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ORIGINAL INVESTIGATIONS

Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients

Results From the ROADMAP Study

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) identify characteristics of ambulatory heart failure patients who may benefit from LVAD therapy; 2) evaluate treatment options for patients with advanced ambulatory heart failure to improve quality of life; 3) discuss with ambulatory heart failure patients the projected benefits and adverse events associated with the use of LVAD therapy or continued optimal medical management; 4) respond to patient concerns about LVAD therapy and provide clinical data to guide therapy decisions; and 5) recognize the difference in the reasons why patients agree to and/or choose LVAD therapy in comparison to continuing with optimal medical management.

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Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients

Results From the ROADMAP Study

ABSTRACT

BACKGROUND Data for left ventricular assist devices (LVADs) in patients with noninotrope-dependent heart failure (HF) are limited.

OBJECTIVES The goal of this study was to evaluate HeartMate II (HMII) LVAD support versus optimal medical management (OMM) in ambulatory New York Heart Association functional class IIIB/IV patients meeting indications for LVAD destination therapy but not dependent on intravenous inotropic support.

METHODS This was a prospective, multicenter (N = 41), observational study of 200 patients (97 LVAD, 103 OMM). Entry criteria included ≥1 hospitalization for HF in the last 12 months and 6-min walk distance (6MWD) <300 m. The primary composite endpoint was survival on original therapy with improvement in 6MWD ≥75 m at 12 months.

RESULTS LVAD patients were more severely ill, with more patients classified as Interagency Registry for Mechanically Assisted Circulatory Support profile 4 (65% LVAD vs. 34% OMM; $p < 0.001$) than 5 to 7. More LVAD patients met the primary endpoint (39% LVAD vs. 21% OMM; odds ratio: 2.4 [95% confidence interval: 1.2 to 4.8]; $p = 0.012$). On the basis of as-treated analysis, 12-month survival was greater for LVAD versus OMM (80 ± 4% vs. 63 ± 5%; $p = 0.022$) patients. Adverse events were higher in LVAD patients, at 1.89 events/patient-year (EPPY), primarily driven by bleeding (1.22 EPPY), than with OMM, at 0.83 EPPY, primarily driven by worsening HF (0.68 EPPY). Most patients (80% LVAD vs. 62% OMM; $p < 0.001$) required hospitalizations. Health-related quality of life (HRQol) and depression improved from baseline more significantly with LVADs than with OMM (Δ visual analog scale: 29 ± 25 vs. 10 ± 22 [$p < 0.001$]; Δ Patient Health Questionnaire-9: −5 ± 7 vs. −1 ± 5 [$p < 0.001$]).

CONCLUSIONS Survival with improved functional status was better with HMII LVAD compared with OMM. Despite experiencing more frequent adverse events, LVAD patients improved more in HRQol and depression. The results support HMII use in functionally limited, noninotrope-dependent HF patients with poor HRQoL. (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device [LVAD] and Medical Management [ROADMAP]; NCT01452802)
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Therapy with a left ventricular assist device (LVAD) is an established treatment for patients with advanced heart failure (HF). Past clinical trials evaluating LVADs for bridge-to-transplant and destination therapy (DT) were designed to assess safety and effectiveness in patients with the most advanced stage of HF (1–3). The American College of Cardiology/American Heart Association guidelines recommend consideration of LVAD support when patients have progressed to stage D HF, the point at which therapeutic options have been exhausted and the projected benefits in quality of life and survival

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outweigh the risks (4). Consequently, the majority of LVAD implantations are performed in patients who are hospitalized and dependent on intravenous inotropic support. At present, there are no data from clinical trials or registries to inform physicians or patients about the relative risks and benefits of LVAD therapy or optimal medical management (OMM) in noninotrope-dependent HF.

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The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) has compiled data from >10,000 LVAD-supported patients since June 2006 (5). Actuarial survival for all patients with continuous-flow LVADs at 1 and 2 years has reached 80% and 70%, respectively, with 1-year survival of 75% for DT. Eighty percent of patients in INTERMACS were treated with pre-implantation inotropes (profiles 1 to 3), with fewer data on patients with less advanced disease (profiles 4 to 7). The risk/benefit tradeoff of LVADs versus OMM in this patient cohort is not well understood. Boyle et al. (6) reported a 95% twelve-month survival, shorter implantation hospitalization, and lower costs in LVAD patients with advanced HF who were classified INTERMACS profiles 4 to 7 at LVAD implantation. Jorde et al. (7) recently published results of the HeartMate II (HMII) DT Post Approval study and reported 1-year survival of 82% for patients not yet treated with inotropes (INTERMACS profiles 4 to 7) compared with 71% survival for those with profiles 1 to 3. Furthermore, Grady et al. (8) showed that health-related quality of life (HRQoL) is significantly improved with LVAD support in all INTERMACS profiles, including 4 to 7.

Relatively high adverse event (AE) rates associated with LVADs (5) may limit adoption of the therapy. Furthermore, there are limited prospective data comparing the relative risks (AEs) and benefits (functional capacity and quality of life improvement) of LVAD treatment versus OMM. The goal of the present study was to report results from a large observational clinical study of the HMII continuous-flow LVAD in advanced, ambulatory HF patients who are not dependent on intravenous inotropic support and who meet U.S. Food and Drug Administration-approved indications for LVAD DT.

METHODS

STUDY DESIGN. ROADMAP is a prospective, nonrandomized, observational study comparing LVAD support versus OMM. Details of the ROADMAP study design, rationale, and power analysis for sample size were previously reported (9). The study was conducted at 41 U.S. centers and supervised by the sponsor (Thoratec Corporation, Pleasanton, California). A complete list of all participating centers is listed in the Online Appendix. Enrollment was between October 2011 and July 2013, and patients are being followed for up to 2 years. The primary endpoint was at 1 year and is the focus of the present analysis. The trial was collaboratively designed by the sponsor and the clinical investigators. Coordinators at each site collected all data, which were entered into an electronic data capture system for analysis by the sponsor. The academic authors had independent access to the data and vouch for the completeness and accuracy of the data and the analyses. Trial enrollment and conduct were monitored by a steering committee of cardiologists, cardiac surgeons, and sponsor representatives. A biostatistician independent of the sponsor and the investigators provided an independent validation of study results. The institutional review board at each participating center approved the protocol.

STUDY SUBJECTS. Inclusion and exclusion criteria were previously reported (9). Patients with advanced HF, defined as New York Heart Association (NYHA) functional class IIIB/IV symptoms, who were not dependent on intravenous inotropic support and met the U.S. Food and Drug Administration-approved indications for HMII LVAD DT, including an ejection fraction ≤25% and treatment with guideline-based OMM for 45 of the past 60 days (or intolerant to these medications), were eligible for study enrollment. Implantable defibrillators and cardiac resynchronization therapy were recommended according to contemporary guidelines, and this resynchronization therapy had to be implanted at least 3 months before enrollment. To capture a higher risk population, patients had to have 1 HF hospitalization or 2 unscheduled emergency department/infusion clinic visits in the previous year and functional exercise impairment with a baseline 6-min walk distance (6MWD) <300 m.

The LVAD cohort comprised subjects who met study entrance criteria and who elected to undergo HMII LVAD implantation. The OMM cohort consisted of subjects who met study entrance criteria, including the DT indications for HMII, but elected to remain on OMM (on the basis of patient and/or physician choice). Participating patients provided written informed consent before enrollment.

