ORIGINAL RESEARCH

Caregiver Health-Related Quality of Life, Burden, and Patient Outcomes in Ambulatory Advanced Heart Failure: A Report From REVIVAL

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BACKGROUND: Heart failure (HF) imposes significant burden on patients and caregivers. Longitudinal data on caregiver health-related quality of life (HRQOL) and burden in ambulatory advanced HF are limited.

METHODS AND RESULTS: Ambulatory patients with advanced HF (n=400) and their participating caregivers (n=95) enrolled in REVIVAL (Registry Evaluation of Vital Information for VADs [Ventricular Assist Devices] in Ambulatory Life) were followed up for 24 months, or until patient death, left ventricular assist device implantation, heart transplantation, or loss to follow-up. Caregiver HRQOL (EuroQol Visual Analog Scale) and burden (Oberst Caregiving Burden Scale) did not change significantly from baseline to follow-up. At time of caregiver enrollment, better patient HRQOL by Kansas City Cardiomyopathy Questionnaire was associated with better caregiver HRQOL (*P*=0.007) and less burden by both time spent (*P*<0.0001) and difficulty (*P*=0.0007) of caregiving tasks. On longitudinal analyses adjusted for baseline values, better patient HRQOL (*P*=0.034) and being a married caregiver (*P*=0.016) were independently associated with better caregiver HRQOL. Patients with participating caregivers (versus without) were more likely to prefer left ventricular assist device therapy over time (odds ratio, 1.43; 95% CI, 1.03–1.99; *P*=0.034). Among patients with participating caregivers, those with nonmarried (versus married) caregivers were at higher composite risk of HF hospitalization, death, heart transplantation or left ventricular assist device implantation (hazard ratio, 2.99; 95% CI, 1.29–6.96; *P*=0.011).

CONCLUSIONS: Patient and caregiver characteristics may impact their HRQOL and other health outcomes over time. Understanding the patient-caregiver relationship may better inform medical decision making and outcomes in ambulatory advanced HF.

Key Words: caregiving ■ heart failure ■ left ventricular assist device ■ quality of life

Heart failure (HF) is a time intensive chronic condition heavily reliant on self-care to maintain health and manage symptoms of congestion, thus imposing significant burden on patients and their caregivers.[1–3] Caregivers play a critical role in daily HF disease management tasks, as well as logistical support for care coordination, emotional support, and participation in complex medical decision making.[4,5] As HF progresses, patients often become more reliant on caregivers, who may experience an increased sense

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CLINICAL PERSPECTIVE

What Is New?

- In an ambulatory cohort of patients with advanced heart failure, we found that surviving patients' health-related quality of life improved modestly over time and that caregivers' health-related quality of life and burden did not change.
- Having a participating, married caregiver was associated with an increased patient willingness to consider ambulatory left ventricular assist device therapy and a lower composite risk of death, urgent transplant, or left ventricular assist device therapy.

What Are the Clinical Implications?

- Caregivers play a fundamental role in the lives of patients with advanced heart failure; however, their impact on clinical outcomes is not commonly considered.
- These data highlight the need for including caregiver perspective and presence when assessing patient longitudinal outcomes and understanding shared decision making in advanced heart failure.
- Efforts are needed to increase caregiver participation in clinical studies to better understand the important role of the caregiver in heart failure.

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Nonstandard Abbreviations and Acronyms

EQ-VAS	EuroQol Visual Analog Scale
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
KCCQ	Kansas City Cardiomyopathy Questionnaire
OCBS	Oberst Caregiving Burden Scale
REVIVAL	Registry Evaluation of Vital Information for VADs (Ventricular Assist Devices) in Ambulatory Life

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of burden as support needs increase[6] or change in health-related quality of life (HRQOL).[7] In addition, as has been shown in qualitative analyses of caregivers, patient decisions about HF treatment preferences may be impacted by caregiver understanding of disease.[8] The HF caregiver's role has become increasingly complex with advances in medical and surgical treatments for HF, as acknowledged by a recent American Heart Association Scientific Statement on family caregiving in HF.[9]

Existing studies of patients with HF and their caregivers have focused primarily on caregivers of patients undergoing advanced HF therapies, such as left ventricular assist device (LVAD) implantation or heart transplantation.[10–12] Despite a recognized association between caregiver HRQOL and patient outcomes, longitudinal data on burden and HRQOL for caregivers of patients with advanced HF are lacking.[13] Furthermore, to our knowledge, burden and HRQOL have not been examined in caregivers of *ambulatory* patients with advanced HF. REVIVAL (Registry Evaluation of Vital Information for VADs [Ventricular Assist Devices] in Ambulatory Life) provides an opportunity to study caregiver burden and HRQOL over time in an ambulatory advanced HF cohort. The purposes of our report from REVIVAL are to: (1) examine change in caregiver HRQOL and burden over time compared with patient HRQOL, (2) identify patient and caregiver factors related to caregiver HRQOL and burden, and (3) examine whether caregiver factors are related to patient HRQOL, preference for LVAD therapy, and clinical outcomes. We hypothesized that (1) advanced HF patient HRQOL and caregiver HRQOL will decline over time, whereas caregiver burden will increase over time, (2) both caregiver characteristics (eg, high perceived burden) and patient characteristics (eg, poor HRQOL) will be related to caregiver HRQOL, whereas patient characteristics (eg, worse HF and worse patient HRQOL) will be related to increased caregiver burden, and (3) caregiver characteristics (eg, being a spouse or partner) will be related to patient preference for LVAD therapy and patient clinical outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

REVIVAL is a prospective, observational, multicenter cohort of ambulatory patients with advanced HF that also includes caregivers.[14] Patients and caregivers were enrolled from 21 centers between July 2015 and June 2016. Patients enrolled were aged 18 to 80 years with New York Heart Association functional class II to IV limitations for at least 45 of the previous 60 days, left ventricular ejection fraction ≤35%, and a HF diagnosis >12 months. All patients were on maximum tolerated doses of evidence-based HF medical and electrical therapies for ≥3 months or had a documented contraindication or intolerance to medication use. In addition, enrollment required subjects to have 1 high-risk feature for mortality (ie, reduced peak oxygen uptake, reduced 6-minute walk distance, elevated

natriuretic peptide level, reduced serum sodium, decreased Seattle Heart Failure Model 1-year predicted survival, or active United Network for Organ Sharing status 2 heart transplant), 1 unplanned HF hospitalization in the prior 12 months with a lesser threshold for natriuretic peptide level, or 2 unplanned HF hospitalizations in the prior 12 months (Tables S1 and S2). Patient participants were enrolled in REVIVAL at the initial baseline A visit, and caregivers were subsequently identified and enrolled at the baseline B visit (≈2 months later). Patients were determined to have participating caregivers if the patient completed a baseline B visit and a caregiver was enrolled at that visit with completion of at least one baseline HRQOL survey. An independent Observational Study Monitoring Board oversaw the conduct of REVIVAL. The Institutional Review Board at each center approved the study. All subjects (patients and caregivers) provided written informed consent before study participation.

