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Relationships Between Changes in Patient-Reported Health Status and Functional Capacity in Outpatients With Heart Failure

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Abstract

Background—Heart failure trials use a variety of measures of functional capacity and quality of life. Lack of formal assessments of the relationships between changes in multiple aspects of patient-reported health status and measures of functional capacity over time limit the ability to compare results across studies.

Methods—Using data from HF-ACTION (N = 2331), we used Pearson correlation coefficients and predicted change scores from linear mixed-effects modeling to demonstrate associations between changes in patient-reported health status measured with the EQ-5D visual analog scale (VAS) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) and changes in peak VO_2 and 6-minute walk distance at 3 and 12 months. We examined a 5-point change in KCCQ within individuals to provide a framework for interpreting changes in these measures.

Results—After adjustment for baseline characteristics, correlations between changes in the VAS and changes in peak VO_2 and 6-minute walk distance ranged from 0.13 to 0.28, and correlations between changes in the KCCQ overall and subscale scores and changes in peak VO_2 and 6-minute walk distance ranged from 0.18 to 0.34. A 5-point change in KCCQ was associated with a 2.50 ml/kg/min change in peak VO_2 (95% confidence interval, 2.21–2.86) and a 112-meter change in 6-minute walk distance (95% confidence interval, 96–134).

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Conclusions—Changes in patient-reported health status are not highly correlated with changes in functional capacity. Our findings generally support the current practice of considering a 5-point change in the KCCQ within individuals to be clinically meaningful.

Trial Registration—clinicaltrials.gov Identifier: NCT00047437

Introduction

Patient-reported outcome measures are important tools for evaluating health status in clinical trials and for monitoring patients in clinical care.[1] Outcome measures that solicit patients' perspectives of their disease offer unique information not captured by other commonly used metrics, such as clinical, functional, or physician-reported measures. Growing use of patient-reported outcome measures led the US Food and Drug Administration to call for more data supporting the construct validity of these instruments, to be supplemented with defined relationships among other outcome measures. However, relatively few studies have formally assessed the relationships between patient-reported outcome measures and other measures of disease severity in large samples of patients with heart failure, and none have comprehensively examined temporal changes in one measure compared with another.

Understanding of correlations between patients' experiences of their disease and objective measures of disease severity over time is incomplete. For example, changes in B-type natriuretic peptide level after 6 weeks are not correlated with changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ), a heart failure–specific patient-reported measure of health status.[4] However, in a comparison between changes in KCCQ overall scores and cardiologists' ratings of clinical change over a 6-week period on a 15-point global change scale, a mean change of 5 points on the KCCQ was considered clinically meaningful and was more strongly associated with assessments of clinical change than generic health status measures (eg, EQ-5D), B-type natriuretic peptide level, and 6-minute walk distance.[5] Changes in the quality-of-life subscale of the KCCQ have been associated with changes in 6-minute walk distance,[6] but no studies have assessed relationships with other KCCQ subscales or the overall scale. Likewise, no studies have assessed relationships between changes in the KCCQ and changes in peak VO_2, the gold standard of functional measures. The KCCQ includes a subscale for physical limitations, which specifically targets patients' reports of their ability to walk 1 block, climb stairs, and jog, among other activities, but no studies have examined how changes in this subscale correlate with changes in functional measures of physical ability.

It is important to understand how overall health status and its components are related to measures of functional capacity to inform study design and interpretation in clinical trials and observational studies that use these measures. With information about how these commonly used measures are related to each other over time, we can (1) add to the demonstrated validity and ability to detect change of the patient-reported health status measures and (2) develop a better framework for choosing study end points. Therefore, we used longitudinal data from a large multicenter study, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), to characterize relationships between changes in health status from the patient's perspective and changes in functional capacity.

