) as high as that of any reported heart failure population. We speculate that the benefits of mechanical circulatory support may be more robust in a patient population with less advanced cardiac disease and/or end-organ failure, because such patients may not experience the high early mortality (24% at 1 month; 36% at 3 months) associated with LVAD insertion.

## Conclusions

This report demonstrates the feasibility of destination LVAD support using the Novacor device, thus accomplishing the primary goal of the INTrEPID trial.

## Acknowledgments

The authors thank Renee Howser, RN, MSN, Debbie Jacobs, RN, MSN, and Frank Beering, BSME, for their assistance with data collection and analysis.

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 **APPENDIX**

**For a list of the INTrEPID centers, please see the online version of this article.**