Data Collection and Outcomes

Patients were followed up for 24 months or until earlier death, heart transplantation, or implantation of durable mechanical circulatory support. Clinical evaluation occurred at enrollment (baseline A), and at 2 (baseline B), 6, 12, 18, and 24 months. The following data were collected for patients at the baseline B visit: demographics, clinical characteristics, medications, laboratory values, physical examination results, and a 6-minute walk test. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) patient profiles were assigned at each visit by the treating cardiologist, according to methods previously described.[15] Outcomes prospectively collected at the time of occurrence included hospitalizations, heart transplantation, mechanical circulatory support, and death. At study entry and each visit, patients were asked to read a 2-page document containing a basic description and illustration of an LVAD, along with information about indications, benefits, and complications of LVAD therapy.[16] The description of LVAD therapy was written at a US eighth-grade education level (Flesch-Kincaid readability ease). The probabilities of survival, recurrent hospitalization, and adverse events following LVAD included in the instrument were based on event rates of approved devices at the time of survey development in 2015. Subjects were then asked to reply on a Likert-type scale to the question: "Based on how you feel right now, how would you feel about having a VAD placed to treat your heart failure?" Subjects were classified into 3 groups based on their responses: (1) wanting LVAD (including "definitely want" and "probably want"), (2) unsure, and (3) not wanting LVAD (including

"probably not want" and "definitely not want"). Other self-report instruments were administered as follows: patients (at study entry [baseline A] and at 2 [baseline B], 6, 12, 18, and 24 months) and caregivers (at study entry at 2 months [baseline B], and at 6, 12, 18, and 24 months).

HRQOL and Burden Instruments

At each visit, patients were asked to complete (via self-report) 2 validated HRQOL instruments, the Kansas City Cardiomyopathy Questionnaire (KCCQ)[17] and EuroQol Visual Analog Scale (EQ-VAS).[18] The KCCQ, an HF-specific tool, consists of 23 multiple-choice questions with 7 domains: Physical Limitations (6 items), Symptom Stability (1 item), Symptom Frequency (4 items), Symptom Burden (3 items), Self-Efficacy (2 items), Quality of Life (3 items), and Social Limitations (4 items). The Overall Summary Score is calculated as an average of the Physical Limitations, Total Symptoms, Quality of Life, and Social Limitations scores.[17] Higher scores (range, 0–100) reflect fewer limitations, lower symptom frequency and burden, and better HRQOL. The EQ-VAS score measures self-rated overall health (range, 0–100) wherein end points are labeled "best imaginable health state" (higher score) and "worst imaginable health state" (lower score). An EQ-VAS score <55 has been considered to represent poor HRQOL in ambulatory advanced HF, and was thus used as a measure of HRQOL in this study.[19] Prior studies have considered clinically important changes in score on the KCCQ and EQ-VAS to be 5 and 10 points, respectively.[20,21] At enrollment, patients were also administered the Personal Health Questionnaire, an 8-question validated measure that screens for depression.[22] Caregivers also completed the EQ-VAS. In addition, caregiver burden was assessed using the validated Oberst Caregiving Burden Scale (OCBS), which measures 15 caregiving physical and emotional tasks in 2 domains (time spent on task and difficulty of task) using 5-point Likert scales: for time: 1=none to 5=a great amount of time; and for difficulty: 1=not difficult to 5=extremely difficult.[23]

Statistical Analysis

Both patient and caregiver demographic and clinical characteristics were summarized as counts and percentages for categorical data and median and interquartile range (IQR) for continuous data. Patient characteristics were compared between groups with and without participating caregivers using χ^2 tests for categorical data and Wilcoxon rank-sum tests for continuous data. Linear mixed model analyses of patient HRQOL (EQ-VAS and KCCQ) as well as caregiver HRQOL (EQ-VAS) and caregiver burden (OCBS time

and difficulty) were performed, with time (study visits) as a continuous variable (visits number 1 [baseline A] to 6 [month 24]) and with adjustment for baseline values, to assess their longitudinal effects. The analyses of patient HRQOL were performed with (1) all enrolled patients (n=400), (2) patients who completed a baseline B visit (n=337) as these were the patients eligible for caregiver enrollment, or (3) the subset of those patients with a participating caregiver (n=95) as indicated. For the purposes of the longitudinal HRQOL analysis of patients, patient baseline instrument score (ie, KCCQ or EQ-VAS) was considered that obtained at patient enrollment (baseline A visit), whereas for caregiver analyses, patient baseline scores were considered those obtained at time of caregiver enrollment (baseline B visit). Univariable and multivariable linear mixed model analyses of caregiver EQ-VAS scores were conducted with patient and caregiver characteristics as predictors. Cross-sectional (at baseline B) effects of patient and caregiver characteristics on caregiver HRQOL and caregiver burden were assessed using univariable and multivariable regression analyses. The following patient characteristics were included as predictors based on known contributions to patient severity of illness and patient-caregiver relationship: EQ-VAS, KCCQ, frailty, gait speed, and Seattle Heart Failure Model score. Caregiver characteristics included: relationship to patient (versus spouse/domestic partner), paid employment, educational level (versus less than high school), number of surgeries, female sex, race (White compared to nonWhite race), and marital status. Univariable and multivariable linear mixed model analyses of patient HRQOL were conducted with caregiver characteristics as predictors: educational level, female sex, marital status, EQ-VAS, and OCBS time and difficulty scores.

Univariable repeated measures logistic regression analysis was performed to assess which caregiver baseline characteristics were related to patient preference for LVAD therapy. To this end, the 5-level patient preference for LVAD therapy was dichotomized into "yes, I want an LVAD placed to treat my HF" (from categories: definitely and probably want) and "no, I don't want an LVAD" (from categories: "not sure," "definitely not," and "probably not"). The composite clinical outcome included the following patient outcomes, which were combined for analysis because of low numbers of individual events: first unplanned HF-related hospitalization, heart transplantation, durable mechanical circulatory support, and death. Univariable and multivariable linear mixed model analyses of patient HRQOL (EQ-VAS and KCCQ) and Cox regression analysis of time to the composite outcome were performed to ascertain which caregiver baseline characteristics were related to these patient outcomes. The corresponding multivariable analyses of these 3

patient outcomes (ie, generalized linear mixed model analyses of patient preference for LVAD therapy and linear mixed model analyses of patient HRQOL as well as Cox regression analysis of time to the composite outcome) were also performed versus caregiver participation, INTERMACS profile, and their interactions. In the latter case, a time trend term for INTERMACS was included in the model because of failure of the hazard proportionality assumption. To assess potential bias resulting from missing caregiver data, Fisher exact and 2-sample Wilcoxon tests were used to compare selected categorical and continuous patient and caregiver characteristics between the groups with missing and nonmissing caregiver HRQOL and burden data, respectively. To further assess survivorship bias and the potential effects of missing data on HRQOL and burden assessments, we used the Wilcoxon rank-sum test to compare differences in baseline HRQOL (patients and caregivers) and burden (caregivers) between those patients who did and did not meet any study end point.