This study is unique in its ability to take advantage of linear mixed models to model trajectories of health status and functional measures over time; no previous studies correlating changes in outcome measures have had more than 2 longitudinal assessments of outcomes available. On the basis of cross-sectional correlations observed in HF-ACTION, we hypothesized that the KCCQ overall scale would have small correlations[7] with peak VO_2 and 6-minute walk distance ($r < 0.30$) and that the EQ-5D visual analog scale (VAS) would

have negligible correlations with peak VO_2 and 6-minute walk distance ($r < 0.10$). We expected that increased peak VO_2 and longer 6-minute walk distance over time would be correlated with improved health status as assessed by the KCCQ overall scale and VAS. Finally, we expected the KCCQ physical limitations subscale to have stronger relationships with peak VO_2 and 6-minute walk distance than the other KCCQ subscales or the overall score.

Methods

HF-ACTION was a multicenter, randomized controlled trial designed to test the long-term safety and efficacy of aerobic exercise training versus usual care in a large, multinational sample of patients with left ventricular dysfunction and heart failure.[8] Enrollment criteria included left ventricular ejection fraction of 35% or less, New York Heart Association (NYHA) class II to IV heart failure, and ability and willingness to undergo exercise training. Patients were excluded if they were unable to exercise, were already exercising regularly, or had experienced a cardiovascular event in the preceding 6 weeks. The relevant institutional review boards of the participating centers and the coordinating center approved the protocol. This work was supported by grants from the National Heart, Lung, and Blood Institute. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Patient-Reported Health Status

The KCCQ is a disease-specific, 23-item, self-administered measure of health status for patients with heart failure with an overall summary score and subscales for physical limitations, symptoms, social limitations, self-efficacy, and quality of life.[9] The KCCQ is scored from 0 to 100, with higher scores representing better health status. The KCCQ was self-administered at the baseline clinic visit, at 3-month intervals during clinic visits for the first 12 months, and annually thereafter for up to 4 years.

The VAS is a single-item “feeling thermometer” on which respondents rate their health state from 0 (worst imaginable) to 100 (best imaginable). It has been used previously to measure health status in patients with heart failure[10–12] and was included in HF-ACTION as a generic measure of health status. The VAS was administered on the same schedule as the KCCQ.

Functional Capacity

The measures of functional capacity in this study were peak VO_2 and 6-minute walk distance. Patients performed a maximal exercise test with gas exchange measurements on a treadmill using the modified Naughton protocol.[13] Patients who were unable to perform an exercise test on a treadmill underwent cycle ergometry testing using a 10 W/min ramp protocol. Patients also performed a 6-minute walk test.[14] These measures were collected at baseline, 3 months, 12 months, and 24 months.

Patient Characteristics

Patient characteristics used as covariates included sociodemographic and clinical history characteristics collected at baseline.

Statistical Analysis

We describe baseline patient characteristics using percentages for categorical variables and medians and interquartile ranges or means and standard deviations for continuous variables. We used SAS version 9.1 for all analyses.

We used Pearson correlation coefficients to demonstrate associations between changes in patient-reported health status and changes in measures of functional capacity. We examined relationships graphically to determine whether this approach was appropriate. Because the use of observed change-from-baseline scores in this context may produce bias due to the influence of measurement error and missing follow-up data,[15] we used full maximum likelihood estimation to model all available data (up to 4 years) from each patient and generate the best linear unbiased prediction ("BLUP") of change from baseline to 3 months and baseline to 12 months from linear mixed effects models. Mixed models take all available longitudinal information into account to model trajectories over time and can result in less bias from measurement error and missing data compared to using observed change-from-baseline scores,[16] assuming unobserved variables do not explain the probability of missingness over and above what is explained by observed variables.[17] Examining raw change-from-baseline scores at 3 and 12 months in a study that collected data at many more time points would be equivalent to ignoring the intermediate data points and the information they supply about patients' underlying trajectories across time (ie, ignoring 5 of 8 data points per participant). Furthermore, such an approach would not include participants who missed the 3- or 12-month assessments. Our approach decreases the influence of missing data on the conclusions by using as much of the data as possible to model underlying trajectories over time.

