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CLINICAL RESEARCH

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

The ROADMAP Study 2-Year Results

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ABSTRACT

OBJECTIVES The authors sought to provide the pre-specified primary endpoint of the ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) trial at 2 years.

BACKGROUND The ROADMAP trial was a prospective nonrandomized observational study of 200 patients (97 with a left ventricular assist device [LVAD], 103 on optimal medical management [OMM]) that showed that survival with improved functional status at 1 year was better with LVADs compared with OMM in a patient population of ambulatory New York Heart Association functional class IIIb/IV patients.

METHODS The primary composite endpoint was survival on original therapy with improvement in 6-min walk distance ≥75 m.

RESULTS Patients receiving LVAD versus OMM had lower baseline health-related quality of life, reduced Seattle Heart Failure Model 1-year survival (78% vs. 84%; $p = 0.012$), and were predominantly INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile 4 (65% vs. 34%; $p < 0.001$) versus profiles 5 to 7. More LVAD patients met the primary endpoint at 2 years: 30% LVAD versus 12% OMM (odds ratio: 3.2 [95% confidence interval: 1.3 to 7.7]; $p = 0.012$). Survival as treated on original therapy at 2 years was greater for LVAD versus OMM (70 ± 5% vs. 41 ± 5%; $p < 0.001$), but there was no difference in intent-to-treat survival (70 ± 5% vs. 63 ± 5%; $p = 0.307$). In the OMM arm, 23 of 103 (22%) received delayed LVADs (18 within 12 months; 5 from 12 to 24 months). LVAD adverse events declined after year 1 for bleeding (primarily gastrointestinal) and arrhythmias.

CONCLUSIONS Survival on original therapy with improvement in 6-min walk distance was superior with LVAD compared with OMM at 2 years. Reduction in key adverse events beyond 1 year was observed in the LVAD group. The ROADMAP trial provides risk-benefit information to guide patient- and physician-shared decision making for elective LVAD therapy as a treatment for heart failure. (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients [ROADMAP]; NCT01452802) (J Am Coll Cardiol HF 2017;5:518–27)

The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) study's 1-year results showed that survival with improved functional status at 1 year was better with left ventricular assist devices (LVADs) compared with optimal medical management (OMM) in a patient population of ambulatory New York Heart Association (NYHA) functional class IIIB/IV patients who were not dependent on intravenous inotropic support (1). Survival was similar in both groups in the intention-to-treat analysis. However, as-treated event-free actuarial survival over a 1-year period was significantly better with LVAD than OMM (80 ± 4% vs. 63 ± 5%). Differences in the primary endpoint between LVAD and OMM were primarily due to the use of delayed LVADs in the OMM group. Factors beyond survival seem paramount to decision making surrounding LVAD implantation in this ambulatory patient population. At 1-year follow-up, patients in the OMM group avoided LVAD surgery and LVAD-associated adverse events (AEs); however, patients observed on OMM did not achieve the primary benefits of functional improvements and patient-reported health-related quality of life (HRQoL) with LVAD support. To better understand the long-term benefits and risks of LVAD compared with OMM, we now provide the pre-specified primary endpoint and other important study results after 2 years of follow-up.

METHODS

STUDY DESIGN. The ROADMAP study was a prospective, multicenter (N = 41), nonrandomized, controlled, observational study to evaluate the effectiveness of LVAD versus OMM (2). Enrollment began in October 2011 with patients being followed for up to 2 years. The primary composite endpoint was survival with improvement in 6-min walk distance (6MWD) ≥75 m at 1 year, which has been previously published (1). This report focuses on the primary endpoint at 2 years and secondary study endpoints, which include actuarial survival, HRQoL, depression, functional status, and AEs, after 2 years of follow-up.

STUDY SUBJECTS. In addition to meeting U.S. Food and Drug Administration–approved indications for HeartMate II LVAD (Thoratec [now Abbott], Pleasanton, California) destination therapy, entrance criteria included NYHA functional class IIIB/IV, at least 1 hospitalization for heart failure (HF) (or 2 unscheduled emergency department/infusion clinic visits) in the last 1 year, and 6MWD <300 m. Subjects were excluded if there was inotrope use within 30 days before enrollment. Of the 200 patients enrolled, 97 selected LVAD therapy and 103 remained on medical management in the OMM arm. Patients in the OMM cohort could receive a delayed LVAD at any point during the study period.

BASELINE AND FOLLOW-UP ASSESSMENTS. Baseline assessments included demographic characteristics, medical history, NYHA functional class, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile, 6MWD, serum chemistry, hematologic data, and medications. Patients also completed a HRQoL survey, the EuroQol 5 dimensions, 5-level questionnaire (EQ-5D-5L) including the visual

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance
AE = adverse event
eppy = events per patient-year
EQ-5D = EuroQol 5 dimensions questionnaire
GI = gastrointestinal
HF = heart failure
HRQoL = health-related quality of life
HTx = heart transplantation
LVAD = left ventricular assist device
NYHA = New York Heart Association
OMM = optimal medical management
PHQ-9 = Patient Health Questionnaire
QoL = quality of life
VAS = visual analog scale

