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Comorbid Conditions and Health-related Quality of Life in Ambulatory Heart Failure Patients: A Report from REVIVAL

Thomas M. Cascino, MD, MS[a], **Michelle M. Kittleson, MD, PhD**[b], **Anuradha Lala, MD**[c], **Josef Stehlik, MD, MPH**[d], **Maryse Palardy, MD**[a], **Salpy V. Pamboukian, MD, MSPH**[e], **Gregory A. Ewald, MD**[f], **Maria M. Mountis, DO**[g], **Douglas A. Horstmanshof, MD**[h], **Shawn W. Robinson, MD**[i], **Palak Shah, MD**[j], **Ulrich P. Jorde, MD**[k], **Rhondalyn C. McLean, MD, MHS**[l], **Blair Richards, MPH**[m], **Shokoufeh Khalatbari, MS**[m], **Cathie Spino, ScD**[m,n], **Wendy C. Taddei-Peters, PhD**[o], **Kathleen L. Grady, PhD, MSc, RN**[p], **Douglas L. Mann, MD**[f], **Lynne W. Stevenson, MD**[q], **Garrick C. Stewart, MD, MPH**[r], **Keith D. Aaronson, MD, MS**[a], **REVIVAL Investigators**

[a]University of Michigan, Division of Cardiovascular Disease, Ann Arbor, MI

[b]Smidt Heart Institute, Cedars-Sinai, Los Angeles, CA

[c]Mount Sinai Hospital, New York, NY

[d]University of Utah Health, Salt Lake City, UT

[e]University of Alabama at Birmingham, Birmingham, AL

[f]Washington University School of Medicine, St. Louis, MO

[g]Cleveland Clinic, Cleveland, OH

[h]INTEGRIS Baptist Medical Center, Oklahoma City, OK

[i]University of Maryland, Baltimore, MD

[j]Inova Heart and Vascular Institute, Falls Church, VA

[k]Montefiore Medical Center, Bronx, NY

[l]University of Pennsylvania, Philadelphia, PA

[m]University of Michigan, Michigan Institute for Clinical and Health Research, Ann Arbor, MI

[n]University of Michigan School of Public Health, Ann Arbor, MI

[o]National Heart, Lung, and Blood Institute, Bethesda, MD

[p]Northwestern University, Chicago, IL

[q]Vanderbilt University, Nashville, TN

[r]Brigham and Women's Hospital, Boston, MA,

Corresponding author: Keith D Aaronson, MD MS, 2381 CVC SPC 5853, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5853 keith@med.umich.edu.

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Abstract

Background: Patients with heart failure (HF) often have multiple chronic conditions that may impact health-related quality of life (HRQOL) despite HF therapy. We sought to determine the association between noncardiac comorbidities and HRQOL in ambulatory patients with advanced HF.

Methods: Baseline data from 373 subjects in Registry Evaluation of Vital Information for Ventricular Assist Devices (VADs) in Ambulatory Life were analyzed using multivariable general linear models to evaluate the relationship between comorbidities and HRQOL (EuroQol-visual analogue scale [EQ-VAS], EQ-5D-3L Index Score, and Kansas City Cardiomyopathy Questionnaire [KCCQ]). The primary independent variables were a comorbidity index (sum of 14 noncardiac conditions), a residual comorbidity index (without depression), and depression alone. The median (25^{th}-75^{th} percentile) number of comorbidities was 3 (2–4).

Results: Increasing comorbidity burden was associated with a reduction in generic (EQ-5D Index, p=0.005) and HF-specific (KCCQ, p=0.001) HRQOL. The residual comorbidity index was not associated with HRQOL when depression included in the model independently, while depression was associated with HRQOL across all measures. Participants with depression (vs. without) scored on average 13 points (95% confidence interval 8–17) lower on the EQ-VAS, 0.15 points (0.12–0.18) lower on the EQ-5D Index, and 24.9 points (21.2–28.5) lower on the KCCQ-overall summary score.

Conclusions: While noncardiac comorbidities were prevalent in ambulatory advanced HF patients, only depression was associated with decreased generic and HF-specific HRQOL. Other than depression, the presence of noncardiac comorbidities should not impact expected gains in HRQOL following VAD, provided the conditions are not a contraindication to implant.