After examining the observed mean trajectories for each of the patient-reported and functional capacity end points, we found that the trajectories were not strictly linear, as the initial increase from baseline to 3 months was very steep. (This was the same period of the trial during which exercise training was supervised.) Thus, we modeled time using a piecewise linear model with a joint point ("jump") at 3 months. A likelihood ratio test for model reduction confirmed the better fit of the piecewise model. The piecewise model was used to produce the best linear unbiased predictions of change. Each of the mixed models included a jump from baseline to 3 months and a linear increase after 3 months, as well as 28 baseline covariates,[18] each of which had less than 1% missing data. All interaction terms between baseline covariates and the jump at 3 months, as well as between baseline covariates and time after 3 months were tested simultaneously using an omnibus likelihood-ratio test. When the omnibus test was significant, we tested the individual interactions separately. We included significant interaction pairs in the final models. For each model, all participants who had at least a baseline score on the outcome variable contributed data to that model. We compared the correlations between peak VO_2 and 6-minute walk distance and the KCCQ physical limitations subscale with the correlations between functional capacity and the other KCCQ subscales and the overall score based on the Fisher *z* transformation adjusted for correlated correlation coefficients.[19]

To graphically display relationships between changes in health status and functional measures over time and to estimate minimally important changes within individuals, we used predicted changes at 12 months, as estimated from the mixed models. Estimating change requires converting a correlation into a regression parameter. Because the size of the regression parameter can depend on which variable is modeled as the outcome, we used ordinary least squares regression in which the KCCQ overall score was regressed on peak VO_2 or 6-minute walk distance. This approach reflects the most common model of patient outcomes, the Wilson and Cleary model, which assumes that patient-reported health status is a function of the patient's underlying physiological status.[20] Other approaches are possible, such as ordinary least squares regression in which the functional end points are regressed on health status, or orthogonal regression, which treats functional end points and the KCCQ overall score symmetrically.[21] However, without underlying conceptual frameworks for these models, their plausibility is not compelling. We used the bootstrap method with

replacement to estimate confidence intervals, and we constructed the confidence intervals using the bias-corrected and accelerated method.[22]

Results

Table 1 shows the baseline characteristics of the study population. Baseline characteristics did not differ by treatment group.[18] Table 2 shows the visit-level missing data through 12 months of follow-up, accounting for patients who died or withdrew from the study.

Table 3 shows the Pearson correlation coefficients comparing changes in patient-reported health status and changes in the functional capacity measures at 3 and 12 months. After adjustment for baseline patient characteristics, there were small correlations between VAS scores and peak VO_2 or 6-minute walk distance. After adjustment for baseline patient characteristics, there were small to moderate correlations between changes in the KCCQ overall score and changes in peak VO_2 and 6-minute walk distance. All correlations were significantly different from zero. The correlations between the measures of functional capacity and the KCCQ physical limitations subscale were slightly higher than for the other KCCQ domains. Where these correlations were significantly different from the correlation with the physical limitations scale, they are noted in the table.

Figures 1 and 2 show the distributions of change in KCCQ overall score and changes in functional capacity measures at 12 months. They also display the LOESS curves and underlying scatter plots of the relationships between KCCQ and functional capacity. These relationships appear consistent with the magnitudes of the reported correlation coefficients.

Table 4 shows estimates of minimally important change. A 5-point change in KCCQ overall score was associated with a 2.50-ml/kg/min change in peak VO_2 (95% CI, 2.21–2.86) and a 111.69-meter change in 6-minute walk distance (95% CI, 95.91–133.67).