BASELINE ASSESSMENT. Baseline assessments included demographic characteristics, health history,

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance
DT = destination therapy
EPPY = events per patient-year
EQ-5D = EuroQol
HF = heart failure
HMII = HeartMate II
HRQoL = health related quality of life
INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support
LVAD = left ventricular assist device
NYHA = New York Heart Association
OMM = optimal medical management
PHQ-9 = Patient Health Questionnaire-9
VAS = visual analog scale

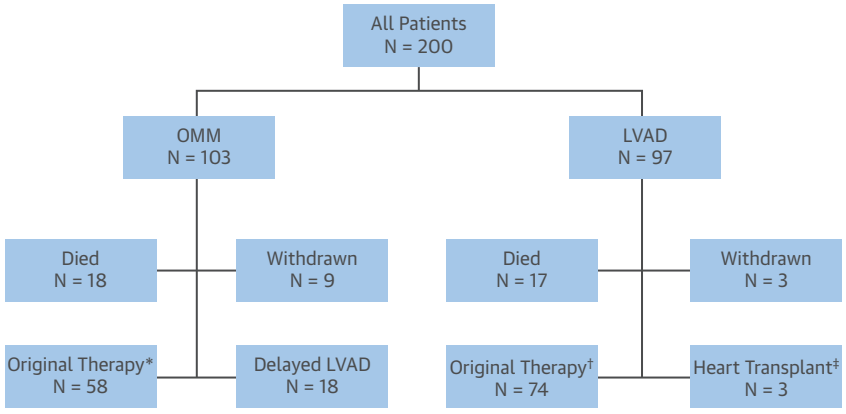
TABLE 1 Baseline Characteristics for All Patients

	OMM (n = 103)	LVAD (n = 97)	p Value
Enrollment age, yrs	66 (54–74)	64 (55–70)	0.269
Male	71 (69)	75 (77)	0.204
Race			0.061
White	60 (58)	72 (74)	
Black	35 (34)	21 (22)	
Other	8 (8)	4 (4)	
Ischemic etiology	51 (50)	58 (60)	0.158
History of atrial fibrillation	36 (35)	42 (43)	0.248
Duration of HF >1 yr	95 (92)	91 (94)	0.784
CRT or CRT-D	43 (42)	44 (45)	0.669
ICD or CRT-D	66 (64)	67 (69)	0.549
Diuretic dose furosemide-equivalent, mg/day	93 (40–200)	133 (40–240)	0.127
ACE inhibitors or ARBs	79 (77)	66 (68)	0.205
Beta-blockers	99 (96)	84 (87)	0.021
BMI, kg/m^2	28 (23–37)	29 (25–33)	0.663
Creatinine, mg/dl	1.3 (1.0–1.8) (n = 103)	1.3 (1.0–1.6) (n = 97)	0.507
BUN, mg/dl	28 (21–40) (n = 103)	26 (18–34) (n = 97)	0.120
eGFR, ml/min/1.73 m^2	63 (45–90) (n = 103)	70 (53–100) (n = 97)	0.123
AST, U/l	26 (20–36) (n = 100)	28 (21–46) (n = 97)	0.067
Albumin, g/dl	4.0 (3.6–4.3) (n = 99)	3.7 (3.4–4.2) (n = 94)	0.045
NT-pro-BNP, pg/ml	2,696 (1,369–6,369) (n = 27)	3,815 (2,160–5,320) (n = 26)	0.922
Serum BNP, pg/ml	737 (274–1,165) (n = 62)	547 (308–829) (n = 59)	0.391
Cardiac index, l/min/m^2	1.9 (1.6–2.3) (n = 50)	1.9 (1.6–2.3) (n = 65)	0.921
PCWP, mm Hg	22 (17–30) (n = 50)	22 (17–27) (n = 61)	0.425
PVR, Wood units	3.3 (2.3 - 4.6) (n = 38)	3.1 (1.7–5.1) (n = 50)	0.797
6MWD, m	219 (157–269) (n = 103)	182 (122–259) (n = 97)	0.057
VO_2 max, ml/kg/min	9.7 (8.5–12.3) (n = 61)	10.2 (8.7–11.5) (n = 72)	0.977
VO_2 max RER ≥ 1.1, ml/kg/min	10.9 (9.6–12.7) (n = 23)	10.2 (8.8–11.3) (n = 27)	0.131
VE/VCO_2	37.4 (34.0–49.0) (n = 51)	44.0 (36.9–49.0) (n = 58)	0.090
EQ-5D VAS	55 (45–75) (n = 99)	50 (30–60) (n = 93)	<0.001
SHFM score	1.43 (0.89–2.03) (n = 103)	1.79 (1.08–2.43) (n = 97)	0.013
SHFM 1-yr predicted survival, %	84 (73–91)	78 (63–89)	0.012
HMRS	1.16 (0.57–1.94) (n = 88)	1.40 (0.93–1.81) (n = 93)	0.312
PHQ-9 score	7 (3–10) (n = 101)	10 (6–15) (n = 96)	<0.001
PHQ-9 depression severity			<0.001
None/minimal (0–4)	40 (40)	12 (13)	
Mild (5–9)	32 (32)	32 (33)	
Moderate (10–14)	16 (16)	27 (28)	
Moderately severe (15–19)	9 (9)	21 (22)	
Severe (20–27)	4 (4)	4 (4)	
NYHA functional class			<0.001
IIIB	77 (75)	47 (48)	
IV	26 (25)	50 (52)	
INTERMACS profile			<0.001
Profile 4	35 (34)	63 (65)	
Profile 5	29 (28)	21 (22)	
Profile 6	35 (34)	10 (10)	
Profile 7	2 (2)	0	

Values are median (quartile 1–3) or n (%).

6MWD = 6-min walk distance; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy-defibrillator; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol; HF = heart failure; HMRS = Heartmate II risk score; ICD = implantable cardioverter-defibrillator; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; NYHA = New York Heart Association; NT-proBNP = N-terminal pro B-type natriuretic peptide; OMM = optimal medical therapy; PCWP = pulmonary capillary wedge pressure; PHQ-9 = Patient Health Questionnaire-9; PVR = pulmonary vascular resistance; RER = respiratory exchange ratio; SHFM = Seattle Heart Failure Model; VAS = visual analog score; VE/VCO_2 = ventilator-equivalent ratio for oxygen and carbon dioxide; VO_2 max = maximal oxygen uptake.

FIGURE 1 The ROADMAP Patients at 1 Year



Flow chart depicts outcomes and events within 12 months of enrollment in the ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device [LVAD] and Medical Management) trial. Patients who withdrew from the study or received an elective heart transplant within 1 year were excluded from the primary endpoint analysis. *12 optimal medical management (OMM) patients missing 6-min walk distance data were excluded from the primary endpoint analysis. †8 left ventricular assist device (LVAD) patients missing 6MWD data were excluded from the primary endpoint analysis. ‡Includes 1 elective and 2 urgent transplants.

NYHA functional class, and INTERMACS profiles as determined at the site by an independent assessor (an advanced practice practitioner other than the principal investigator), blood chemistry, hematological data, and concomitant medications. Two surveys were also used, 1 on HRQoL (i.e., the EuroQol [EQ-5D-5L] [10], including the visual analog scale [VAS]) and a depression-screening questionnaire, the Patient Health Questionnaire-9 (PHQ-9) (11). Additional baseline functional status was assessed by using the 6MWD.

Cardiopulmonary exercise testing (maximal oxygen consumption) data were captured when available. Factors related to patient and physician decisions to proceed with LVAD therapy or continue on OMM, as well as patients' perceptions of survival on current therapy, were captured by using baseline questionnaires.