Registration: Clinicaltrials.gov; Unique identifier: NCT01369407.

Keywords

health-related quality of life; systolic heart failure; mechanical circulatory support; assessment

Ambulatory patients with advanced heart failure (HF) treated with oral medical therapy have comparable survival to those undergoing left ventricular assist device (LVAD) implantation.[1] Such ambulatory HF patients, classified as Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profiles 4–7, comprise ~16% of those undergoing contemporary LVAD implantation.[2] Absent improved survival, the rationale for LVAD therapy in these patients is improved health-related quality of life (HRQOL).

HF patients have multiple chronic conditions,[3] and these comorbidities may impact HRQOL as much as HF does.[4] One potential contributor to continued low HRQOL after LVAD could be the persistence of noncardiac comorbidities. Understanding the influence of noncardiac comorbidities on HRQOL in advanced HF is critical to understanding the potential for improvement in HRQOL after LVAD.

We sought to determine the impact of noncardiac comorbid conditions that would be expected to persist beyond LVAD therapy on HRQOL in ambulatory HF patients eligible for

advanced therapies and thereby identify those patients most likely to anticipate improvement in HRQOL following LVAD. We hypothesized that ambulatory HF patients with multiple noncardiac comorbidities as measured by an integrated comorbidity index would have reduced HRQOL irrespective of HF severity.

Methods

Patient Population

We performed a cross-sectional study of 373 of the 400 ambulatory patients in the Registry Evaluation of Vital Information for VADs in Ambulatory Life (REVIVAL) at the baseline visit. REVIVAL is a 2-year prospective, observational cohort study of ambulatory systolic HF patients with INTERMACS 4–7 profiles recruited from 21 U.S. LVAD centers between July 2015 and June 2016.[5] Of the 400 patients enrolled, 27 did not complete HRQOL surveys and were not included in this analysis. Patients with New York Heart Association (NYHA) class II-IV symptoms despite optimal medical therapy and a recent non-elective HF hospitalization, heart transplant listing, objective functional limitation, or evidence of neurohormonal activation were eligible for enrollment. Patients were excluded if they had a condition other than HF that would result in ≥50% 2-year risk of death or obvious contraindications to LVAD therapy.

The Institutional Review Board at each clinical site and the Data Coordinating Center approved the study. All subjects provided written informed consent before study participation. The data for REVIVAL has been uploaded to NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and will become available per NIH policy.

Determination of comorbidities

Baseline data included demographics, HF severity, medical history, physical exam, submaximal exercise capacity (6-minute walk distance [6MWD]), and laboratory results. The comorbid conditions assessed were selected from those collected in the registry and included in the INTERMACS list of contraindications to transplantation,[6] the Charlson Comorbidity Index,[7] or the Elixhauser Comorbidity Index.[8] Recognizing the complex interplay between HF and comorbid conditions, a noncardiac comorbidity was defined as a condition that may not resolve after either LVAD implantation or heart transplantation. The comorbid conditions included: peripheral vascular disease; chronic obstructive pulmonary disease (COPD); diabetes mellitus (DM); DM with complications (DM and either coronary artery disease, peripheral vascular disease, neurological event, or eGFR <60 ml/min/ 1.73m2); connective tissue disease; unintentional weight loss; liver disease; hypertension (blood pressure ≥140/80 mmHg); obesity (body mass index ≥30 kg/m^2); electrolyte disorder (Na ≤135 or ≥145 mEq/L or K <3.5 or >5 mEq/L); anemia (Hgb <13 g/dL for men and <12 g/dL for women); coagulopathy (platelets <150 /microL or INR>1.2 while not on warfarin); chronic kidney disease (CKD) (eGFR <60 ml/min/1.73m2); and depression (Patient Health Questionnaire (PHQ)-8 score ≥ 10). A comorbidity index of the conditions was created by taking the sum of these noncardiac comorbidities for a total score of up to 14.