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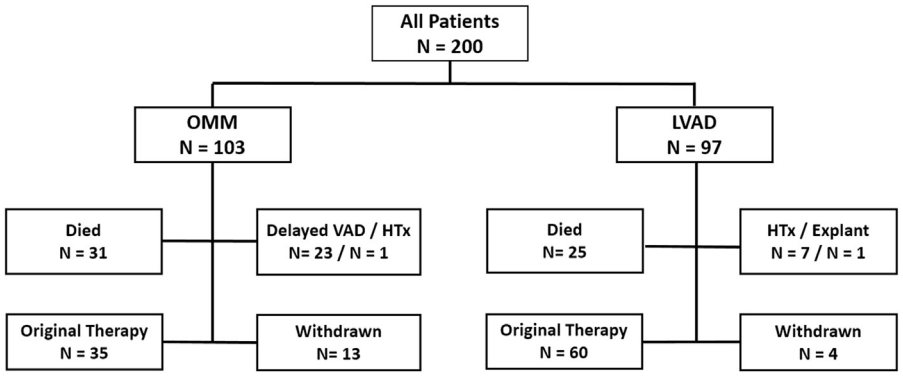
FIGURE 1 Roadmap Study Patients at 2 Years



HTx = heart transplantation; LVAD = left ventricular assist device; OMM = optimal medical management; VAD = ventricular assist device.

analog scale (VAS), and a depression screening questionnaire, the Patient Health Questionnaire (PHQ-9). A summary of baseline patient characteristics has been previously published (1). Clinical follow-up took place every 6 months for up to 2 years and included assessment of HRQol, depression, functional status, and laboratory parameters. Prevalence, incidence, causes of rehospitalizations, and causes of death were documented by study sites, but not adjudicated. AEs were captured using standardized INTERMACS definitions as reported by investigators.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or SE, or median and quartiles, and categorical data are reported as percentages. Differences between groups were analyzed by the Fisher exact test. Differences between groups of independent, normally distributed, continuous variables were evaluated using the 2-sample Student *t* test. Variables that were not normally distributed were compared between treatments using the Wilcoxon rank sum test. A 2-sided p value <0.05 is significant.

The primary endpoint evaluated at 2 years was a composite of survival and improvement in 6MWD of ≥75 m. Urgent heart transplantation (HTx) and explant after LVAD complications in LVAD patients were considered treatment failures. Receipt of delayed LVADs and urgent HTx in OMM patients were also considered treatment failures. Patients who withdrew from the study were excluded from the 2-year primary endpoint analysis.

Actuarial survival as treated on original therapy was performed with the Kaplan-Meier method for LVAD patients free of urgent HTx or explant, and for OMM patients free of LVAD implantation or urgent HTx. Intent-to-treat survival was also determined through 2 years post-enrollment. Differences between groups were determined with the log-rank test.

The prevalence of patients with AEs within 2 years and the incidence rate of events per patient-year (eppy) were determined for both groups. 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 using Cochran-Mantel-Haenszel statistics.

Paired changes in 6MWD, PHQ-9, and EQ-5D VAS from baseline to 2 years were compared between patients surviving to 2 years on original therapy using

TABLE 1 Primary Endpoint Evaluated at 2 Years

	OMM (n = 77)	LVAD (n = 67)
Alive at 2 yrs on original therapy with increase in 6MWD by 75 m	9 (12)	20 (30)
		(OR: 3.2 [95% CI: 1.3 to 7.7]; p = 0.012)
First event that prevented success:	68 (88)	47 (70)
Death in 1st yr	18 (23)	17 (25)
Death in 2nd yr	13 (17)	8 (12)
Urgent HTx in 1st yr	0 (0)	2 (3)
Urgent HTx in 2nd yr	1 (1)	1 (2)
Delayed LVAD in 1st yr*	18 (23)	NA
Delayed LVAD in 2nd yr	5 (7)	NA
Δ 6MWT <75 m at 2 yrs	13 (17)	19 (28)

Values are n (%). Excluded OMM patients: 13 withdrawn, 13 missing 6MWD. Excluded LVAD patients: 4 withdrawn, 5 elective HTx/explant, 21 missing 6MWD. *1 total artificial heart included.

6MWD = 6-min walk distance; CI = confidence interval; HTx = heart transplantation; LVAD = left ventricular assist device; NA = not applicable; OMM = optimal medical management; OR = odds ratio.

mixed-effects modeling on ranks with Tukey adjustment for pairwise comparisons. Post hoc composite endpoints of favorable outcomes at 2 years were determined, defined as patients alive on original therapy at 2 years with improvement in NYHA functional class, increase in VAS of more than 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). A biostatistician independent of the sponsor and the investigators provided an independent validation of study results.