FOLLOW-UP AFTER DEVICE IMPLANTATION OR CONTINUED MEDICAL THERAPY. After LVAD implantation, an antithrombotic regimen (typically heparin, followed by warfarin and aspirin) was implemented and managed according to each center's standard of care. Follow-up assessments were made every 3 or 6 months for up to 24 months (9). Clinical follow-up included assessment of HRQol, depression, functional status, and laboratory parameters. The prevalence, incidence, and cause of rehospitalizations were documented. AEs were captured by using standardized INTERMACS definitions.

STATISTICAL ANALYSIS. The primary endpoint was a composite of survival and improvement ≥75 m in 6MWD at 12 months. This outcome was evaluated on all patients without adjustments for baseline severity of illness. Differences between groups were analyzed by using the Fisher exact test. LVAD patients who received an urgent transplant after LVAD complications were counted as failures. OMM patients who

TABLE 2 Patient Questionnaire on QoL Satisfaction and Perception of Longevity on Medical Management at Baseline

	OMM	LVAD	p Value
At baseline, is the patient satisfied with current QoL on medical therapy?			
n	101	95	
Not or slightly satisfied	48 (48)	75 (79)	<0.001
Moderately to extremely satisfied	53 (52)	20 (21)	
I believe my current treatment (on medical therapy at baseline) will allow me to live:			
n	100	90	
<1 yr	9 (9)	48 (53)	<0.001
>1 yr	91 (91)	42 (47)	
I believe my QoL on current treatment (at baseline) will:			
n	101	94	
Decline	28 (28)	71 (76)	<0.001
Remain the same	24 (24)	6 (6)	
Improve	49 (49)	17 (18)	
Was the patient previously aware of LVAD therapy?			
n	100	93	
Yes	56 (56)	43 (46)	0.196
No	44 (44)	50 (54)	

Values are n (%) of patients responding to question.
QoL = quality of life; other abbreviations as in Table 1.

TABLE 3 Patient and Physician Reasons Provided for LVAD or OMM

Patient reasons*: LVAD, n = 95	
It will improve chances to live longer	81 (85)
It will improve QoL	79 (83)
It will help improve HF symptoms	72 (76)
It will help me return to activities I enjoy	72 (76)
Patient reasons: OMM, n = 101	
Don't like the idea of major device implantation surgery	40 (40)
Don't want to depend on a machine	26 (26)
Don't feel sick enough	25 (25)
Worried about too many complications with a LVAD	21 (21)
Don't think an LVAD will improve QoL	13 (13)
Don't think an LVAD will improve chances to live longer	10 (10)
Physician reasons: OMM, n = 103	
Patient is not a good surgical candidate†	14 (14)
Patient is not sick enough	11 (11)
Other (e.g., substance abuse, financial, compliance concerns)	9 (9)

Values are n (%) of patients who completed questionnaire. *Patients may select >1 response. †Surgical reasons provided: history of anticardiolipin antibody and splenectomy (high risk of clotting); lack of social support and noncompliance; medical nonadherence; interstitial fibrosis; obesity; liver cirrhosis; severe chronic obstructive pulmonary disease; concern regarding post-operative recovery; large sacral decubitus ulcer; recent stroke.

Abbreviations as in Tables 1 and 2.

crossed over to mechanical circulatory support, including a total artificial heart, were counted as delayed LVADs and as failures. Patients who withdrew from the study before 12 months were not included as either successes or failures in the primary endpoint analysis. Actuarial survival as-treated was determined with the Kaplan-Meier method through 12 months of support for LVAD patients free of urgent transplantation and OMM patients free of LVAD or transplantation. Survival was also determined under the intention-to-treat principle. Differences between groups were determined with the log-rank test. A 2-sided p value <0.05 was considered significant.

TABLE 4 Primary Endpoint and Components that Prevented Success

	OMM (n = 82)*	LVAD (n = 85)†	Odds Ratio (95% Confidence Interval)
Alive at 12 months on original therapy with increase in 6MWD by 75 m	17 (21)	33 (39)	2.4 (1.2–4.8) p = 0.012
First event that prevented success:	65 (79)	52 (61)	
Death within 1 yr	18 (22)	17 (20)	
Delayed LVAD	18 (22)‡	NA	
Delta 6MWD <75 m	29 (35)	33 (39)	
Urgent transplant	0	2 (2)	

Values are n (%). Odds ratio is calculated (95% confidence interval) as LVAD versus OMM. *Excluded OMM patients: 9 withdrawn, 12 missing 6MWD. †Excluded LVAD patients: 3 withdrawn, 8 missing 6MWD, 1 elective heart transplant. ‡Including 1 total artificial heart.

NA = not applicable; other abbreviations as in Table 1.

Continuous variables are reported as mean ± SD or SE or as median and quartiles. Categorical data are reported as percentages with 2-sided 95% confidence limits. Differences between groups of independent, normally distributed, continuous variables were evaluated by using the 2-sample Student *t* test. Variables that were not normally distributed were compared between treatments by using the Wilcoxon rank sum test. The prevalence of patients with AEs within 12 months and the incidence rate in events per patient-year (EPPY) using all data were determined for both groups. As a measure of the total burden of major AEs, a composite event rate was calculated as the sum of EPPY for bleeding, driveline infection, pump thrombus, stroke, arrhythmias, and worsening HF. Risk ratio evaluation and comparison of AE rates were performed by using Cochran-Mantel-Haenszel statistics.

Paired changes in functional parameters, 6MWD, PHQ-9, and EQ-5D VAS from baseline to 12 months were compared between treatments in patients surviving to 12 months on original therapy by using mixed-effects modeling on ranks; a Tukey adjustment was used for pairwise comparisons. Post-hoc composite endpoints were determined by using the percentage of patients alive on original therapy at 12 months with improvement in the following parameters: 1) NYHA functional class; and 2) VAS of >20 points in subjects with impaired HRQoL at baseline, as defined by baseline VAS <68 (top quartile of values) and depression score improvement of at least 5 points in patients at baseline with at least mild depression (PHQ-9 ≥5). Differences between groups were analyzed by using the Fisher exact test.

RESULTS

A total of 200 patients were enrolled in the study for LVAD DT support (n = 97) or continuing on OMM (n = 103) (Table 1, Figure 1). Most subjects were men with a median age of 65 years (range 21 to 82 years). Many baseline parameters were characteristic of a patient population with advanced HF and were overall similar between the LVAD and OMM groups. However, patients in the LVAD group compared with the OMM group were more severely ill (NYHA functional class IV: 52% vs. 25%; INTERMACS profile 4: 65% vs. 34%), had lower baseline HRQol, had more severe depression (87% vs. 60% [at least mild depression]), and had lower predicted Seattle Heart Failure Model 12-month survival rates.

Patient questionnaires at baseline demonstrated that more LVAD patients reported that they were not satisfied or only slightly satisfied with their quality of

life on baseline medical therapy (79%) compared with those who remained on OMM (48%) (Table 2). Significantly more LVAD patients at baseline also reported a perception that they were going to live <1 year (53% vs. 9%). The main patient reasons given for choosing OMM instead of LVAD include not wanting major device surgery, not wanting to depend on a machine, and not feeling sick enough (Table 3). For patients who agreed to LVAD therapy, the main reasons given were anticipated improvement in survival and improvements in quality of life and HF symptoms.