Discussion

To our knowledge, ours is the first study to use longitudinal data to characterize relationships between changes in multiple aspects of patient-reported health status and changes in 2 commonly used functional measures of disease severity. The study population in HF-ACTION was large, relatively diverse, and balanced with respect to heart failure etiology, and the patients received evidence-based, guideline-supported therapy. We used a conservative approach to model these relationships and adjusted for 28 important potential confounders, such as age, depression, and functional class, as well as their interactions with time. As expected, increasing functional capacity was correlated with improved patient-reported health status. Changes in the KCCQ physical limitations subscale, which was designed to quantify patients' exertional capacity, had the largest correlations with changes in functional measures of exercise capacity, consistent with previous cross-sectional analyses,[23] though the differences between the physical limitations subscale and other domains were not always statistically significant.

In a cross-sectional analysis of group differences in patient-reported health status and functional capacity in HF-ACTION, there were small correlations between the KCCQ overall score and peak VO_2 ($r = 0.22$) and 6-minute walk distance ($r = 0.28$) and negligible correlations between the VAS and peak VO_2 ($r = 0.09$) and 6-minute walk distance ($r = 0.11$).[24] Our findings examining changes over time show slightly higher correlations, though all correlations were still modest. Our findings support the clinical observation that patients with the same level of functional capacity can report different daily functioning, symptoms, and quality of life. The findings are also consistent with findings in other diseases,[20] supporting the idea that patient-reported outcome measures like the KCCQ provide

additional information to profiles of patient health. The KCCQ offers unique information in that it quantifies, from patients' perspectives, the severity of heart failure symptoms and their impact on physical and social function and quality of life. This information is highly relevant to patients and should be used in conjunction with other objective outcome measures (eg, as co-primary end points in clinical trials).

Previous studies of outpatients assessed at baseline and 6 weeks set the minimally important change for the KCCQ at 5 points.[5] This determination was made by expert consensus and validated against physician-rated change using a 15-point scale. Thus, another goal of our study was to understand how a 5-point change translates into changes in commonly used measures of functional capacity over a longer period of time. Given the small correlations between the measures, the uncertainty in mapping patient-reported outcome scores onto measures of functional capacity must be recognized. Certainty will be greatest where the correlation between the self-reported health status outcome and the functional capacity outcome is large. Ironically, in such a situation, the utility of assessing both types of measures will be substantially lower because it will not provide much additional information. Based on work by Wilson and Cleary,[20] which posits that functional capacity determines self-reported health status, our data suggest that a 5-point change in the KCCQ is clinically relevant, inasmuch as a 5-point change in the KCCQ corresponds to changes in measures of functional capacity that can be considered clinically meaningful. For example, the metabolic equivalent has traditionally been valued at 3.5 mL/kg/min, though recent research in patients with coronary heart disease suggests an even lower baseline (range, 2.47–2.84 ml/kg/min),[25] similar to the change in peak VO_2 that we found to be associated with a 5-point change in KCCQ (ie, 2.5 mL/kg/min). Furthermore, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) demonstrated that resynchronization therapy —which improves the mortality rate among patients with NYHA class III and IV heart failure symptoms[26]—was associated with a 1.1 mL/kg/min change in peak VO_2.[27] Likewise, 112-meter change in 6-minute walk distance is greater than the values considered meaningful in previous studies, such as 20% change[6] or ± 25 to 45 meters.

Limitations

Our study has some limitations. First, because the data are from a clinical trial, men and younger patients may be overrepresented compared with the typical heart failure population. Second, at the time of enrollment, patients were medically stable with respect to heart failure symptoms and were willing to perform exercise on a regular basis. Furthermore, only 23 patients in NYHA class IV enrolled in the trial, so the generalizability of our findings to patients with severe heart failure symptoms is unclear. Third, we used mixed models to estimate change scores, which assume that unobserved variables do not explain the probability of missingness over and above what is explained by observed variables. Given the large number of observed variables included in the models, we believe this was an appropriate approach and that the benefits of using mixed models for this application.

Conclusions

Changes in patient-reported health status, as measured by the VAS and the KCCQ and its subscales, are not highly correlated with changes in functional capacity, including peak VO_2 and 6-minute walk distance. According to the predominant model of patient outcomes,[20] our findings do not alter the recommendation of considering a 5-point change in the KCCQ within individuals to be clinically meaningful.[5] This information will help to inform study design and interpretation in heart failure trials and observational studies that use the VAS or KCCQ.