RESULTS

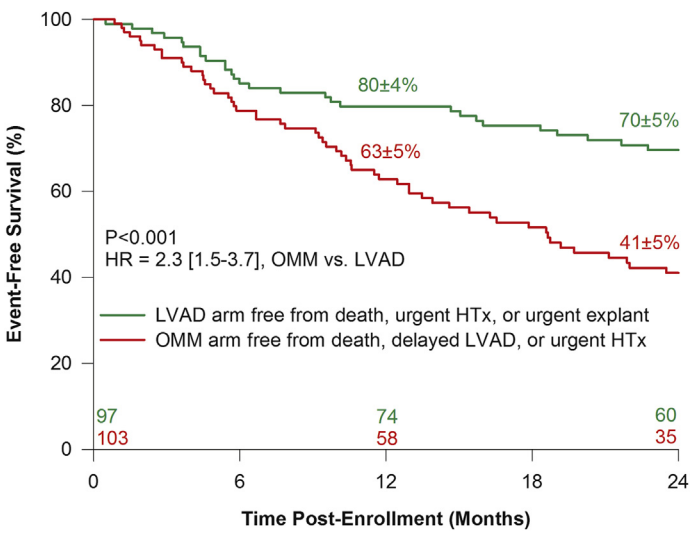
STUDY COURSE. A chart of all patients and main outcomes over the 2-year study period is shown in Figure 1. Of the 103 OMM patients, 18 died, 18 received delayed LVADs, and 9 withdrew during the first year. During the second year, an additional 13 OMM patients died, 5 received delayed LVADs, 1 received a HTx, and 4 withdrew from the study. Of the 97 LVAD patients, 17 died, 3 received HTx, and 3 withdrew during the first year of the study. Of the 74 patients remaining on LVAD support at 1 year, an additional 8 died, 4 received HTx, 1 was explanted, and 1 withdrew from the study during the second year. At the end of 2 years, 35 (34%) OMM patients and 60 (62%) LVAD patients were alive on their original therapy.

PRIMARY ENDPOINT. At 2 years, more LVAD patients (30%) met the primary endpoint of alive on original therapy with improvement in 6MWD of at least 75 m than OMM patients (12%) (odds ratio: 3.2 [95% confidence interval: 1.3 to 7.7]; p = 0.012). The main reason for fewer OMM patients meeting the primary endpoint compared with the LVAD group was the use of delayed LVADs. In the second year, a larger percentage of deaths and additional delayed LVAD implants in OMM patients contributed to fewer OMM patients meeting the primary endpoint at 2 years (Table 1). A sensitivity analysis for the effect of missing data on the primary endpoint is shown in Online Table 1. Significantly more LVAD patients met the primary endpoint compared with OMM patients even when those withdrawn from the study or with missing 6-min walk test were counted as either treatment successes or failures.

ACTUARIAL SURVIVAL. Twenty-four-month survival as treated on original therapy (event-free survival) was greater for LVAD versus OMM (70 ± 5% vs. 41 ± 5%; p < 0.001) (Figure 2). There was no difference in intent-to-treat survival for LVAD versus OMM (70 ± 5% vs. 63 ± 5%; p = 0.307) (Figure 3). A competing outcomes analysis for all LVAD and OMM patients is also shown in Online Figure 1.

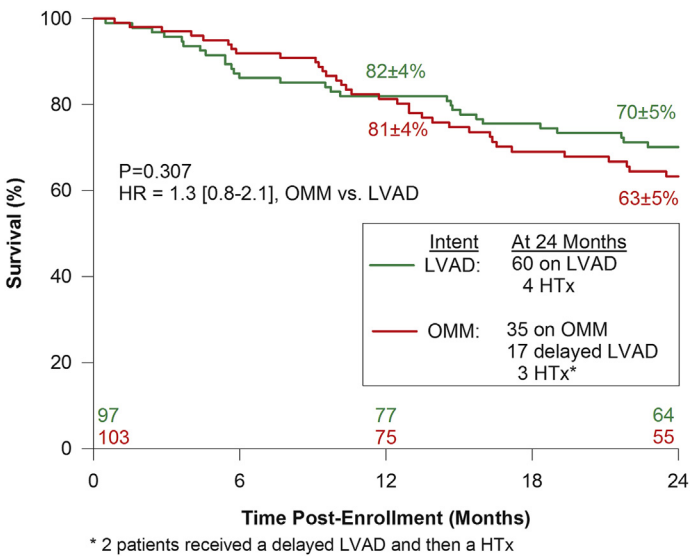
FUNCTIONAL STATUS AND QUALITY OF LIFE. At 2 years, in patients still on original therapy, LVAD

FIGURE 2 Survival as Treated



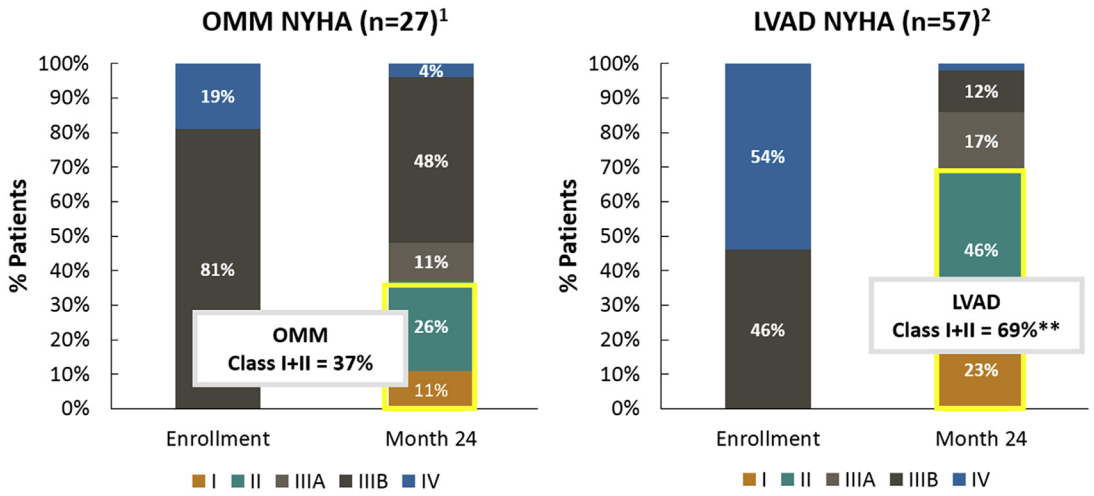
HR = hazard ratio; other abbreviations as in Figure 1.