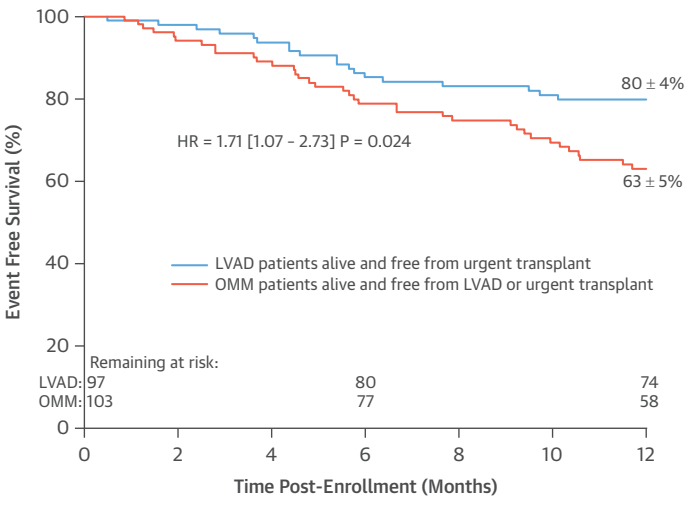
STUDY COURSE. A flow chart of all patients and outcomes over the first year is shown in Figure 1. Of the 103 OMM patients, 18 died, 18 received a delayed LVAD at least 1 month after enrollment (including 1 patient receiving a total artificial heart), and 9 patients withdrew from the study before reaching an outcome, leaving 58 patients alive on original OMM therapy at 12 months. The median time from enrollment to delayed LVAD was 138 days (quartiles 1 to 3: 72 to 203 days). For the 97 patients in the LVAD arm, 17 died, 3 received a heart transplant (2 urgent and 1 elective), and 3 withdrew from the study within 30 days of enrollment before receiving an LVAD, leaving 74 patients on LVAD support at 12 months.

PRIMARY ENDPOINT. More patients who received LVAD support achieved the primary composite endpoint than patients who received OMM (39% [33/85] vs. 21% [17/82]; odds ratio: 2.4 [95% confidence interval: 1.2 to 4.8]; p = 0.012) (Table 4). The main reason why fewer OMM patients met the primary endpoint compared with the LVAD group was the use of delayed LVADs in OMM patients.

ACTUARIAL SURVIVAL. Thirty-day operative mortality after LVAD implantation was 1%, the same as the mortality rate in the OMM group within 30 days after enrollment. The median hospitalization length of stay after LVAD implantation was 17 days (quartiles 1 to 3: 13 to 22 days). The 12-month as-treated (event-free) survival (freedom from death, urgent heart transplantation, or delayed LVAD) was significantly greater for LVAD versus OMM (80 ± 4% vs. 63 ± 5%; hazard ratio: 1.71 [95% confidence interval: 1.07 to 2.73], p = 0.024) (Figure 2). Using an intention-to-treat analysis, Kaplan-Meier survival (freedom from death) at 12 months was similar in both groups (82 ± 4% vs. 81 ± 4%; p = 0.931) (Figure 3).

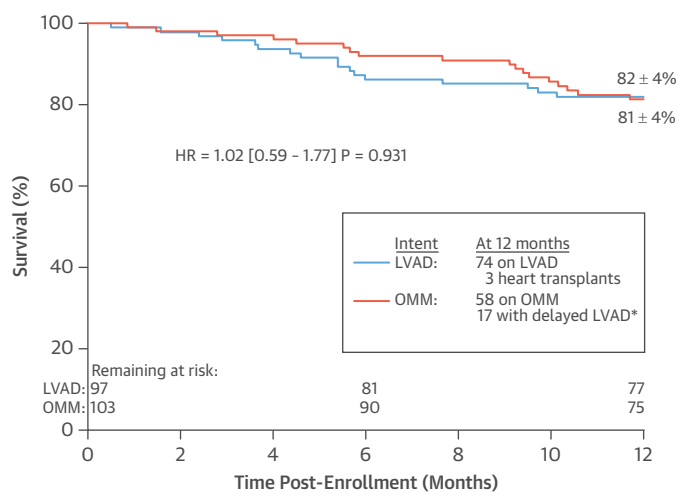
FUNCTIONAL STATUS AND QUALITY OF LIFE. LVAD patients experienced greater improvements in functional status and quality of life. Compared with 0% before implantation, 77% of LVAD patients improved with NYHA functional class I (25%) or II (52%) at 12 months (Figure 4). Compared with 0% with class I or II symptoms at baseline, 29% of OMM patients alive at 12 months had NYHA functional class II (no class I) symptoms. For LVAD patients, 39 of 71 (55%) improved at least 2 NYHA functional classes compared with 2 of 52 (4%) OMM patients (p < 0.001).

FIGURE 2 Survival As-Treated



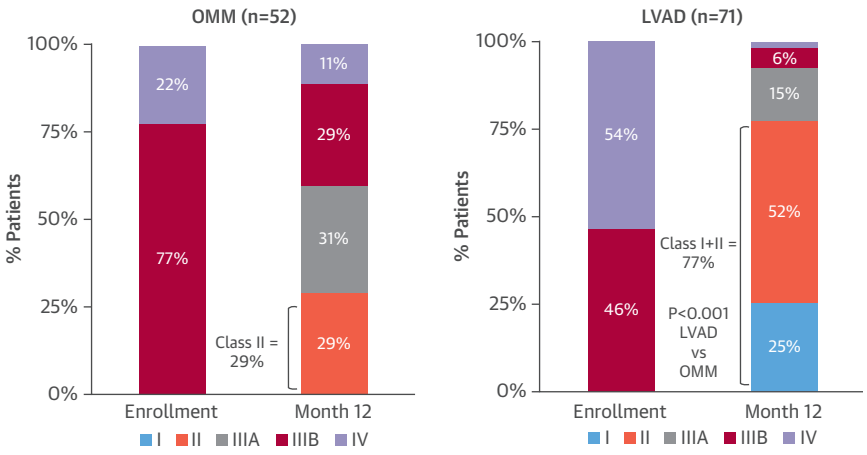
At 1 year, survival as-treated was significantly higher in LVAD versus OMM patients. Hazard ratio (HR) was calculated for OMM versus LVAD. Abbreviations as in Figure 1.

FIGURE 3 Intention-to-Treat Survival



Intention-to-treat survival was not significantly different between OMM and LVAD patients. HR was calculated for OMM versus LVAD. *One patient received a total artificial heart and was censored alive, then withdrawn from the study. Abbreviations as in Figures 1 and 2.

FIGURE 4 Changes in NYHA Classification



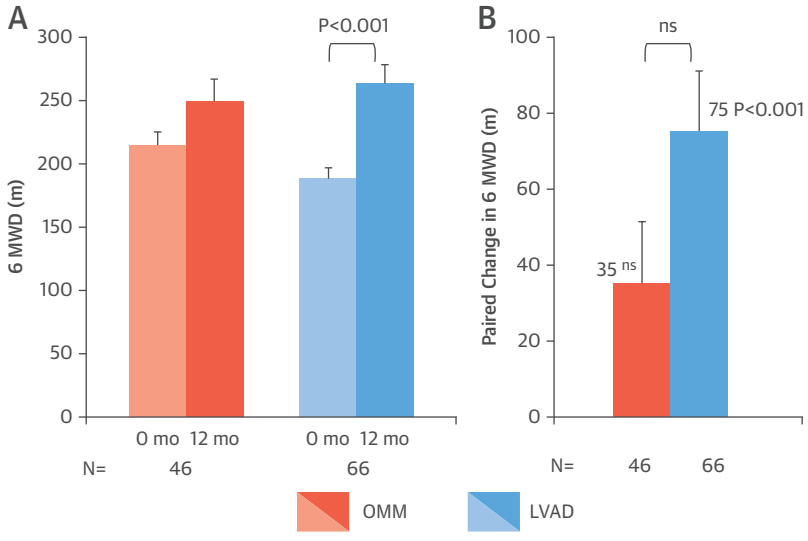
For 1-year survivors on original therapy, significantly more LVAD patients improved to New York Heart Association (NYHA) functional class I or II compared with OMM patients. Patients with missing NYHA classifications were excluded (6 OMM, 3 LVAD). Abbreviations as in Figure 1.