Characteristics with $P<0.15$ in all above univariable analyses were entered into the corresponding stepwise multivariable analyses, and those variables with $P<0.05$ were considered statistically significant in the final multivariable models. No adjustments were made for multiple hypotheses testing. Analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

Study Cohort

A total of 400 patients with ambulatory advanced HF were enrolled in REVIVAL. Over the length of the REVIVAL study, 61 subjects died, 57 subjects received a durable LVAD, and 30 subjects underwent heart transplantation (23 as a United Network for Organ Sharing status 1A or 1B and 7 as a status 2). Of the 400 patients, 337 completed a baseline B visit, of which 95 had participating caregivers. The clinical outcomes of subjects based on whether they completed baseline B visits are depicted in Figure 1.

Table 1 describes baseline characteristics of patients with (n=95) and without (n=242) participating caregivers. Patients with participating caregivers were more frequently older and White race, and more had a postgraduate degree, compared with those without participating caregivers. There were no differences in HF severity based on INTERMACS profile, New York Heart Association functional class, or Seattle Heart Failure Model score. Participating caregivers (n=95) were mostly women, White race, and the spouse or domestic partner of the patient (Table 2).

Forty-three caregivers did not have end of study EQ-VAS or OCBS assessments for the following
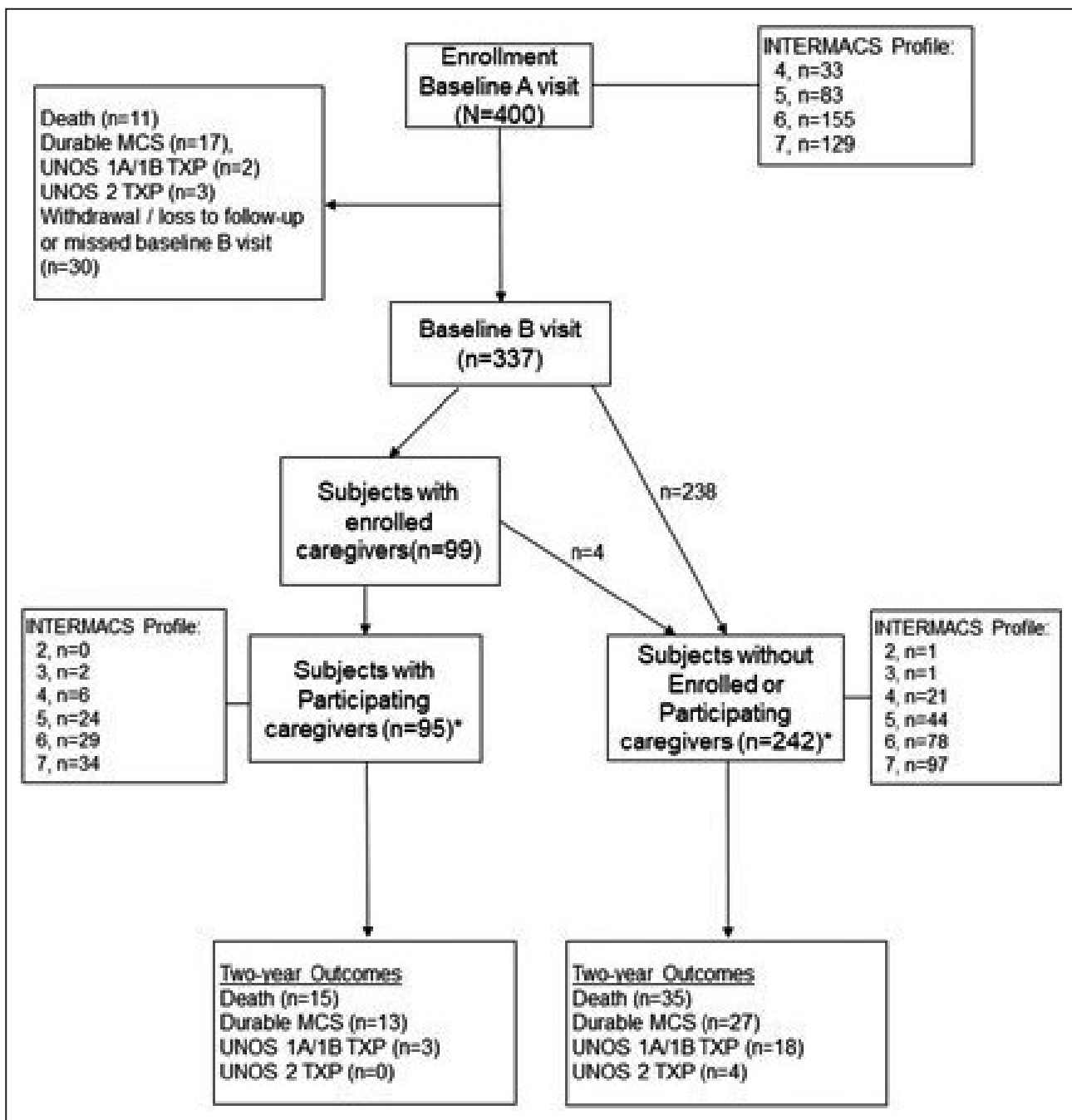
Figure 1. REVIVAL (Registry Evaluation of Vital Information for VADs [Ventricular Assist Devices] in Ambulatory Life) enrollment flowchart.
*Caregivers who signed informed consent and completed at least one baseline quality-of-life survey. INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; TXP, transplant; and UNOS, United Network for Organ Sharing.

reasons: 15 patients died, 8 patients received an LVAD, 4 patients withdrew consent, 3 caregivers were withdrawn because of investigator withdrawal of study subject, 1 caregiver withdrew consent (while the patient remained in study), and 12 were otherwise lost to follow-up for unknown reasons. Differences in patient and caregiver baseline characteristics based on caregiver missingness at 24 months are presented

in Table S3. Patients with missing caregiver HRQOL and burden data were significantly younger than those without missing caregiver data. There were more female caregivers in the missing group compared with the nonmissing group. There were no differences in baseline HRQOL (patients or caregivers) and burden (caregivers) scores based on whether patients experienced the composite study end point (death, durable