FIGURE 3 Intention-to-Treat Survival



Abbreviations as in Figures 1 and 2.

FIGURE 4 Changes in NYHA Classification in Patients Who Are Alive on Original Therapy at 2 Years



[1]Excluded OMM patients: 8 missing NYHA classification
[2]Excluded LVAD patients: 3 missing NYHA classification
**P<0.01 LVAD vs. OMM

NYHA = New York Heart Association; other abbreviations as in Figure 1.

patients experience greater improvements in functional status and quality of life (QoL) compared with OMM patients. At study enrollment, no patients were in NYHA functional class I or II. By 2 years, 69% of LVAD patients had improved to class I or II, which was significantly >37% of the remaining OMM patients ($p < 0.01$) (Figure 4). LVAD patients exhibited a significant increase in 6MWD from baseline by an average of 74 m ($p < 0.05$) after 2 years of support compared with no significant change in OMM patients (Table 2).

TABLE 2 Paired Changes in 6MWD, EQ-5D VAS, and PHQ-9 Scores in 2-Yr Survivors on Original Therapy

	Arm	N (Missing N)	Baseline	2 Yrs	Change	p Value Within Arm
6MWD (m)	OMM	22 (13)	213 ± 81	277 ± 106	64 ± 103	0.312
	LVAD	39 (21)	180 ± 88	254 ± 134	74 ± 141	0.030
p Value between arms			0.622	0.869	0.768	
EQ-5D VAS	OMM	28 (7)	66 ± 18	74 ± 18	8 ± 20	0.282
	LVAD	53 (7)	44 ± 19	71 ± 21	27 ± 24	<0.001
p Value between arms			<0.001	0.787	<0.001	
PHQ-9 score	OMM	27 (8)	6.8 ± 6.4	5.0 ± 5.7	−1.8 ± 6.3	0.480
	LVAD	54 (6)	10.0 ± 5.6	5.4 ± 5.6	−4.6 ± 6.9	<0.001
p Value between arms			0.055	0.958	0.084	

A lower PHQ-9 score indicates lower depression.

EQ-5D VAS = EuroQol 5 dimensions questionnaire–visual analog scale; PHQ-9 = Patient Health Questionnaire; other abbreviations as in Table 1.

Baseline health-related QoL measures are shown in Table 2. The EQ-5D VAS increased significantly more for LVAD versus OMM at 2 years with an average improvement of 27 points for LVAD patients compared with 8 points for OMM patients ($p < 0.001$) (Table 2). At 2 years, the PHQ-9 depression score for LVAD patients improved significantly from enrollment by an average of 4.6 points, with no significant change in OMM patients (Table 2).

The primary and secondary composite endpoints showing the percentage of patients alive at 2 years on original therapy with improvements in NYHA functional class, EQ-5D VAS, and depression all showed significant improvements in LVAD versus OMM patients (Figure 5).

DELAYED VADs. The 22 patients with delayed VADs (not including the 1 with a total artificial heart) received implants after a median time from enrollment of 4.9 (min to max: 1.2 to 19.7) months (Table 3). The median INTERMACS profile at enrollment was 5 (min to max: 4 to 6) and dropped to 4 (min to max: 2 to 6) at the time of implantation. Fifty-five percent of OMM patients receiving delayed VADs were inotrope dependent when they received implants, but 45% remained INTERMACS 4 to 6. Median Seattle Heart Failure Model–predicted survival dropped from 89% (quartile 1 to 3: 81% to 92%) at enrollment to 71% (quartile 1 to 3: 40% to 86%) before delayed implant,

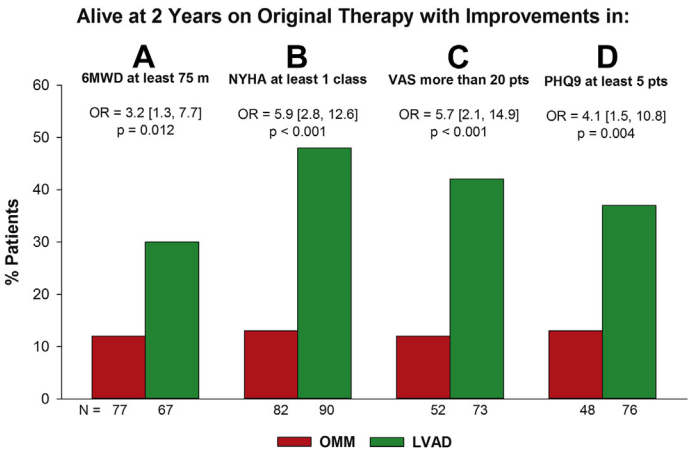
and median 6MWD decreased from 219 (quartile 1 to 3: 192 to 272) m to 90 (quartile 1 to 3: 0 to 221) m before implantation. There were no deaths within 30 days after delayed LVAD, and survival at 1 year was 90 ± 6%, which was not different from the original LVAD cohort ($p = 0.33$ log-rank). Additional comparisons of baseline characteristics of LVAD patients implanted at enrollment and before implantation in the delayed group are shown in Online Table 2. Survival curves of both groups are shown in Online Figure 2.