Similarly, the average 6MWD improved significantly in LVAD patients (187 m to 263 m; average increase of 75 m; $p < 0.001$) compared with no significant change in OMM patients (214 to 249 m; average change of 35 m; $p = 0.325$) (Figure 5).

The EQ-5D VAS improved to a significantly greater degree in the LVAD versus OMM groups at 12 months, with an average improvement of 29 points for LVAD compared with 10 points for OMM ($p < 0.001$) (Figure 6). This outcome was due to LVAD patients starting with worse baseline VAS scores, which increased to levels similar to OMM at 12 months.

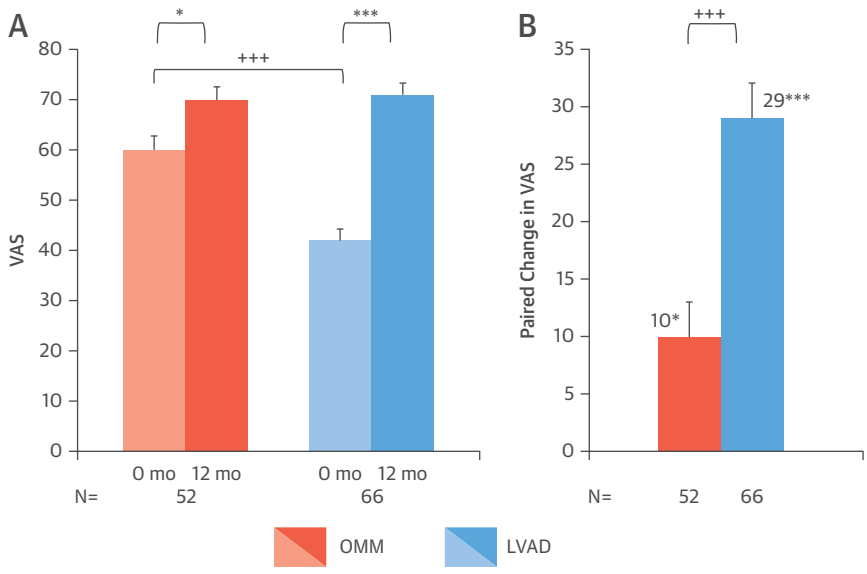
The baseline PHQ-9 scores in paired analysis were higher for LVAD (average: 11 [moderate depression])

FIGURE 5 Changes in 6MWD



(A) Paired 6-min walk distance (6MWD) measurements at baseline and 12 months for 1-year survivors on original therapy. **(B)** Average change in 6MWD from baseline to 12 months. Values are mean ± SE. Patients with missing 6MWD were excluded (12 OMM, 8 LVAD). Abbreviations as in Figure 1.

FIGURE 6 Changes in Health-Related Quality of Life From the EQ-5D VAS



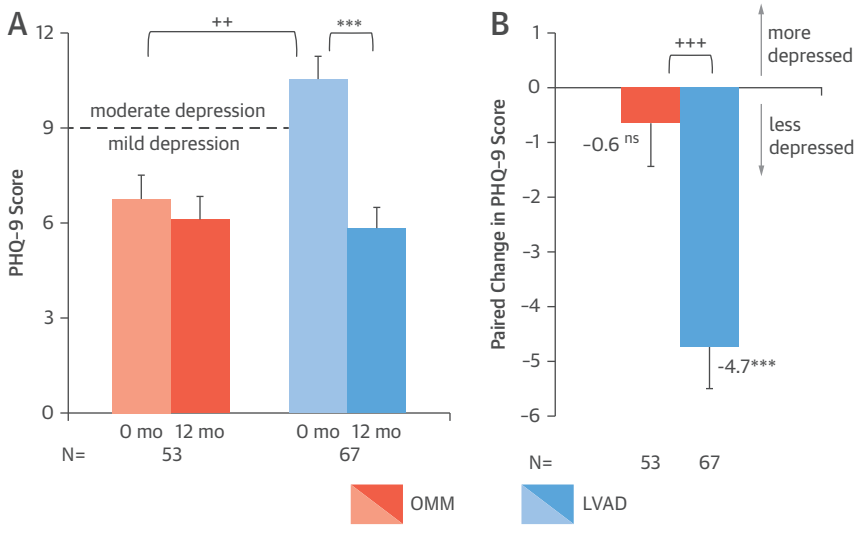
(A) Paired visual analog scale (VAS) at baseline and 12 months for 1-year survivors on original therapy. **(B)** Average change in VAS from baseline to 12 months for 1-year survivors on original therapy. Patients with missing VAS were excluded (6 OMM, 8 LVAD). *$p < 0.05$, ***$p < 0.001$ for paired changes within study arm. +++$p < 0.001$ for OMM versus LVAD. EQ-5D = EuroQol; other abbreviations as in Figure 1.

compared with OMM patients (average: 7 [mild depression]). Over 12 months, the average values for OMM patients remained the same, compared with LVAD patients who improved from moderate to mild (Figure 7). The composite measures combining survival on original therapy with improvements in NYHA functional class, HRQoL, and depression all showed significantly greater change for LVAD than OMM (Table 5).

ADVERSE EVENTS. AEs were more frequent in LVAD patients than in OMM patients (Table 6). Bleeding was the primary driver of LVAD AEs; together, surgical and nonsurgical bleeding accounted for 65% of LVAD events. Worsening HF, which accounted for 82% of OMM events, was the primary driver of OMM AEs. Pump thrombus occurred in 6 LVAD patients, 4 requiring pump exchange, with only 1 early event within 90 days of implantation. The median international normalized ratio at 6 and 12 months after LVAD implantation was 2.1 (quartiles 1 to 3: 1.8 to 2.5) and 2.1 (quartiles 1 to 3: 1.7 to 2.5), respectively. At 12 months, 70% of patients were receiving warfarin and antiplatelet therapy (mostly aspirin), 19% were receiving warfarin only, 8% were receiving antiplatelet therapy only, and 3% were on neither warfarin nor antiplatelet agents. The composite AE rate for bleeding, driveline infection, pump thrombosis, stroke, ventricular arrhythmias, and worsening HF was 1.89 EPPY (LVAD) versus 0.83 EPPY (OMM), resulting in a relative risk for OMM versus LVAD of 0.44 (95% confidence interval: 0.35 to 0.56; $p < 0.001$). Gastrointestinal bleeding was the main bleeding event, accounting for almost two-thirds of all bleeding events, and one-half of the events occurred in 4 patients. Without bleeding, the composite AE rates were similar. More LVAD patients (80%) than OMM patients (62%) had rehospitalizations within 1 year of enrollment, with the reasons shown in Table 7. The leading causes of rehospitalizations were bleeding for LVAD patients and worsening HF for OMM patients. OMM patients who received delayed LVADs had deteriorated from baseline, as evidenced by decreased serum albumin levels, 6MWD, NYHA classification, and INTERMACS profile (Table 8).