Table 1. Patient Characteristics by Caregiver Participation

Characteristic	Caregiver Participation		Total (n=337)	P Value
	No (n=242)	Yes (n=95)		
Age, y	61 (52 to 67)	64 (57 to 71)	62 (54 to 68)	0.004*
Sex				
Women	67 (27.7)	19 (20)	86 (25.5)	0.15
Men	175 (72.3)	76 (80)	251 (74.5)	
Race				
Black	69 (28.5)	10 (10.5)	79 (23.4)	0.0001*
White	155 (64.0)	83 (87.4)	238 (70.6)	
Other	18 (7.4)	2 (2.1)	20 (5.9)	
Ethnicity				
Hispanic or Latino	26 (10.7)	2 (2.1)	28 (8.3)	0.006*
Non-Hispanic or non-Latino	208 (86)	93 (97.9)	301 (89.3)	
Unknown/undisclosed	8 (3.3)	0 (0)	8 (2.4)	
Education				
Grade school (grades 1–8)	8 (3.3)	0 (0)	8 (2.4)	0.035*
High school	65 (26.9)	26 (27.4)	91 (27)	
Attended college/technical school	60 (24.8)	28 (29.5)	88 (26.1)	
Associate degree	17 (7.0)	7 (7.4)	24 (7.1)	
Bachelor degree	30 (12.4)	11 (11.6)	41 (12.2)	
Postgraduate degree	13 (5.4)	13 (13.7)	26 (7.7)	
Unknown	49 (20.2)	10 (10.5)	59 (17.5)	
Ischemic cardiomyopathy	104 (43.0)	43 (45.3)	147 (43.6)	0.70
Diabetes mellitus (n=336)	91 (37.8)	34 (35.8)	125 (37.2)	0.74
Atrial fibrillation (n=331)	92 (39.0)	40 (42.1)	132 (39.9)	0.6
Heart failure diagnosis >5 y	134 (55.4)	56 (58.9)	190 (56.4)	0.55
Frailty (n=284)				
Not frail	94 (48.2)	39 (43.8)	133 (46.8)	0.02*
Prefrail	61 (31.3)	41 (46.1)	102 (35.9)	
Frail	40 (20.5)	9 (10.1)	49 (17.3)	
NYHA class				
I	7 (2.9)	4 (4.2)	11 (3.3)	0.73
II	84 (34.7)	28 (29.5)	112 (33.2)	
III	117 (48.3)	52 (54.7)	169 (50.1)	
IIIb	22 (9.1)	8 (8.4)	30 (8.9)	
IV	12 (5)	3 (3.2)	15 (4.5)	
INTERMACS profile				
2	1 (0.4)	0 (0)	1 (0.3)	0.40
3	1 (0.4)	2 (2.1)	3 (0.9)	
4	21 (8.7)	6 (6.3)	27 (8)	
5	44 (18.2)	24 (25.3)	68 (20.2)	
6	78 (32.2)	29 (30.5)	107 (31.8)	
7	97 (40.1)	34 (35.8)	131 (38.9)	
PHQ ≥10 (+depression screen) (n=306)	53 (24.8)	22 (23.9)	75 (24.5)	0.87
Left ventricular ejection fraction (n=319)	28.08 (23 to 33.4)	29.0 (23.2 to 33)	28.5 (23 to 33.4)	0.87
6-MWD, m (n=299)	361.4 (280 to 416)	364.2 (300.2 to 417)	362.7 (292.6 to 417)	0.89
No. of heart failure hospitalizations	1 (0 to 2)	0 (0 to 1)	1 (0 to 2)	0.40

(Continued)

Table 1.   Continued

Characteristic	Caregiver Participation		Total (n=337)	P Value
	No (n=242)	Yes (n=95)		
BMI, kg/m^2	29.5 (25.3 to 35.1)	28.5 (25.2 to 33.4)	29.1 (25.3 to 34.4)	0.68
EQ-VAS score(n=305)	70 (50 to 80)	70 (50 to 80)	70 (50 to 80)	0.78
KCCQ (n=308)	66 (51 to 81)	63 (43 to 77)	66 (48 to 80)	0.26
Seattle Heart Failure Model score	0.45 (−0.2 to 1.1)	0.7 (−0.3 to 1.2)	0.5 (−0.2 to 1.2)	0.43

Number (percentage) and χ^2 P values are given for categorical characteristics, and median (interquartile range) and Wilcoxon rank-sum P values are given for continuous characteristics. 6-MWD indicates 6-minute walk distance; BMI, body mass index; EQ-VAS, EuroQol Visual Analog Scale (range, 0 [worst health state] to 100 [best health state]); INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; KCCQ, Kansas City Cardiomyopathy Questionnaire overall summary score (range, 1 [worse] to 100 [better]); NYHA, New York Heart Association; and PHQ, personal health questionnaire.

*Significant P value < 0.05.

mechanical circulatory support, or heart transplantation) (Table S4).

Patient and Caregiver HRQOL and Burden Over Time

When examining the baseline A patient cohort (n=400), patient HRQOL, as measured using the EQ-VAS score and KCCQ Overall Summary Score, demonstrated

Table 2.   Baseline Characteristics of Participating Caregivers

Characteristic	Value
Age, y	62 (50–68)
Sex	
Women	76 (81.7)
Men	17 (18.3)
Race	
Black	8 (8.7)
White	82 (89.1)
Other	2 (2.2)
Relationship to patient	
Spouse/domestic partner	72 (76.6)
Son/daughter	8 (8.5)
Other family member	8 (8.5)
Friend	3 (3.2)
Other	3 (3.2)
Employed	45 (49.5)
Marital status	
Married	82 (87.2)
Single	7 (7.4)
Widowed	3 (3.2)
Divorced/separated	2 (2.1)
Oberst Caregiver Burden Scale	
Time spent average score	2.2 (1.7–2.8)
Difficulty average score	1.1 (1–1.5)

Data are given as number (percentage) for categorical characteristics and median (interquartile range) for continuous characteristics. Oberst Caregiver Burden Scale time spent on task: 1=none to 5=a great amount of time; and difficulty of task: 1=not difficult to 5=extremely difficult.

improvement over time. At baseline A (patient enrollment), the median patient EQ-VAS score was 65 (IQR, 50–75) and KCCQ score was 64 (IQR, 48–78). By the 24-month visit, the patient KCCQ score increased by a median of 3 points (IQR, −7 to 13 points), whereas the EQ-VAS score increased by a median of 5 points (IQR, −5 to 17 points). In a linear mixed model adjusting for scores at time of patient enrollment, both EQ-VAS scores (estimate, 0.88; 95% CI, 0.44–1.32; P<0.0001) and KCCQ score (estimate, 0.49; 95% CI, 0.13–0.84; P=0.007) increased significantly, demonstrating longitudinal improvement in HRQOL that was dependent on baseline values. This result remained significant when further adjusted for INTERMACS profile (Table 3). We repeated the above analysis for those patients (n=337) completing a baseline B visit, the visit at which caregivers were enrolled, and found similar results. When adjusted for INTERMACS profile, both patient EQ-VAS (P=0.0006) and KCCQ (P=0.016) scores improved over time (Table 3).