ADVERSE EVENTS. Table 4 lists the prevalence and cumulative AE rates for the entire 2-year follow-up period. Over the 2-year study, the composite event rate was significantly higher for LVAD versus OMM (1.74. vs 0.98 eppy; $p < 0.001$). Gastrointestinal (GI) bleeding is the most common AE for LVAD patients, and 5 patients contributed more than one-half of all GI bleeding events in the LVAD group. Worsening HF is the most frequent event for OMM patients. Table 5 shows the AE occurrence in the first and the second year of follow-up. The AE profile for OMM did not change significantly over time. In LVAD patients, there was no change in pump thrombus or driveline infection rates from the first to second year. However, LVAD event rates for GI bleeding and ventricular arrhythmias decreased significantly from the first to second year. As a result, the composite event rate was no longer significantly different between LVAD and OMM in the second year of follow-up. Right HF also showed a trend for reduction in the second year. LVAD patients had more hospitalizations than OMM patients throughout the study. Freedom from re-hospitalization at 2 years (Online Figure 3) was 16% for OMM patients and 8% for LVAD patients ($p = 0.005$). The main reason for readmission of OMM patients was worsening HF. Hospitalizations for LVAD patients were largely due to AEs (predominantly bleeding). In the second year, there was a decrease in the number of LVAD patient readmissions related to AEs (Table 6).

Of the 25 LVAD patients who expired, the leading cause of death was infection (n = 6), followed by stroke (n = 3), device thrombosis (n = 3), multiorgan failure (n = 3), HF (n = 3), and 1 each for bleeding, driveline disconnect, ventricular fibrillation, pleural effusion, respiratory failure, car accident, and unknown. The most common cause of death among the 31 OMM patients who expired was worsening HF (n = 21), followed by cancer (n = 2), 1 each for sudden cardiac death, chronic obstructive pulmonary disease, sepsis, multiorgan failure, and bleeding, and 3 were unknown.

RISK-BENEFIT ANALYSIS. Figure 6 summarizes the benefits and risks of LVAD therapy versus OMM for patients in the ROADMAP study. In the second year of the ROADMAP study, LVAD patients continue to be more likely to reach the primary composite endpoint and their survival as treated on original therapy is significantly better. LVAD patients also continue to be more likely to show improvements in NYHA functional class, HRQoL, and depression at 2 years compared with OMM patients. The composite AE rate during the second year between LVAD and OMM patients is not significantly different.

FIGURE 5 Primary and Secondary Composite Endpoints



Primary **(A)** and secondary **(B, C, D)** composite endpoints. 6MWD = 6-min walk distance; OR = odds ratio; PHQ = Patient Health Questionnaire; VAS = visual analog scale; other abbreviations as in Figures 1 and 4.

DISCUSSION

The principal findings after 2 years of follow-up in the ROADMAP study include: 1) higher survival with

TABLE 3 Paired Changes in OMM Patients Receiving Delayed VAD

	All Delayed LVAD Patients (N = 22) Time to Implantation = 4.9 [2.7-12.4] Months			
		Enrollment	Delayed Implantation	Paired p Value
Inotrope dependent	22	0 (0)	12 (55)	<0.001
INTERMACS profile	18	5 [4-6]	4 [2-4]	<0.001
NYHA functional class IV	20	5 (25)	14 (70)	0.004
SHFM 1-yr survival (%)*	22	89 [81-92]	71 [40-86]	0.001
Albumin (g/dl)	20	3.9 [3.6-4.2]	3.5 [3.4-3.7]	0.009
6MWD (m)	15	219 [192-272]	90 [0-221]	<0.001
VAS	13	45 [33-50]	40 [28-50]	0.473
PHQ-9	15	7 [2-10]	9 [4-12]	0.423

Values are n, n (%), or median [quartile 1 to 3]. *Mean predicted survival was 85 ± 11% at enrollment and 61 ± 31% at delayed implant.

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; SHFM = Seattle Heart Failure Model; VAD = ventricular assist device; other abbreviations as in Tables 1 and 2.