The leading causes of death among the 17 patients who died with LVAD support were as follows: sepsis (n = 3 [17.6%]); multiorgan/renal failure (n = 3 [17.6%]); right HF/ventricular tachycardia (n = 2 [11.7%]); thrombus (n = 2 [11.7%]); and 1 (5.8%) each for hemorrhagic stroke, ischemic stroke, bleeding/pleural effusion, respiratory failure, car accident, pulmonary embolism, and unknown. Among the 18 patients in the OMM group, the leading causes of death were

FIGURE 7 Changes in Depression From PHQ-9



(A) Paired Patient Health Questionnaire-9 (PHQ-9) scores at baseline and 12 months for 1-year survivors on original therapy. **(B)** Average change in PHQ-9 score from baseline to 12 months for 1-year survivors on original therapy. Patients with missing PHQ-9 scores were excluded (5 OMM, 7 LVAD). ***$p < 0.001$ for paired change within study arm. ++$p < 0.01$, +++$p < 0.001$ for OMM versus LVAD. Values are mean ± SE. Abbreviations as in Figure 1.

progressive HF (n = 13 [72.2%]), with 1 (5.6%) each for sudden cardiac death, chronic obstructive pulmonary disease, sepsis, cancer, and unknown.

RISK/BENEFIT ANALYSIS. Figure 8 displays a summary of the benefits and risks of LVAD therapy versus OMM for patients in the ROADMAP study. LVAD patients were >2 times as likely to reach the primary composite endpoint, and their survival as-treated on original therapy was significantly greater. LVAD patients also had a significantly greater chance of being alive at 12 months with improvements in NYHA functional class, HRQoL, and depression. However, OMM patients experienced less than one-half the AEs as LVAD patients.

DISCUSSION

The success of LVAD therapy, predominantly in patients with INTERMACS profiles 1 to 3, has been well documented in clinical trials (2,3,5,12). The ROADMAP study, as the first prospective controlled study in patients with advanced ambulatory, noninotrope-dependent HF, found that LVAD therapy significantly improved survival, with improvement in 6MWD ≥75 m at 12 months relative to OMM. The study's observational nature resulted in an imbalance in the severity of illness between the OMM and LVAD patients, as many centers are more likely to delay use of LVAD in the least ill patients. Comparisons of the study arms are made with the acknowledgement that

TABLE 5 Secondary Composite Endpoints

Alive at 12 Months on Original Therapy With:	OMM	LVAD	Odds Ratio (95% Confidence Interval)	p Value
Improvement in NYHA functional class of at least 1 functional class	17/88 (19)	62/91 (68)	8.9 (4.5–17.8)	<0.001
Improvement in NYHA functional class of at least 2 functional classes	2/88 (2)	39/91 (43)	32.3 (7.5–139.2)	<0.001
Improvement in HRQoL VAS of more than 20 points in patients with impaired baseline HRQoL*	13/56 (23)	41/74 (55)	4.1 (1.9–8.9)	<0.001
Improvement in PHQ-9 of at least 5 points in patients with at least mild or worse depression†	8/51 (16)	33/75 (44)	4.2 (1.7–10.2)	<0.001

Values are n/N (%). Odds ratio is calculated (95% confidence interval) LVAD versus OMN. *Includes patients in bottom 3 quartiles of baseline VAS (<68). †Includes patients with baseline PHQ-9 ≥5 (mild or more severe), thus excluding those with no or minimal depression.

HRQoL = health-related quality of life; other abbreviations as in Table 1.

these 2 cohorts had different underlying disease severity. Survival was similar in both groups in the intention-to-treat analysis. As-treated event-free actuarial survival over a 12-month period was significantly better with LVAD than OMM. The LVAD survival rate of 80 ± 4% at 1 year is similar to the recently published post-approval DT HMII study that reported a 12-month survival of 82 ± 5% in patients with INTERMACS profiles 4 to 7 compared with 71 ± 3% for those with INTERMACS profiles 1 to 3 (7). Differences in the primary endpoint between LVAD and OMM were primarily due to the use of delayed LVADs in the OMM group. Thus, the intention-to-treat analysis suggests no mortality penalty for either early or delayed use of LVADs in these patients, indicating that factors beyond survival are paramount to decision-making surrounding LVAD implantation in this population. Patients in the OMM group avoid complex LVAD surgery and LVAD AEs; however, watchful waiting on OMM would not achieve the primary benefits of functional improvements and patient-reported HRQoL with LVAD support. A full examination to understand the benefits and risks of delayed LVAD decision is planned at the 2-year study follow-up.

Pilot data from the medical arm of INTERMACS (MEDAMACS), launched in January 2013, showed that the 1-year event-free survival of death, LVAD, or heart transplant while receiving OMM was approximately 47% (13). These observations demonstrate that advanced, ambulatory, noninotrope-dependent HF patients with high-grade symptoms of shortness of breath (NYHA functional class IIIB/IV) have a poor 12-month prognosis. Considering that many medically managed HF patients with INTERMACS profiles 4 to 7 could potentially benefit from LVAD therapy, early referral may be warranted to carefully weigh the projected benefits versus risks for individual patients when considering LVAD or continued OMM in this less sick patient population with advanced HF.

Concerns persist that LVADs predispose patients to an undue burden of AEs, including thromboembolic and bleeding events. In the ROADMAP patient population, bleeding, which accounted for two-thirds of all events, was the primary driver of the high event rate in LVAD patients and were almost 9 times the rate of stroke-related thromboembolic events and pump thrombus, which were comparable to findings in past HMII trials. The rates of ischemic and hemorrhagic stroke among LVAD patients (0.06 and 0.03 EPPY, respectively) are similar to those among patients with advanced HF who underwent implantation in the HMII DT trial (0.05 and 0.03 EPPY, respectively) but greater than the rate in patients with advanced HF enrolled in the OMM group of ROADMAP (0.01 EPPY each for ischemic and hemorrhagic stroke). The stroke incidence in those treated with OMM in ROADMAP was lower than that among patients with

TABLE 6 Adverse Events

	OMM (n = 103)	LVAD (n = 94)	DT Trial§ (EPPY)
Bleeding	1 (1) [0.02]	44 (47) [1.22]‡	1.13
GI bleeding	1 (1) [0.02]	29 (31) [0.76]‡‖	–
Driveline infection	–	9 (9.6) [0.14]‡	0.22
Pump thrombus	–	6 (6.4) [0.08]†	0.07¶
Within 90 days	–	1 (1.1)	–
Pump exchange yr 1	–	4 (4.3)	2.1%
Stroke	2 (2) [0.02]	8 (8.5) [0.09]*	0.08
Ischemic	1 (1) [0.01]	5 (5.3) [0.06]*	0.05
Hemorrhagic	1 (1) [0.01]	4 (4.3) [0.03] NS	0.03
Arrhythmias VT/VF	6 (5.8) [0.12]	17 (18.1) [0.23]*	0.46
Worsening HF#	36 (35) [0.68]	10 (10.6) [0.12]‡	–
Rehospitalizations	64 (62) [1.43]	75 (79.8) [2.49]‡	2.64**
Composite event rate††	39 (38) [0.83]	62 (66) [1.89]‡	2.09
Relative risk (95% CI)	OMM/LVAD: 0.44 (0.35–0.56)‡		–

Values are n (%) for prevalence of patients within 1 year and events/patient-year [EPPY] on all data, unless otherwise indicated. p values OMM vs. LVAD: *p < 0.05. †p < 0.01. ‡p < 0.001. §Park et al. (16). ‖4 patients had 50% of all gastrointestinal bleeding events. ¶Thrombus plus hemolysis. #HF symptoms resulting in unexpected hospitalization, emergency department visit, or urgent clinic visit requiring intravenous therapy. **Slaughter et al. (3). ††Sum of bleeding, infection, thrombus, stroke, arrhythmias, and worsening HF.