Health Status

Patients completed the EQ-5D-3L, which includes the EQ-visual analogue scale (EQ-VAS) and five single-item dimensions of HRQOL for assessment of generic health status,[9] and the Kansas City Cardiomyopathy Questionnaire (KCCQ) for disease-specific health status.[10] The EQ-VAS and the KCCQ overall summary score (OSS) each range from 0–100, and the EQ-5D-3L Index (calculated from the dimension scores) ranges from 0–1. Higher scores for each reflect better health status.

Statistical Analysis

Descriptive statistics for categorical and continuous variables are reported. Multivariable general linear models (GLM) were used to examine the relationship between each HRQOL score and the individual comorbidities and the comorbidity index, with the HRQOL scores as the dependent variables and the individual comorbidities and the comorbidity index (in separate models) as the primary predictors. Assumptions for GLM were met. Age, sex, race, INTERMACS profile, and 6MWD were candidate variables for the multivariable models. INTERMACS profiles 4 and 5 were combined due to the small number of profile 4 participants. The final multivariable models were determined by stepwise backwards selection using the Akiake information criterion (AIC). The contribution of each variable to the overall model (the percent of the variance explained by the variable) was determined by the semipartial omega^2.

Given the well-established relationship between depression and HRQOL among ambulatory HF patients,[11] depression was removed from the index, and the analysis was repeated with inclusion of the residual comorbidity index (without depression as a comorbidity) and depression as a separate candidate variable in the multivariable model. In order to illustrate the association between the comorbidities and the HRQOL measures, the predicted marginal effect of the comorbidities on HRQOL was determined using the least squares mean scores and 95% confidence intervals (CI). The relationship between depression (dependent variable) and INTERMACS levels (as an indicator of HF severity) was assessed using logistic regression. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Demographic characteristics, including the prevalence of comorbidities and HRQOL scores, are depicted in Table 1. Of the 373 ambulatory HF patients enrolled, 32 (9%) were INTERMACS profile 4, 78 (21%) profile 5, 144 (39%) profile 6, and 119 (32%) profile 7. The most common comorbidities were CKD (60%), obesity (44%), and DM (38%). Depression was present in 100 (27%) of the patients. The median (25^{th}-75^{th} percentile) number of comorbidities in the cohort was 3 (2–4).

The results of the multivariable general linear models are depicted in Table 2. The comorbidity index was associated with a reduction in the KCCQ-OSS and the EQ-5D Index. For each additional comorbidity, HRQOL as measured by the EQ-5D index (scale 0–1) and

KCCQ-OSS (scale 0–100) was reduced 0.013 units (−0.022 – −0.004; p-value = 0.005) and 2.0 units (−3.1 – −0.8; p-value = 0.001), respectively.

After removal of depression from the comorbidity index, the residual index was not associated with reduced HRQOL by any of the HRQOL measures (Table 2). In the final multivariable general linear models, only depression and 6MWD were associated with worse generic (EQ-VAS and EQ-5D Index) and disease-specific (KCCQ-OSS) HRQOL. HF severity as measured by INTERMACS profile was associated with a reduction in the KCCQ score but not generic HRQOL measures.

The amount of variance in HRQOL explained by the models improved with the addition of depression. Depression was found to have the highest semipartial omega^2, the amount of variation in the HRQOL outcome attributable to a variable, across all surveys (EQ-VAS = 0.08 (95% CI 0.03–0.14); EQ-5D Index = 0.19 (0.12–0.26); KCCQ-OSS = 0.27 (0.20 – 0.35)) and contributed greater than half of the variance explained in each model (omega^2 from Table 2). For example, in the KCCQ-OSS model, depression accounted for 27% (95% CI 20–35%) of the 48% (41–54%) of the variance explained by the multivariable model. Compared to participants without depression, those with depression would be expected to score 12.5 points (95% confidence interval 8.2–16.7) lower on the EQ-VAS, 0.15 points (0.12–0.18) lower on the EQ-5D Index, and 25.2 points (21.6–28.9) lower on the KCCQ-OSS as determined by the marginal mean effect of depression on each HRQOL survey. Compared to INTERMACS profile 7 participants, the odds of having depression were similar in INTERMACS profile 6 participants (OR 1.6, 95% CI 0.9–3.0; p=0.14) and higher in INTERMACS profile 4 and 5 participants (OR 3.4, 1.8–6.6; p<0.001).