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References

1. Spertus JA. Evolving applications for patient-centered health status measures. Circulation. 2008; 118:2103–10. [PubMed: 19001034]
2. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2006. (Accessed at http://www.fda.gov/CDER/GUIDANCE/5460dft.pdf.)
3. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health. 2007; 10 (Suppl 2):S125–37. [PubMed: 17995471]
4. Luther SA, McCullough PA, Havranek EP, et al. The relationship between B-type natriuretic peptide and health status in patients with heart failure. J Card Fail. 2005; 11:414–21. [PubMed: 16105631]
5. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005; 150:707–15. [PubMed: 16209970]
6. Masoudi FA, Rumsfeld JS, Havranek EP, et al. Age, functional capacity, and health-related quality of life in patients with heart failure. JCard Fail. 2004; 10:368–73. [PubMed: 15470645]
7. Cohen, J. Statistical power analysis for the behavioral sciences. 2. Hillsdale, New Jersey: Lawrence Erlbaum Associates, Publishers; 1988.
8. Whellan DJ, O'Connor CM, Lee KL, et al. Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): design and rationale. Am Heart J. 2007; 153:201–11. [PubMed: 17239677]
9. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000; 35:1245–55. [PubMed: 10758967]
10. Schweikert B, Hahmann H, Leidl R. Validation of the EuroQol questionnaire in cardiac rehabilitation. Heart. 2006; 92:62–7. [PubMed: 15797936]
11. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. Health Qual Life Outcomes. 2006; 4:89. [PubMed: 17125512]
12. Konstam MA, Neaton JD, Poole-Wilson PA, et al. Comparison of losartan and captopril on heart failure-related outcomes and symptoms from the losartan heart failure survival study (ELITE II). Am Heart J. 2005; 150:123–31. [PubMed: 16084158]
13. Wilson JR. Exercise and the failing heart. Cardiol Clin. 1987; 5:171–81. [PubMed: 3555795]
14. Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators JAMA. 1993; 270:1702–7.
15. Bryk, AS.; Raudenbush, SW. Hierarchical Linear Models. Newbury Park: 1992.
16. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry. 1993; 50:739–50. [PubMed: 8357299]
17. Schafer, JL. Analysis of Incomplete Multivariable Data. Chapman & Hall/CRC; 1997.
18. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301:1451–9. [PubMed: 19351942]
19. Meng XL, Rosenthal R, Rubin DB. Comparing correlated correlation coefficients. Psychological Bulletin. 1992; 111:172–5.
20. Wilson IIB, Cleary PPD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995; 273:59–65. [PubMed: 7996652]

21. Isobe T, Feigelson ED, Akritas MG, Babu GJ. Linear Regressions for Astronominy. Astrophysical Journal. 1990; 364:104–13.

22. Efron, B.; Tibshirani, RJ. An Introduction to the Bootstrap. New York: Chapman & Hall; 1993.

23. Myers J, Zaheer N, Quaglietti S, Madhavan R, Froelicher V, Heidenreich P. Association of functional and health status measures in heart failure. JCard Fail. 2006; 12:439–45. [PubMed: 16911910]

24. Flynn KE, Lin L, Ellis SJ, et al. Outcomes, health policy, and managed care: relationships between patient-reported outcome measures and clinical measures in outpatients with heart failure. Am Heart J. 2009; 158:S64–71. [PubMed: 19782791]

25. Savage PD, Toth MJ, Ades PA. A re-examination of the metabolic equivalent concept in individuals with coronary heart disease. J Cardiopulm Rehabil Prev. 2007; 27:143–8. [PubMed: 17558194]

26. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352:1539–49. [PubMed: 15753115]

27. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003; 289:2685–94. [PubMed: 12771115]

28. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002; 346:896–903. [PubMed: 11907289]

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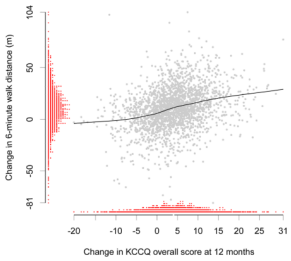

Figure 1.