Participating caregivers' overall HRQOL (EQ-VAS) and burden (OCBS) were assessed at baseline B and follow-up. Baseline caregiver median EQ-VAS was 90 (IQR, 76–90). Baseline caregiver OCBS scores for each of the 15 items addressing time on task and difficulty of task are described in Figure S1. The 3 items with the most time spent on tasks were emotional support, providing transportation or "company," and watching for/monitoring symptoms and progress. The tasks identified as most difficult were managing finances/forms related to illness, performing additional household tasks for the patient, and managing patient behavior problems. Although OCBS scores did not change significantly from baseline to end of study (Figure 2), caregivers scored "time spent on tasks" higher than they scored "difficulty of tasks" at both time points. Median change in caregiver instrument scores from baseline to 24-month follow-up among those 51 caregivers with these data available were as follows: EQ-VAS, 0 (IQR, −5 to 5; P=0.77); mean

Table 3.　Longitudinal Analysis of Patient HRQOL Over Time, Adjusted for Baseline Values and INTERMACS Profile in Total Baseline A Patient Cohort and Also Those Patients Completing a Baseline B Visit

| Variable | Baseline A Cohort (n=400) | | | | Baseline B Cohort (n=337) | | | |
| | EQ-VAS(n=367) | | KCCQ (n=373) | | EQ-VAS(n=313) | | KCCQ (n=317) | |
	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value
EQ-VAS, baseline A	0.64 (0.59 to 0.69)	<0.0001			0.62 (0.57 to 0.68)	<0.0001		<0.0001
KCCQ, baseline A			0.79 (0.75 to 0.84)	<0.0001		<0.0001	0.78 (0.73 to 0.82)	
Time	0.77 (0.33 to 1.21)	0.0006*	0.39 (0.05 to 0.74)	0.025*	0.80 (0.34 to 1.25)	0.0006*	0.44 (0.08 to 0.80)	0.016*
INTERMACS profile overall effect		<0.0001		<0.0001		<0.0001		<0.0001
INTERMACS 5 vs 1–4	1.92 (−1.31 to 5.15)	0.244	4.46 (1.86 to 7.06)	0.0008	1.50 (−1.88 to 4.88)	0.384	4.33 (1.61 to 7.05)	0.002
INTERMACS 6 vs 1–4	5.12 (2.05 to 8.19)	0.001	7.91 (5.41 to 10.4)	<0.0001	5.18 (1.99 to 8.38)	0.002	8.02 (5.41 to 10.63)	<0.0001
INTERMACS 7 vs 1–4	7.61 (4.57 to 10.65)	<0.0001	11.99 (9.50 to 14.48)	<0.0001	7.67 (4.50 to 10.83)	<0.0001	12.14 (9.54 to 14.73)	<0.0001

EQ-VAS indicates EuroQol Visual Analog Scale; HRQOL, health-related quality of life; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and KCCQ, Kansas City Cardiomyopathy Questionnaire overall summary score.
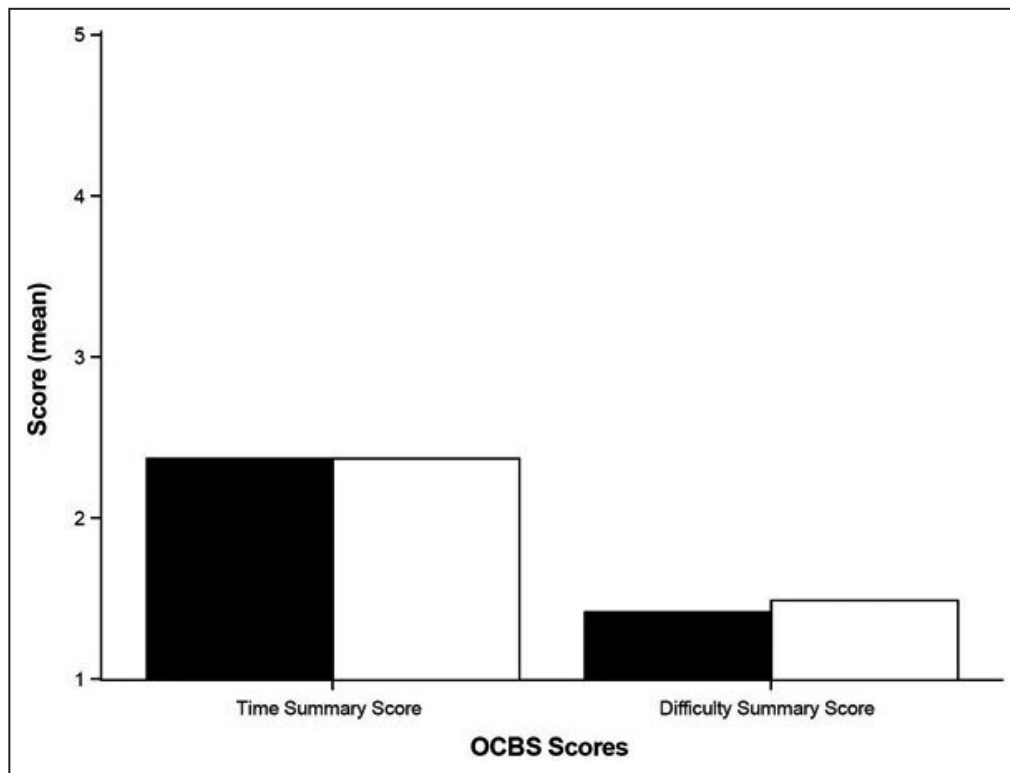*Significant P value < 0.05.

Figure 2. Caregiver mean time (n=51) and difficulty (n=52) summary scores at baseline (black bars) and end of study 24-month follow-up (white bars) on the Oberst Caregiving Burden Scale (OCBS).

OCBS time score, 0 (IQR, −0.33 to 0.33; *P*=0.93); and mean OCBS difficulty score, 0 (IQR, −0.2 to 0.23; *P*=0.58). Caregiver overall HRQOL and burden did not demonstrate change over time in a linear mixed model with time as a continuous variable and with adjustment for baseline scores (Table 4).

Baseline Characteristics Related to Caregiver HRQOL

In cross-sectional analysis at the time of caregiver enrollment (baseline B visit), a higher patient KCCQ overall summary score was significantly associated with a higher caregiver EQ-VAS score (estimate, 0.18; 95% CI, 0.05–0.31; *P*=0.007), less caregiver OCBS time (estimate, −0.02; 95% CI, −0.02 to −0.01; *P*<0.0001), and less caregiver OCBS difficulty (estimate, −0.01; 95% CI, −0.01 to −0.004; *P*=0.0007).

In the longitudinal multivariable analysis of patient and caregiver characteristics on the outcome of caregiver overall HRQOL, adjusted for the baseline caregiver EQ-VAS score, a higher patient time-dependent KCCQ overall summary score (estimate, 0.10; 95% CI, 0.01–0.19; *P*=0.034) and being a married caregiver (estimate, 7.05; 95% CI, 1.34–12.8; *P*=0.016) were independently associated with higher

caregiver overall HRQOL (Table 5). Of note, of the 82 caregivers who were married, 72 were spouses of the patient.

Caregiver Characteristics Related to Patient HRQOL and Outcomes Over Time

In the multivariable analysis, higher patient EQ-VAS scores were associated with higher caregiver EQ-VAS scores over time (estimate, 0.26; 95% CI, 0.15–0.37; *P*<0.0001), whereas lower patient EQ-VAS scores were significantly related to higher caregiver mean OCBS time scores (estimate, −5.43; 95% CI, −8.25 to −2.62; *P*=0.0002). Similarly, worse patient KCCQ overall summary scores were correlated with higher caregiver mean OCBS time scores (estimate, −10.6; 95% CI, −13.3 to −7.8; *P*<0.0001).