TABLE 4 Cumulative AEs Within 2 Yrs of Enrollment

	OMM (n = 103) Patients (%) (eppy)	LVAD (n = 94) Patients (%) (eppy)	DT Trial as Reference (eppy)*
Bleeding	3 (3) (0.02)	51 (54) (1.09)†	1.13
GI bleeding	2 (2) (0.02)	31 (33) (0.68‡)†	NA
Driveline infection	NA	16 (17) (0.15)†	0.22
Pump thrombus	NA	11 (12) (0.08)‡‡	0.07§
Within 90 days		1 (1.1)	
Pump replacement††		7 (7.4)	
Stroke	4 (3.9) (0.03)	11 (11.7) (0.09)	0.08
Ischemic	3 (2.9) (0.02)	8 (8.5) (0.06)	0.05
Hemorrhagic	1 (1.0) (0.01)	4 (4.3) (0.03)	0.03
Arrhythmias VT/VF	13 (13) (0.12)	21 (22) (0.21)	0.46
Worsening heart failure‖	51 (50) (0.80)	13 (14) (0.13)†	NA
Right heart failure¶	3 (3) (0.02)	10 (11) (0.07)	0.13
Rehospitalizations	78 (76) (1.51)	81 (86) (2.55)†	2.64#
"Composite" event rate**	55 (53) (0.98)	72 (77) (1.74)†	2.09
Relative risk [95% CI]	OMM/LVAD: 0.56 [0.41–0.77]†		

*Park et al. (4). †p < 0.001. ‡Five patients had ~50% of GI bleeding events. §Thrombus + hemolysis. ‖Worsening HF: symptoms resulting in unexpected hospitalization, emergency room visit, or urgent clinic visit requiring intravenous therapy for HF. ¶Right HF: symptoms and signs of persistent right ventricular dysfunction requiring right VAD implantation or requiring inhaled nitric oxide or inotropic therapy. #Slaughter et al. (3). **Sum of bleeding, driveline infection, thrombus, stroke, arrhythmias, and worsening HF. ††For thrombus, there were 2 additional pump replacements for infection and percutaneous lead failure. ‡‡p < 0.01

AE = adverse event; CI = confidence interval; DT = Destination Therapy; eppy = events per patient-year; GI = gastrointestinal; HF = heart failure; VT/VF = ventricular tachycardia/ventricular fibrillation; other abbreviations as in Table 1.

improved functional status, improved QoL, and reduced depression in the LVAD group; 2) no increased mortality with delaying LVAD implant while being monitored closely; 3) more hospitalizations in the LVAD than the OMM group throughout the study; and 4) greater rate of major AEs in LVAD than OMM subjects in year 1 but with a reduction in LVAD AEs in year 2. The second-year ROADMAP study results demonstrate the benefit of the HeartMate II LVAD in select functionally limited non-inotrope-dependent HF patients.

TABLE 5 AEs During the First and Second Yr of Follow-Up

	Yr 1		Yr 2	
	OMM AE Rate (eppy) 79.7 Patient-Yrs	LVAD AE Rate (eppy) 82.4 Patient-Yrs	OMM AE Rate (eppy) 45.2 Patient-Yrs	LVAD AE Rate (eppy) 68.7 Patient-Yrs
Bleeding	0.03	1.49*	0.02	0.60*†
GI bleeding	0.01	0.92*	0.02	0.39*†
Infection	0.09	0.97*	0.13	0.68*
Driveline infection	NA	0.13§	NA	0.17§
Sepsis	0.01	0.23*	0	0.13‡
Pump thrombus	NA	0.07‡	NA	0.09
Stroke	0.025	0.12‡	0.04	0.04
Ischemic	0.013	0.07	0.04	0.04
Hemorrhagic	0.013	0.05	0	0
Arrhythmias VT/VF	0.10	0.33§	0.16	0.07†
Worsening heart failure	0.90	0.16*	0.62	0.09*
Right heart failure	0.03	0.11‡	0.02	0.01
Rehospitalizations	1.77	2.67‡	1.04†	2.40*
"Composite" event rate‖	1.05	2.31*	0.84	1.06¶
Relative risk [95% CI]	OMM/LVAD: 0.46 [0.31–0.68]*		OMM/LVAD: 0.79 [0.46–1.36]	

*p < 0.001 (OMM vs. LVAD). †p < 0.05 (yr 2 vs. yr 1). ‡p < 0.05 (OMM vs. LVAD). §p < 0.01 (OMM vs. LVAD). ‖Sum of bleeding, driveline infection, thrombus, stroke, arrhythmias, and worsening HF. ¶p < 0.001 (yr 2 vs. yr 1).

Abbreviations as in Tables 1 and 4.

Advanced HF is a lethal condition with few options to extend survival and QoL; due to donor shortage, heart transplantation is limited to a fraction of the patients in need. The advent of continuous-flow LVAD therapy heralded the hope to save many lives, and initial encouraging reports sparked a proliferation of LVAD implantations (3–6). Enthusiasm grew with new devices, and subsequently, a National Heart, Lung, and Blood Institute workshop was convened to design a clinical trial to determine whether LVAD use could be safely expanded to "less ill" patients (7). The REVIVE-IT (Registry Evaluation of Vital Information for VADS in Ambulatory Life; NCT01369407) trial intended to compare the effectiveness of LVAD and medical therapy in non-inotrope-dependent patients through a design randomizing patients to the 2 respective treatment approaches. The REVIVE-IT trial faced numerous challenges and was never completed, and has evolved into a registry. The ROADMAP study was conceived at the same time and designed as a nonrandomized trial in which patients and their physicians could determine the choice of LVAD versus OMM therapy, and outcomes of these choices would be carefully assessed. Our goals included determining functional capacity, and the primary endpoint included a clinically relevant incremental walk distance of 75 m on original therapy. Detailed efforts were made to collect data to understand why both physicians and patients chose a therapy and to capture patient-reported outcomes.