Discussion

Noncardiac comorbidities are common in patients with ambulatory advanced HF. While there was an association between the comorbidity index and a reduction in HRQOL, this association was no longer present when depression was removed from the comorbidity index. Depression was highly associated with a reduction in disease-specific and generic HRQOL. Collectively, these findings provide novel insight into our understanding of LVAD candidacy in patients with noncardiac comorbidities. Our study suggests that noncardiac comorbidities (other than depression) that are not severe enough to be a contraindication to LVAD should not impact the potential gains in HRQOL after LVAD implantation. Conversely, HF severity, which would be expected to improve after LVAD implantation, was strongly associated with depression.

Current mechanical circulatory support guidelines support screening for comorbid conditions.[12] There is limited guidance about how individual comorbidities, much less multiple comorbidities, should be considered in the evaluation of candidacy for advanced therapies beyond ensuring that a condition is not life-limiting or associated with increased mortality after LVAD implantation. Despite this, the presence of multiple comorbidities has been suggested as a reason why LVAD implantation may be inappropriate in the majority of patients[13] and is associated with increased decisional conflict.[3] Our study confirms that

multiple comorbid conditions are present in ambulatory advanced HF patients and clarifies the relationship between multiple conditions and patient-centered outcomes.

The lack of an association between HRQOL and individual noncardiac comorbidities other than depression, either individually or together, has important implications in ambulatory advanced HF patients who are candidates for LVAD implantation and heart transplantation. Noncardiac comorbid conditions such as COPD and DM would be expected to persist after receipt of advanced therapies. Our findings suggest that the presence of the assessed comorbidities, if not severe enough to contraindicate LVAD, do not impact HRQOL. The clinician's focus should be to prevent the progression of these comorbid conditions to the point that they may negatively impact LVAD candidacy. Notably, the lack of an association between comorbid conditions and HRQOL is likely the result of purposeful selection bias in our cohort, as participants could not have conditions severe enough to limit their functional status or 2-year life expectancy.

Depression, conversely, has consistently been strongly associated with worse HRQOL than other factors in ambulatory HF patients, including NYHA functional class.[11] In our study, depression was associated with a profound decrease in both generic and disease-specific HRQOL. The 25-point decrease in the KCCQ-OSS associated with depression in this analysis is five times greater than the reported minimal clinically important difference in the measure (5 points).[14]

The current consensus document on psychosocial evaluation of candidates for LVAD recommends a detailed psychosocial screen in all patients being considered for LVAD with a formal consultation with a psychiatrist and treatment as needed.[15] The optimal method for pre-screening for depression is not certain,[15] and there is likely variation in practice. Without identification of depression in patients without a formal diagnosis of depression, patients who may benefit from increased resources and therapies may not receive additional psychosocial support. Given the increasing literature on the association of outcomes and depressive symptoms determined by PHQ surveys, performing a standardized assessment that includes either the two-item PHQ-2 survey, which if positive leads to the PHQ-8 or 9 survey, or the PHQ-8 or 9 survey upfront followed by referral to a mental health professional if positive, should be explored in registries and clinical practice.

Our study has limitations. First, the comorbidity index was unweighted, and it is possible that the impact of different comorbidities on HRQOL would differ, though this method has frequently been used to assess the impact of multiple comorbid conditions on outcomes.[16] Second, the presence of depression was determined from the results of the PHQ-8. While the PHQ-8 does not replace a formal psychiatric evaluation and diagnosis of depression, using a screen has been employed in prior HF studies and removes the potential subjectivity of a depression diagnosis.[17]

Our findings suggest that while noncardiac comorbid conditions are common in ambulatory advanced HF patients, depression is uniquely associated with decreased generic and disease-specific HRQOL. The presence of multiple noncardiac comorbid conditions other than depression, if not severe enough to otherwise contraindicate LVAD, should not impact

expected gains in HRQOL after LVAD implantation and should not affect candidacy for advanced therapies. Future research may focus on whether the association of depression and reduced HRQOL is modifiable in this population. Furthermore, a greater understanding of the impact of depression symptoms on post-implant HRQOL may better inform discussions on the potential benefits of LVAD in ambulatory HF patients. In the meantime, improved screening and best evidence-based practice for the management of depression should be emphasized.