Distributions of and Relationship Between Changes in KCCQ and Changes in Peak VO_2 at 12 Months

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.

*LOESS fit curve between the predicted change in KCCQ overall score and change in peak VO_2 at 12 months.

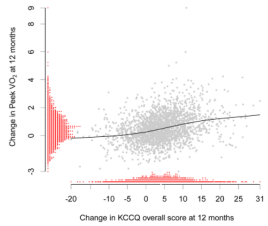

Figure 2.

Distributions of and Relationship Between Changes in KCCQ and Changes in 6-Minute Walk Distance at 12 Months

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.

*LOESS fit curve between the predicted change in KCCQ overall score and change in 6-minute walk distance at 12 months.

Table 1

Baseline Characteristics of the Study Population (N = 2331)*

Characteristic†	Patients
Treatment group, No. (%)	
Usual care	1172 (50.3)
Exercise training	1159 (49.7)
Age, median (IQR), y	59.3 (51.1–68.0)
Female, No. (%)	661 (28.4)
Diabetes mellitus, No. (%)	748 (32.1)
Peripheral vascular disease, No. (%)	157 (6.8)
Chronic obstructive pulmonary disease, No. (%)	249 (10.8)
Previous myocardial infarction, No. (%)	979 (42.0)
Previous revascularization, No. (%)	903 (38.7)
Atrial fibrillation/atrial flutter, No. (%)	488 (20.9)
Ischemic etiology of heart failure, No. (%)	1197 (51.4)
Ejection fraction, median (IQR), %	24.7 (20.2–30.1)
Implantable cardioverter-defibrillator, No. (%)	938 (40.2)
Biventricular pacemaker, No. (%)	419 (18.0)
Use of β-blocker, No. (%)	2203 (94.5)
Use of angiotensin-converting enzyme inhibitor, No. (%)	1736 (74.5)
Use of HMG-CoA reductase inhibitor, No. (%)	1097 (47.1)
Presence of 2 diuretics, No. (%)	136 (5.8)
Spironolactone or eplerenone, No. (%)	1051 (45.1)
New York Heart Association classification, No. (%)	
II	1477 (63.4)
III/IV	854 (36.6)
Canadian Cardiovascular Association functional classification	
of angina, No. (%)	
I	200 (8.6)
II	136 (5.8)
III	36 (1.6)
IV	6 (0.3)
No angina	1950 (83.8)
Systolic blood pressure, median (IQR)	111 (100–126)
Diastolic blood pressure, median (IQR)	70 (60–78)
Heart rate, median (IQR)	70 (63–77)
Body mass index, median (IQR)	29.9 (26.0–35.1)
Exercise duration, median (IQR), min	9.6 (6.9–12.0)
Smoking status, No. (%)	

Characteristic†	Patients
Never	866 (37.3)
Current	388 (16.7)
Past	1066 (46.0)
No. of heart failure–related hospitalizations in the past 6 months, No. (%)	
0	1701 (73.6)
1	464 (20.1)
2	94 (4.1)
3+	52 (2.3)
Beck Depression Inventory II, median (IQR)	8.0 (4.0–15.0)
Perceived Social Support Scale, median (IQR)	6.0 (5.2–6.7)
6-minute walk distance, mean (SD), m	364.5 (104.7)
Peak VO_2, mean (SD), mL/kg/min	14.9 (4.7)
EQ-5D visual analog scale, mean (SD)	65.5 (19.0)
KCCQ overall summary scale, mean (SD)	66.2 (20.6)
KCCQ subscales, mean (SD)	
Physical limitations	69.4 (21.9)
Symptoms	73.1 (20.8)
Quality of life	59.7 (24.7)
Social limitations	62.4 (27.5)

Abbreviations: IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire.