The observation that LVAD patients more often met the primary endpoint was anticipated and not surprising based on the 1-year results (1). This finding was also sustained at 2 years with more LVAD patients on original therapy alive and able to walk with an improvement of more than 75 m. For this non-inotrope-dependent population, LVAD mortality in the initial 30 days was a remarkably low 1%; however, the observed AE rates remain similar to what has been reported with contemporary devices (3,4,8–12). What is provocative is that despite the LVAD cohort having more AEs, frequent hospitalizations, and worse pre-LVAD self-reported QoL, LVAD therapy resulted in greater improvement in depression and in QoL at both 1 and 2 years compared with OMM, although potential bias in these types of assessments must be recognized. The AEs at 2 years in patients choosing LVAD included 11% stroke, 12% LVAD

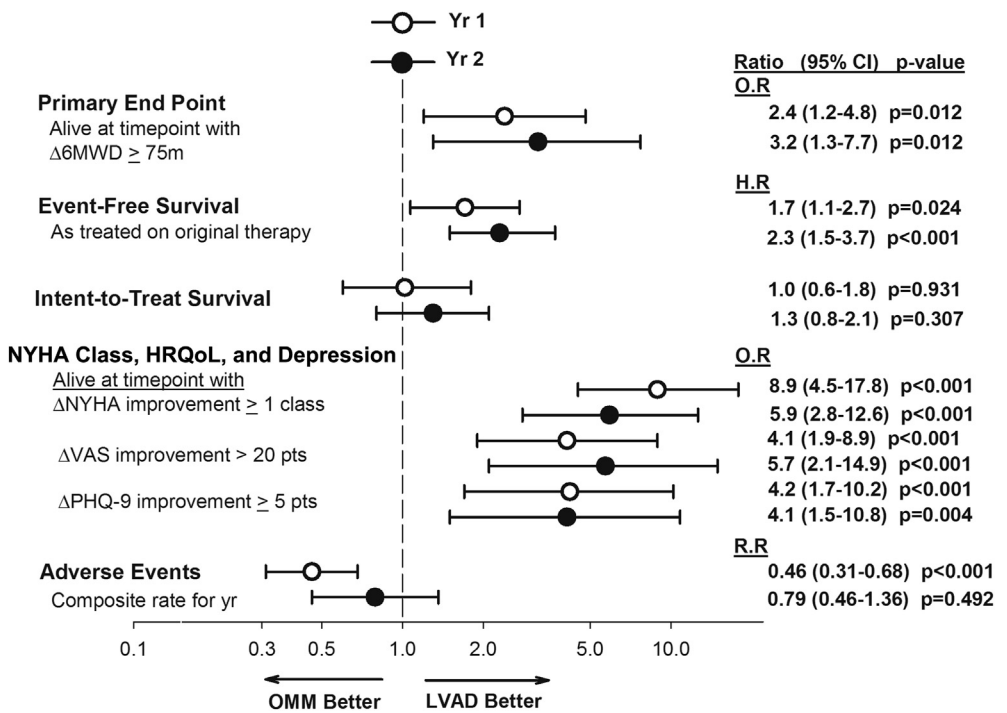
TABLE 6 Reasons for Rehospitalizations

	Yr 1		Yr 2	
	OMM (n = 141)	LVAD (n = 220)	OMM (n = 47)	LVAD (n = 165)
Adverse events	85 (60) 1.07	142 (65) 1.72	32 (68) 0.71	92 (56) 1.34
Elective procedure	10 (7) 0.13	15 (7) 0.18	1 (2) 0.02	15 (9) 0.22
Comorbidity management	10 (7) 0.13	10 (5) 0.12	4 (9) 0.09	12 (7) 0.17
Blood pressure/volume management	4 (3) 0.05	12 (5) 0.15	0 (0) 0	4 (2) 0.06
Pain	4 (3) 0.05	4 (2) 0.05	2 (4) 0.04	12 (7) 0.17
Trauma	1 (1) 0.01	4 (2) 0.05	2 (4) 0.04	9 (5) 0.13
LVAD alarms/driveline and controller problems	0 (0) 0	5 (2) 0.06	0 (0) 0	7 (4) 0.10
Dizziness/syncope	9 (6) 0.11	7 (3) 0.08	0 (0) 0	2 (1) 0.03
LVAD implantation or exchange/heart transplantation	10 (7) 0.13	2 (1) 0.02	3 (6) 0.07	6 (4) 0.09
Anticoagulation management	0 (0) 0	6 (3) 0.07	0 (0) 0	2 (1) 0.03
Rehabilitation/hospice	3 (2) 0.04	5 (2) 0.06	1 (2) 0.02	1 (1) 0.01
Other	5 (4) 0.06	8 (4) 0.10	2 (4) 0.04	3 (2) 0.04

Values are events (%) eppy.
Abbreviations as in Tables 1 and 4.

thrombosis, 22% arrhythmias, 33% GI bleeding, and 86% required hospitalization, whereas of those choosing to stay on OMM, 50% experienced worsening HF, 13% arrhythmias, 4% stroke, and 76% also required hospitalization. AEs/complications remain a challenge for LVAD therapy (13). However, we are encouraged that in the ROADMAP study, there was a reduction in AEs in the second year of follow-up; this observation was also noted in a

FIGURE 6 Risk-Benefit Analysis



CI = confidence interval; R.R. = risk ratio; other abbreviations as in Figures 1, 2, 4, and 5.

single-center report with a reduction in AEs after 6 months (8).