Factors Related to Patient Preferences for LVAD Therapy and Composite Patient Clinical Outcomes

Patients with participating caregivers (versus without) had a higher odds of a "yes" response for preference for LVAD therapy over time (odds ratio, 1.43; 95% CI, 1.03–1.99; *P*=0.034), adjusted for time-dependent

Table 4. Longitudinal Model of Caregiver HRQOL (Measured Using EQ-VAS) and Burden (Measured Using OCBS) Over Time, Adjusted for Baseline Values

Variable	EQ-VAS		OCBS Mean Difficulty		OCBS Mean Time	
	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value
EQ-VAS, baseline	0.64 (0.49 to 0.79)	<0.0001*				
OCBS mean difficulty, baseline			0.72 (0.63 to 0.82)	<0.0001*		
OCBS mean time, baseline					0.74 (0.64 to 0.84)	<0.0001*
Time	0.003 (–1.12 to 1.12)	0.996	0.019 (–0.01 to 0.05)	0.179	–0.0004 (–0.04 to 0.04)	0.985

EQ-VAS indicates EuroQol Visual Analog Scale; HRQOL, health-related quality of life; and OCBS, Oberst Caregiver Burden Scale.
*Significant P value < 0.05.

INTERMACS profile (*P*>0.05). Of those with a participating caregiver, 5 of 32 (16%) patients who had an initial preference of "yes" for LVAD underwent LVAD implantation during study follow-up (additional 2 were transplanted), whereas 8 of 59 (14%) of those saying "no" underwent LVAD (additional 2 were transplanted). For patients with a participating caregiver, the risk of experiencing the composite clinical outcome event (first unplanned HF-related hospitalization, heart transplantation, LVAD placement, or death) was assessed in a multivariable Cox proportional hazard model including INTERMACS profile and baseline participating caregiver characteristics. Both worsening INTERMACS profile (hazard ratio [HR], 1.52; 95% CI, 1.13–2.04; *P*=0.005) and having a nonmarried participating caregiver (HR, 2.99; 95% CI, 1.29–6.96; *P*=0.011) significantly increased the hazard of a patient having an event.

DISCUSSION

Among ambulatory patients with advanced HF, we determined that: (1) patient HRQOL improved over time when adjusted for the baseline value, whereas participating caregiver HRQOL and burden did not, contrary to our hypothesis that these would worsen over time; (2) caregiver HRQOL and burden were positively associated with patient HRQOL, as hypothesized; and (3) having a participating caregiver increased likelihood of patient preference for LVAD therapy, whereas having a nonmarried participating

Table 5. Longitudinal Analysis of Caregiver HRQOL Over Time, Adjusted for Baseline Values

Variable	Estimate (95% CI)	P Value
Caregiver EQ-VAS	0.61 (0.45–0.77)	<0.0001
Patient KCCQ	0.10 (0.01–0.19)	0.034
Caregiver marital status	7.05 (1.34–12.80)	0.016

EQ-VAS indicates EuroQol Visual Analog Scale; HRQOL, health-related quality of life; and KCCQ, Kansas City Cardiomyopathy Questionnaire overall summary score.

caregiver increased the risk of having a clinical event. Although HRQOL in patients with HF and cross-sectional caregiver HRQOL are well characterized in the literature, we describe, for the first time, longitudinal HRQOL and burden of caregivers of an ambulatory cohort of patients with advanced HF.

Patient HRQOL

Patients with HF have poor HRQOL when compared with those without HF.[24] More important, HRQOL is associated with other HF-related outcomes, with improvement in HRQOL being associated with better event-free survival.[25] In our overall cohort of ambulatory patients with advanced HF, we found that patient HRQOL significantly improved over time among survivors when adjusted for baseline values by both the KCCQ and the EQ-VAS. Change in patient HRQOL is linked to comorbidities[26] as well as HF symptom severity.[27] Our study corroborates these prior findings as we showed that the less severe the INTERMACS profile, the better the patient HRQOL. When adjusted for INTERMACS profile and presence of a caregiver, EQ-VAS scores continued to improve over time, whereas KCCQ overall summary scores did not. This may be attributable to differences in the measures (ie, the EQ-VAS is a generic instrument, whereas the KCCQ is an HF-specific instrument). Also, the EQ-VAS is a single item measuring overall HRQOL, whereas the KCCQ overall summary score is derived from multiple items and domains. More important, although change over time was seen in the KCCQ (median increase, 3 points) and EQ-VAS (median increase, 5 points), these changes were small relative to what is considered a minimal clinically important difference in these scores (5 and 10 points, respectively).[20,21] However, the lack of either clinically or statistically significant deterioration in these measures of HRQOL in survivors over the 2-year course of the study is also notable.

Caregiver Burden and HRQOL

Caregivers play a fundamental role in the care of patients with HF, including personal and emotional care.[2,28] Increased caregiver burden is associated with poor health outcomes for caregivers and patients alike,[6,29] although interestingly, results of prior studies have also demonstrated an association between higher caregiver burden and lower patient clinical event risk.[30] In our study, using the OCBS, caregivers experienced higher burden with *time* spent rather than *difficulty* of tasks, with time providing emotional support being highest. The latter finding has been reported in other studies of caregiving in HF.[7] Caregiver burden did not increase over time, contrary to our hypothesis that caregiver burden increases over time in patients with advanced stages of HF. Pressler and colleagues demonstrated in a general ambulatory HF cohort (with 10% loss to follow-up attributable to death/severity of illness) that caregiver burden, also measured using the OCBS, actually improved over a 9-year period.[7] In Pressler's study, the Medical Outcomes Study Short Form-12 was used to demonstrate lack of worsening in caregiver HRQOL. We also did not find a significant decline in caregiver HRQOL using the EQ-VAS.

Potential explanations for our findings that caregiver HRQOL and burden did not worsen over time include: (1) REVIVAL was composed of a HF cohort that, based on inclusion criteria, already had medically advanced disease at time of patient and caregiver enrollment; (2) there was a survivorship effect, with loss of follow-up data on a substantial proportion of sicker patients who went on to meet clinical end points (although one would still have expected deterioration of clinical status, including quality of life, among survivors), which decreased caregiver participation over time; and (3) caregivers may not perceive their care for patients as burdensome or may adapt over time to caregiving related tasks, making the perceived burden low and unchanging, which may also impact caregiver HRQOL in a positive way.

Our study uniquely aimed to describe the effects of caregiver and patient baseline characteristics on overall caregiver HRQOL over time. Among patients with participating caregivers, we found that caregiver HRQOL and burden were better when patient HRQOL was better, at baseline and longitudinally. In the HF literature, better caregiver HRQOL and lower burden have been described for patients with less severe HF symptoms, which ultimately also affect patient HRQOL. Studies have demonstrated conflicting results on the relationship of a caregiver or spouse's HRQOL with a patient's HRQOL.[30,31] Our and prior findings highlight the complex interdependence between patient and caregiver HRQOL, which may also depend on changes over time in patient and caregiver health status. In addition, the dynamic effect of patient HRQOL on caregiver HRQOL and vice versa most likely results in a bidirectional relationship on HRQOL over time.