CI = confidence interval; DT = destination therapy; EPPY = events per patient-year; GI = gastrointestinal; NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

TABLE 7 Reasons for Rehospitalizations

	OMM Rehospitalizations (n = 160)	LVAD Rehospitalizations (n = 328)
Adverse events	97 (61)	207 (63)
Bleeding	1 (1)	79 (24)†
Worsening HF	72 (45)*	16 (5)
Elective procedure	10 (6)	22 (7)
Comorbidity management	13 (8)	16 (5)
Blood pressure/volume management	6 (4)	16 (5)
Pain	5 (3)	12 (4)
Trauma	0	9 (3)
LVAD alarms/driveline and controller problems	0	9 (3)
Dizziness/syncope	9 (6)	8 (2)
LVAD implantation or exchange/ heart transplant	11 (7)	7 (2)
Anticoagulation management	0	7 (2)
Rehabilitation/hospice	4 (3)	5 (2)
Other‡	5 (3)	10 (3)

Values are n (%) of rehospitalizations. *Most frequent OMM rehospitalization reason was worsening HF, which included 9 delayed HMII and 1 total artificial heart implantation. †Most frequent LVAD rehospitalization reason was bleeding. ‡Includes thoracentesis, depression, fever, failure to thrive, peripherally inserted central catheter line pulled out, dyspnea, and cellulitis.

Abbreviations as in Table 1.

TABLE 8 OMM Patients Receiving Delayed LVAD

	At Enrollment (Baseline)	Before Delayed LVAD	p Value
Albumin, g/dl (n = 15)	3.9 (3.7–4.1)	3.5 (3.4–3.7)	<0.001
6 MWD, m (n = 11)	213 (192–271)	90 (0–221)	0.004
EQ-5D VAS (n = 9)	45 (38–58)	40 (28–55)	0.373
PHQ-9 (n = 10)	7.5 (3.5–11.0)	10.5 (7.8–12.5)	0.289
SHFM 1-yr survival, % (n = 17)	89 (82–92)	73 (54–84)	0.012
INTERMACS profile (n = 14)			0.031
Profile 2–3	0	6 (43)	
Profile 4–7	14 (100)	8 (57)	
NYHA functional class IV (n = 15)	4 (27)	10 (67)	0.031

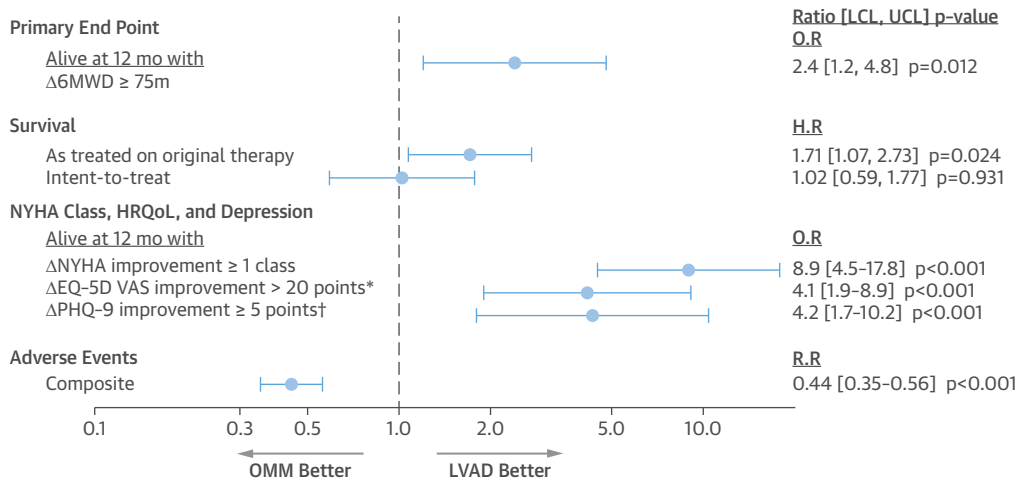
Values are median (quartile1–3) or n (%).
Abbreviations as in Table 1.

advanced HF who do not have device support and have other cardiovascular conditions, such as atrial fibrillation (14,15).

In the recent past, many centers reduced the targeted international normalized ratio to 2.0 ± 0.5 (quartile 1 to quartile 3: 1.5 to 2.5) for HMII continuous-flow LVADs. The median international normalized ratio in ROADMAP of 2.1 (quartile 1 to quartile 3: 1.8 to 2.5) is higher than that reported in the DT trial of 1.8 (quartile 1 to quartile 3:1.4 to 2.3) (16). In ROADMAP patients, pump thrombosis was only 6.4% at 12 months, which was much lower than in a recent 3-center report (17) but comparable to an INTERMACS investigation (18). In addition, LVAD patients had a low device-related infection rate (0.14 EPPY), nearly 50% of HMII DT trial patients (16), but similar to the low driveline infection rate (0.11 EPPY) recently reported in the SSI (Silicone-Skin-Interface) Registry, where the driveline velour was buried below the skin (19). AEs in the OMM patients were less than one-half that of LVAD patients, and worsening HF (the leading cause) accounted for >80% of events. Not all AEs in the OMM group resulted in rehospitalization, as worsening HF may be treated as an unscheduled outpatient visit in which intensified diuretic or other pharmacotherapy is applied. In contrast, rehospitalizations for the LVAD group are often due to reasons less amenable to outpatient solutions. Many rehospitalizations may be less likely associated with a serious adverse outcome.

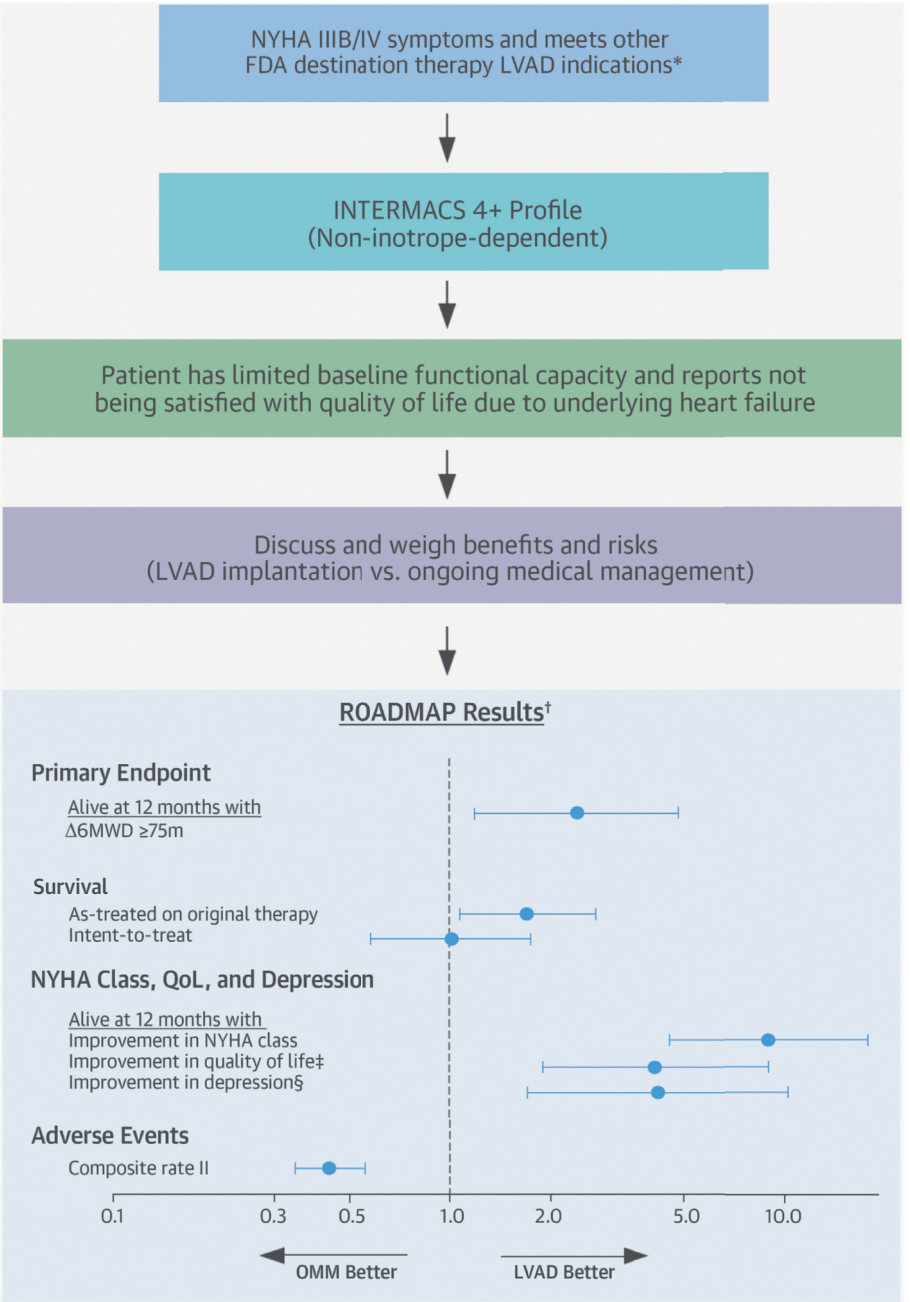
Enhancing quality of life and functional capabilities remains a critical therapeutic goal in treating patients with advanced HF. In our study, the use of LVAD compared with OMM was associated with significant reduction in worsening HF-related readmissions, as well as improved quality of life and functional capacity. The exercise and quality of life benefit with LVAD occurred even with AEs being more frequent. Benefits included a 75-m increase in 6MWD, a 30-point improvement in EQ-5D VAS comparable to the HMII