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Table 1.

Characteristics of 373 subjects at enrollment

Characteristic	N (%); or Mean ± SD; or Median (25th percentile, 75th percentile)
Age (years)	60.3 ± 11.3
Male sex	279 (74.8)
Race	
African American	89 (23.9)
White	262 (70.2)
Other*	22 (5.9)
Hispanic Ethnicity	26 (7.0)
INTERMACS Profile	
4	32 (8.6)
5	78 (20.9)
6	144 (38.6)
7	119 (31.9)
Comorbid Conditions	
Peripheral vascular disease	15 (4.0)
Hypertension	17 (4.6)
COPD	46 (12.3)
Diabetes	140 (37.5)
Complicated diabetes	119 (31.9)
Chronic kidney disease	224 (60.1)
Liver disease	52 (13.9)
Connective tissue disease	12 (3.2)
Coagulopathy	69 (18.5)
Obesity	164 (44.0)
Unintentional weight loss	3 (0.8)
Electrolyte disorder	112 (30.0)
Anemia	120 (32.2)
Depression symptoms	100 (26.8)
Number of Comorbid Conditions (CC Index)	3 (2, 4)
6 Min Walk Distance (meters)	341 (280, 401)
EQ-VAS (n=367)	65 (50, 75)
EQ-5D Index (n=372)	0.82 (0.71, 0.86)
KCCQ-OSS (n=373)	64 (48.0, 78.0)

* Other includes American Indian/Alaskan native, Asian, more than one race, none of the above, or undisclosed.

SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Scor

Table 2.

Results of the multivariable general linear models predicting health status

	EQ-VAS		EQ-5D Index		KCCQ OSS	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Comorbidity index	Not in final model	---	-0.013† (−0.022,−0.004)	---	-2.0† (−3.1,−0.8)	---
Residual CI	---	Not in final model	---	Not in final model	---	Not in final model
Depression (vs no depression)	---	-12.5‡ (−16.7,−8.2)	---	-0.153‡ (−0.184,−0.123)	---	-25.2‡ (−28.9,−21.6)
6MWD (per 100 m)	5.2‡ (3.1,7.3)	4.7‡ (2.7,6.6)	0.050‡ (0.034,0.066)	0.044‡ (0.030,0.058)	5.6‡ (3.4,7.7)	4.9‡ (3.2,6.7)
Age (per 10 yrs)	1.6§ (−0.1,3.4)		0.027‡ (0.014,0.041)	0.015* (0.003,0.027)	4.2‡ (2.4,5.9)	2.3† (0.8,3.7)
INTERMACS Profile:						
4 & 5	−6.1* (−11.2,−1.0)				−11.1‡ (−16.3–6.0)	−7.0† (−11.3,−2.7)
6	−3.2 (−7.9,1.5)				−6.9† (−11.6,−2.2)	−5.5† (−9.4,−1.7)
7 (ref)	---				---	---
Black/African Amer. (vs other)	5.1* (0.4,9.9)				8.1‡ (3.4,12.8)	5.6† (1.7,9.5)
Female (vs male)		4.2§ (−0.3,8.6)				
Variance explained by the model (omega^2)	0.10 (0.04,0.16)	0.15 (0.09,0.22)	0.15 (0.09,0.22)	0.32 (0.25,0.40)	0.22‡ (0.15,0.30)	0.48 (0.41,0.54)

Results displayed as beta coefficient and 95% CI. Model 1 with complete comorbidity index. Model 2 with residual comorbidity index (CI) without depression.

*P value <0.05,

†p value <0.01,

‡p value <0.001.

§Not significant but included as part of final model selection.

EQ-VAS, EuroQol-visual analogue scales; KCCQ, Kansas City Cardiomyopathy Questionnaire; CI, comorbidity index; 6MWD, six-minute walk distance; m, meters; yrs, years; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.