We also found that caregiver HRQOL was better over time when caregivers were married, but not otherwise associated with several caregiver characteristics. The positive effect of marital status on caregiver HRQOL (noting that most married caregivers in our study were partners of the patient) deserves further study, as we did not measure "quality" of the marital relationship. Although studies to date do not describe health of a spouse as impacting HF outcomes in patients,[31] the health of a patient with HF has been shown to impact the caregiving partner.[32]

Factors Related to Patient Clinical Outcomes and Preferences for LVAD Therapy

Patient HRQOL is associated with HF clinical outcomes. In the nonrandomized ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management) study, among subjects with worse HRQOL (EQ-VAS score, <55), survival on the original therapy was lower with medical management than with ambulatory LVAD therapy.[19] From REVIVAL, our group has recently described that patients with worse baseline KCCQ scores were more likely to prefer LVAD therapy.[16,33] Therefore, in addition to standard clinical risk factors, patient-reported outcomes, such as HRQOL, should be incorporated into shared decision making on advanced HF therapies. The addition of longitudinal assessment of patient HRQOL in HF may lend even further insight.

We found that the presence of a participating caregiver was the only assessed caregiver characteristic that was predictive of patient preference for LVAD therapy. As noted above, although we cannot speak to the quality of the caregiver-patient relationship, perhaps patients with participating caregivers had more engaged, supportive caregivers, which may have influenced their inclination to undergo LVAD implantation. In a recent analysis of the entire REVIVAL cohort, we demonstrated that patient socioeconomic status influenced preference for LVAD therapy, with patients more likely to prefer LVAD therapy if they had a lower income or lower education level.[16] In the present study, patients who had a participating caregiver were more likely to both prefer LVAD therapy and have a *higher* education level compared with patients without a participating caregiver. The reason for these discrepant findings on education level and LVAD preference are unclear and may be influenced by the presence of a participating caregiver. Further investigation into better understanding the interplay of socioeconomic factors and caregiver role in patient preferences

for advanced HF therapies is warranted. Notably, having a nonmarried caregiver increased patient risk of reaching a clinical end point, independent of HF severity based on INTERMACS profile. This finding requires further study, as the number of nonmarried caregivers in our study was small and included individuals with a variety of relationships with the patient.

This study has several important limitations. Patients were recruited from centers with HF programs and therefore may not be representative of all patients with ambulatory advanced HF. Patients and caregivers were also enrolled at different baseline visits; patients were enrolled 2 months earlier than caregivers, which may influence outcomes and result in selection bias. Caregivers included in this study may not be representative of all patient caregivers who existed, for several reasons. First, a low proportion of REVIVAL advanced HF patient cohort had a participating caregiver in the registry, and there was dropout in caregiver participation over time. This limitation resulted in a moderately small caregiver sample size. Furthermore, caregivers lacked diversity (ie, predominantly women, White race, and spouses), which reduced generalizability. Lack of participating caregivers may reflect caregiver time constraints or disinterest and does not exclude the presence of an actively engaged caregiver. We also do not know about the quality of the caregiver-patient relationship. These limitations importantly highlight challenges that exist in conducting caregiver research. Future research to elucidate reasons for low caregiver participation and improve caregiver recruitment is warranted. More important, the results of this study pertain only to patients surviving the duration of the study and their caregivers. The association between worse INTERMACS profile (ie, sicker patients) and meeting a clinical end point (death, transplant, or LVAD) is well established. Therefore, the sickest patients and their caregivers are missing from longitudinal HRQOL assessments, which likely contributes to overestimation of HRQOL over time. Interestingly, we noted that female caregivers were less likely to have complete study data at 24 months, and a significant proportion of missing caregiver data was attributable to patients meeting clinical end points earlier in the study. One could hypothesize that sex differences in rates of HF outcomes played a role in these observed differences. However, notably, prior work from the REVIVAL cohort demonstrated that women and men had similar HF profiles as well as 1-year combined risk of death, LVAD, or transplantation (24% versus 22%; P=0.94).[34]

CONCLUSIONS

In an ambulatory cohort of patients with advanced HF, we found that surviving patients' HRQOL improved modestly over time and that caregivers' HRQOL and

burden did not change. Having a participating, married caregiver was associated with an increased patient willingness to consider ambulatory LVAD therapy and a lower composite risk of death, urgent transplant, or ventricular assist device. These data highlight the need for more research on the central role of the caregiver-patient relationship on longitudinal outcomes and decision making in advanced HF.

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Supplemental Material

Table S1. REVIVAL Inclusion Criteria.

1. Ambulatory.

2. Chronic systolic heart failure ≥ 12 months.

3. NYHA II - IV for at least 45 of the last 60 days.

4. Last documented left ventricular ejection fraction ≤ 35% by any imaging modality.

5. Age 18 - 80 years.

6. Currently under the care of a cardiologist at study site.

7. On appropriate evidenced -based heart failure medications – ACE inhibitor, ARB or

   sacubitril--valsartan; beta blocker; aldosterone antagonist; hydralazine/long-acting nitrate

   [required of African-American subjects only] for ≥ 3 months absent contraindications or

   intolerances.

8. Has ICD or CRT-D. If CRT-D, present for ≥ 3 months.

9. Demonstrated advanced heart failure, including any of the following*:

   i.Serum sodium ≤ 135 mEq/L (obtained as an outpatient)**

   ii.Serum BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL** (obtained as an outpatient)

   iii.Seattle Heart Failure Model (SHFM) one year predicted survival ≤ 85%**

   iv.Heart Failure Survival Score (HFSS) ≤ 7.19**

   v.Peak VO$_2$ ≤ 55% of predicted for age by Wasserman equation or ≤ 14 ml/kg/min, with

      RER ≥ 1.05 ***

   vi.VE/VC02 slope ≥ 40***

   vii.6-minute walk test (6MWT) distance ≤ 350 m without significant non-cardiac

      limitation**

viii.Currently listed as Heart Transplant Status 2 due to heart failure limitation OR History

   of one (1) hospitalization (≥ 24 hours) for acute or acute on chronic heart failure in the

   past year with either serum BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL**

   (obtained as an outpatient)

10. History of two (2) hospitalizations (≥ 24 hours) for acute or acute on chronic heart failure in the past

   year.

11. Willingness to continue to receive heart failure care from the enrolling advanced heart failure clinic

   over the next two (2) years and to come for all scheduled study visits.

12. Written Informed consent given.

* Qualifying measure must be the most recent of that type of measure obtained (i.e., a BNP ≥

1000 obtained 2 months prior would not qualify the heart failure subject if a more recent BNP

was < 1000)

**Using values obtained within the prior 90 days, except for peak VO_2 within 365 days

***Obtained within the prior 365 days

Table S2. REVIVAL Exclusion Criteria.

1. Known serious medical problem other than heart failure that would be expected to limit 2-year survival (≥50% mortality within 2 years from non-heart failure diagnosis).