FIGURE 8 Risk/Benefit Analysis



Survival, changes in functional capacity, health-related quality of life (HRQol), and depression favor LVAD therapy, but the adverse event rate favors OMM. *Includes patients with baseline VAS <68 (lowest 3 quartiles). †Includes patients with baseline PHQ-9 scores >4 (mild or worse depression severity). LCL = lower confidence limit; OR = odds ratio; UCL = upper confidence limit; other abbreviations as in Figures 1, 2, 6, and 7.

CENTRAL ILLUSTRATION **LVAD and Medical Management in Ambulatory HF: Treatment Algorithm to Guide Decisions on Noninotrope-Dependent Patients With Advanced HF**



Estep, J.D. et al. J Am Coll Cardiol. 2015; 66(16):1747–61.

*U.S. Food and Drug Administration (FDA) destination therapy indication includes: New York Heart Association (NYHA) functional class IIIB or IV, left ventricular ejection fraction ≤25%, not listed (or planned) for heart transplantation, and on optimal medical management (OMM). †The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device [LVAD] and Medical Management) trial results with odds, hazard, and relative risk ratios as defined in Figure 8. ‡EuroQol visual analog scale improvement >20 points in patients with baseline score <68. §Patient Health Questionnaire-9 score improvement ≥5 points in patients with baseline mild or worse depression severity. ||Sum of bleeding, infection, thrombus, stroke, arrhythmias, and worsening heart failure. 6MWD = 6-min walk distance; HF = heart failure; LVAD = left ventricular assist device.

DT post-approval study (7), and the 35-point improvement in INTERMACS data at 1-year follow-up (8), a reduction in depression, and improvement in symptoms corresponding to a reduction by at least 1 NYHA functional class. The 6MWD absolute improvement at 12 months is also greater than the 45-m increase observed in NYHA functional class IV patients treated with cardiac resynchronization therapy (20). Compared with the LVAD arm, OMM patients had a higher baseline 6MWD, in addition to other baseline parameters, consistent with a less sick patient population, a marginal 6MWD increase, and a smaller improvement in the EQ-5D VAS. At 12 months, 71% of OMM patients had persistent NYHA functional class III/IV symptoms.

The ROADMAP trial is complementary to the recent National Institutes of Health–funded REVIVE-IT (Randomized Evaluation of VAD Intervention before Inotropic Therapy) trial. The intent of REVIVE-IT was to examine LVAD versus OMM in patients with even less advanced HF (NYHA III symptoms/INTERMACS profile 7) than ROADMAP. However, REVIVE-IT was closed due to failed recruitment and the national principal investigators putting the study on hold due to concern regarding clinical equipoise (projected benefits vs. current AEs associated with LVADs). We hope that ROADMAP provides some clarity regarding the projected benefits versus risks in a less sick patient population (INTERMACS profile 4 to 7), and we remain optimistic that randomized trials will ultimately be designed and completed.

STUDY LIMITATIONS. ROADMAP was a nonrandomized, controlled observational study of current practice and decisions, and hence there is potential for bias. Selection bias was not unexpected, as seen in the baseline characteristics, which indicated that OMM patients were appropriately less ill than LVAD patients. Thus, the risk/benefit analyses presented may underestimate the benefit and overestimate the risk of LVAD versus OMM. Despite these differences, more LVAD patients still met the primary endpoint. The withdrawn percentage was 3 times greater in the OMM (9%) versus the LVAD (3%) group and may influence the results. The LVAD used in this study was HMII, and the risk/benefit analyses are not generalizable to other mechanical circulatory support devices. There is well-known bias regarding patient-reported questionnaires and outcomes, including HRQoL and depression. AEs were reported by treating physicians and not adjudicated by a clinical events committee; we do not believe that this affected the study primary endpoint. In addition, important determinants of the appropriateness of LVADs, including frailty, nonadherence to therapy, and social support, were not collected but may have important implications that could skew the results. The study was also performed in a selected patient population, and applicability to the broader population of noninotropic-dependent patients with HF, including those with less hemodynamic and functional compromise than ROADMAP patients, would be speculative. Many findings and endpoints of this observational study should be considered hypothesis generating and need to be confirmed with other studies, including randomized controlled trials where appropriate.

CONCLUSIONS

To the best of our knowledge, this study is the first prospective clinical evaluation of patients with advanced ambulatory HF demonstrating a favorable outcome comparing treatment with LVADs versus OMM. Survival with improved functional status was better with LVADs in this less sick HF population. There was low LVAD operative mortality. HRQoL and depression improved more with LVADs, even with AEs being more frequent. ROADMAP provides new and very important risk/benefit information to guide patient and physician decision-making regarding LVAD therapy in an ambulatory, advanced HF population (**Central Illustration**). The results support the use of the HMII LVAD under existing approved indications in functionally limited noninotrope-dependent HF patients with poor quality of life.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Certain ambulatory patients with advanced HF who are not inotrope-dependent but have indications for destination therapy treated with assist devices (LVADs) exhibit better event-free survival, functional capacity, and quality of life than those receiving OMM without device support, despite a greater frequency of AEs that are typically not fatal or disabling.

TRANSLATIONAL OUTLOOK: Randomized studies are needed to define the benefits and risks of LVADs in patients with less severe HF.

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KEY WORDS functional status, HeartMate II, quality of life, risk/benefit analysis, ROADMAP

APPENDIX For a supplemental acknowledgment of the surgeons, cardiologists, and study coordinators who participated in this study, please see the online version of this article.

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