The results show there was no increase in mortality in the delayed LVAD group compared with the original LVAD group post-implant. The delayed LVAD patients were enrolled in the OMM arm with a median INTERMACS profile of 5. At the time of delayed LVAD implantation (a median of 4.9 months after enrollment), the median INTERMACS profile had changed incrementally to 4, which is the same as the original LVAD cohort at implantation. Thus, one would expect similar survival rates post-LVAD. Patients implanted with LVADs later in the ROADMAP study are not delayed compared with standard clinical practice, where most patients today are inotrope dependent in profiles 2 or 3. Hence, results cannot be generalized to patients with greater clinical deterioration before implantation.

The ROADMAP study has demonstrated that patients may make choices contrary to what might be intuitive to the physician. Patients who are living with HF may be willing to accept a burden of AEs to improve their functional capacity and QoL. Earlier referral enables better education and shared decision making with the patient, which is important for weighing benefits and risks of LVAD therapy. Patients may be willing to accept a "trade off": improvement in QoL and functional capacity versus potential AEs. Bruce et al. (14) described the importance of a patient-centered perspective and discussions that include 3 domains for patient education and decision making regarding LVADs: survival, functional capacity/QoL, and AEs. The importance of developing decision aids for patients with advanced HF considering the extremely complex process and lifestyle of LVAD therapy has been highlighted recently (15).

STUDY LIMITATIONS. The study was nonrandomized; hence, a potential exists for bias regarding patient selection and patient-reported outcomes including HRQoL and depression, which were nonblinded. There was a high withdrawal rate from the study, with more withdrawing in the OMM arm than in the LVAD arm, thus introducing a potential bias. However, if the primary endpoint is reanalyzed counting all withdrawn patients as treatment failures, the study findings are maintained, with more LVAD than OMM patients still meeting the endpoint (28% vs. 10%; odds ratio: 3.5 [95% confidence interval: 1.5 to 8.4]; $p = 0.004$) (Online Table 1). Data were also missing for some endpoints, including the 6-min walk test, as noted in **Table 2**, which could have an effect on the results. The event free survival analysis did not include pump replacement as an event. However, if pump replacement is included, event-free survival for LVAD patients remains significantly higher than for OMM patients (Online Figure 4). AEs were reported by treating physicians and not adjudicated by a clinical events committee. Patient management was per center practices, thus variations in medical management, anticoagulation, bleeding, and other events may not have been attributed solely to patient or device characteristics. Nonetheless, the ROADMAP study provides important information for clinicians prescribing LVAD therapy. Some patients and clinicians were not at equipoise and either believed LVAD therapy was superior or that OMM therapy was superior, and they made decisions based on this belief. Many HF specialists feel that current LVAD technology is not ready to be utilized in randomized trials of less-sick patients, but the severity of illness of the target patient population is a critical factor. On the basis of our observed 24-month intent-to-treat survival in LVAD (70%) and OMM (63%) patients, a trial would be difficult to enroll, and would need to randomize approximately 700 patients in each arm to have 80% power to demonstrate a significant difference in 2-year survival. However, if restricted to INTERMACS profile 4 patients, where our observed intent-to-treat survival was 66% in LVAD and 49% in OMM patients, a trial would only need to randomize approximately 130 patients in each arm to show such a difference.

CONCLUSIONS

The ROADMAP study has demonstrated the role of LVAD therapy in non-inotrope-dependent patients with advanced HF to improve functional capacity and QoL, albeit with concomitant AEs. Delaying the decision for LVAD therapy when monitored closely by a HF specialist with access to LVAD therapy and transplantation does not impair survival, though it does delay QoL and functional improvements. The need for a randomized clinical trial in expanded patient populations that are not inotrope dependent remains. Hopefully, such trials can be realized with the emerging generation of LVADs, which new technology shows promise for reduced AEs (16–18).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The ROADMAP trial provides the first evidence that non–inotrope-dependent patients electing LVAD therapy will gain functional capacity and QoL compared with similar patients electing medical therapy. Although 22% of patients treated medically received delayed LVADs after clinical deterioration, their survival rates were equivalent. AEs are prevalent with both strategies, and readmissions are not reduced after LVAD. Despite the limitations, LVAD therapy will be preferred by some patients with advanced HF who are not yet inotrope dependent. The ROADMAP trial provides information to assist caregivers when counselling HF patients making important treatment decisions.

TRANSLATIONAL OUTLOOK: LVAD therapy improves functional capacity and QoL, but not survival, compared with medical therapy in less ill patients who are non-inotrope dependent. The observation that QoL and functional capacity improve despite frequent AEs and frequent need for hospitalization is counterintuitive. Patients, in shared decisions with their physicians, should decide what treatment option is preferred. New technology is needed to reduce LVAD AEs. A randomized clinical trial in "less ill" patients with new LVAD technology should be forthcoming with endpoints related to functional capacity and QoL.

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KEY WORDS heart failure, left ventricular assist device, pharmacological therapy

APPENDIX For supplemental tables and figures, and acknowledgment of the study investigators and participating institutions, please see the online version of this article.