2. Patient is not likely to be compliant with the protocol, in the opinion of the Investigator.

3. Currently hospitalized.

4. Current use of an intravenous inotrope.

5. Primary functional limitation from non-cardiac diagnosis even if not likely to limit survival.

6. Chronic hemodialysis or peritoneal dialysis or serum creatinine value of ≥ 3 mg/dL at time of enrollment.

7. Cardiac amyloidosis, cardiac sarcoidosis, constrictive pericardial disease, active myocarditis or congenital heart disease with significant structural abnormality.

8. Hypertrophic cardiomyopathy unless dilated LV and no outflow gradient.

9. Cardiac conditions that are amenable to surgical or percutaneous procedures (other than VAD or transplant) that would substantially improve prognosis and for which this subject is a reasonable candidate, regardless of whether the procedure will or will not be performed.

10. Uncorrected hyperthyroidism or hypothyroidism.

11. Pregnancy.

Table S3. Patient and Caregiver Baseline Characteristics by Caregiver EQ-VAS and OCBS missingness at 24 months.

	Missing (n=43)	Not missing (n=52)	p
PATIENT			
Age, years	59.6 (13.2)	64.5 (10.1)	0.048
Sex			0.076
Male	38 (88.4)	38 (73.1)	
Female	5 (11.6)	14 (26.9)	
Race			0.441
African-American/Black	6 (14.0)	4 (7.7)	
White	37 (86.0)	46 (88.5)	
Other	0 (0.0)	2 (3.8)	
New York Heart Association Class			0.773
I	1 (2.3)	3 (5.8)	
II	15 (34.9)	13 (25.0)	
III	22 (51.2)	30 (57.7)	
IIIb	4 (9.3)	4 (7.7)	
IV	1 (2.3)	2 (3.8)	
6 minute walk distance (m)	342.5±105.2	362±88.4	0.417
Normalized peak VO_2 (ml/kg/min)	14.49±4.43	14.61±4.19	0.853

Presence of ICD or CRT	23 (53.5)	27 (51.9)	1
Number of heart failure hospitalizations	1.00 (1.13)	0.79 (1.16)	0.246
CAREGIVER			
Age	56.8 (16.1)	60.5 (11.9)	0.272
Sex			0.014
Male	3 (7)	14 (28)	
Female	40 (93)	36 (72)	
Race			0.730
African-American/Black	5 (11.9)	3 (6)	
White	36 (85.7)	46 (92)	
Other	1 (2.4)	1 (2)	
Relationship to patient			0.123
Other	1 (2.3)	2 (3.9)	
Friend	3 (7)	0 (0)	
Other family member	6 (14)	2 (3.9)	
Son/Daughter	3 (7)	5 (9.8)	
Spouse/Domestic Partner	30 (69.8)	42 (82.4)	

Data presented as mean (SD), or counts and percentages.

CRT, chronic resynchronization therapy; ICD, implantable cardiac defibrillator; VO_2: oxygen consumption

Table S4. Baseline health-related quality of life and burden based on patient meeting study
endpoint.

	Patient outcome		
	Without event Median (P25,P75)	With event* Median (P25-P75)	p
Patient KCCQ (Baseline A cohort, n=400)	64.5 (49, 80), n=242	62 (46-76), n=131	**0.07**
Patient EQ-VAS (Baseline A cohort, n=400)	70 (50, 75), n=238	60 (50, 75), n=129	**0.16**
Patient KCCQ (Baseline B cohort, n=337)	64 (49, 80), n=214	63 (48, 77), n=103	**0.22**
Patient EQ-VAS (Baseline B cohort, n=337)	69 (50-75), n=211	62.5 (50-75), n=102	**0.55**
Caregiver EQ-VAS (n=95)	85 (75, 90), n=65	90 (77.5, 94), n=32	**0.39**
Caregiver OCBS, time (n=95)	2.27 (1.67, 2.77), n=61	2.03 (1.80, 2.83), n=30	**0.74**
Caregiver OCBS, difficulty (n=95)	1.2 (1.00, 1.47), n=63	1.07 (1.00, 1.33), n=30	0.20

*Those with missing HRQoL data due to reaching study endpoint (Death, mechanical circulatory support or UNOS

1A/1B transplant)

Figure S1. Oberst Caregiving Burden Scale Scores*

	Time on Task		Difficulty of Task	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
1. Medical or nursing treatments (giving medications, skin care, dressings, etc.)	1.80 (0.97)	2 (1-2)	1.21 (0.59)	1 (1-1)
2. Personal care (bathing, toileting, getting dressed, feeding, etc.)	1.38 (0.84)	1 (1-1)	1.18 (0.61)	1 (1-1)
3. Assistance with walking, getting in and out of bed, exercises, etc	1.55 (0.87)	1 (1-2)	1.18 (0.59)	1 (1-1)
4. Emotional support, 'being there' for the patient	3.50 (1.12)	3 (3-5)	1.43 (0.74)	1 (1-2)
5. Watching for and reporting the patient's symptoms, watching how the patient is doing, monitoring the patient's progress	3.06 (1.28)	3 (2-4)	1.36 (0.69)	1 (1-2)
6. Providing transportation or 'company' (driving, riding along with patient, going to appointments, driving patient around for errands, etc.)	3.21 (1.31)	3 (2-4)	1.38 (0.74)	1 (1-2)
7. Managing finances, bills, and forms related to the patient's illness	2.80 (1.55)	2 (1-4)	1.48 (0.89)	1 (1-2)
8. Additional household tasks for the patient (laundry, cooking, cleaning, yard work, home repairs, etc.)	2.81 (1.37)	3 (2-4)	1.49 (0.85)	1 (1-2)
9. Additional tasks outside the home for the patient (shopping for food and clothes, going to the bank, running errands, etc.)	2.68 (1.37)	2 (2-3)	1.43 (0.74)	1 (1-2)
10. Structuring/ planning activities for the patient (recreation, rest, meals, things for the patient to do, etc.)	2.22 (1.26)	2 (1-3)	1.31 (0.71)	1 (1-1)
11. Managing behavior problems (moodiness, irritability, confusion, memory loss, etc.)	2.25 (1.14)	2 (1-3)	1.70 (1.02)	1 (1-2)
12. Finding and arranging someone to care for the patient while you are away	1.40 (0.80)	1 (1-2)	1.25 (0.66)	1 (1-1)
13. Communication (helping the patient with the phone, writing or reading, explaining things, trying to understand what the patient is trying to say, etc.)	1.76 (1.10)	1 (1-2)	1.26 (0.65)	1 (1-1)
14. Coordinating, arranging, and managing services and resources for the patient (scheduling appointments, arranging transportation, locating equipment and services, and finding outside help)	1.90 (1.14)	1 (1-3)	1.31 (0.76)	1 (1-1)
15. Seeking information and talking with doctors, nurses, and other professional health care workers about the patient's condition and treatment plans	2.52 (1.19)	2 (2-3)	1.35 (0.71)	1 (1-1)

*Three highest scoring items in each category are highlighted.