*Percentages may not sum to 100 because of rounding.

†The number of missing values was 20 in history of chronic obstructive pulmonary disease, 1 in history of atrial fibrillation/atrial flutter, 3 in Canadian Cardiovascular Association functional classification of angina, 4 in systolic blood pressure, 5 in diastolic blood pressure, 5 in heart rate, 7 in body mass index, 22 in CPX duration, 11 in smoking status, 20 in number of heart failure-related hospitalization in the past 6 month, 9 in Beck Depression Inventory II, and 17 in Perceived Social Support Scale. Missing data for KCCQ, Peak VO2, EQ-5D VAS, and 6-minute walk distance are reported in Table 2. There was no missing data for other baseline variables.

Table 2

Patients With Missing Data by Study Visit

	Expected No. of Patients	Patients With Missing KCCQ, No. (%)*	Patients With Missing EQ-5D VAS, No. (%)*	Patients With Missing Peak VO_2, No. (%)*	Patients With Missing 6-Minute Walk Distance, No. (%)*
Baseline	2331	1 (< 0.1)	57 (2.4)	56 (2.4)	51 (2.2)
3 months	2281	243 (10.7)	280 (12.3)	399 (17.5)	434 (19.0)
6 months	2240	332 (14.8)	374 (16.7)	—	—
9 months	2196	383 (17.4)	423 (19.3)	—	—
12 months	2101	345 (16.4)	379 (18.0)	649 (30.9)	646 (30.7)

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire; VAS, visual analog scale.

*Percentages are calculated from the number of patients expected at each visit, accounting for patients who died or withdrew from the study.

Table 3

Correlations Between Changes in Health Status and Changes in Functional Capacity

Health Status and Functional Capacity	3 Months, *r* (95% CI)*†	12 Months, *r* (95% CI)*†
KCCQ overall score		
Peak VO_2, mL/kg/min	0.29 (0.21 to 0.39)	0.31 (0.24 to 0.39)
6-minute walk distance, m	0.26 (0.20 to 0.34)[c]	0.31 (0.26 to 0.38) c
KCCQ subscales		
Physical limitation		
Peak VO_2, mL/kg/min	0.28 (0.19 to 0.40)	0.32 (0.25 to 0.41)
6-minute walk distance, m	0.31 (0.23 to 0.42)	0.34 (0.28 to 0.43)
Symptoms		
Peak VO_2, mL/kg/min	0.26 (0.18 to 0.35)	0.27 (0.20 to 0.35)[c]
6-minute walk distance, m	0.25 (0.17 to 0.35)[c]	0.29 (0.22 to 0.37) [c]
Quality of life		
Peak VO_2, mL/kg/min	0.24 (0.15 to 0.34)[c]	0.26 (0.18 to 0.34)[c]
6-minute walk distance, m	0.18 (0.11 to 0.25)[c]	0.23 (0.17 to 0.30)[c]
Social limitation		
Peak VO_2, mL/kg/min	0.28 (0.20 to 0.38)	0.30 (0.23 to 0.38)
6-minute walk distance, m	0.22 (0.16 to 0.30)[c]	0.29 (0.23 to 0.37)[c]
EQ-5D Visual Analog Scale		
Peak VO_2, mL/kg/min	0.13 (0.02 to 0.25)	0.16 (0.07 to 0.27)
6-minute walk distance, m	0.18 (0.07 to 0.31)	0.28 (0.19, to 0.39)

Abbreviations: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire.

*Adjusted for all significant patient characteristics listed in Table 1 and their interactions.

†Confidence intervals estimated using the bootstrap method with replacement and constructed using the bias-corrected and accelerated method.

‡Correlation coefficient significantly different from corresponding coefficient with KCCQ physical limitation subscale at $P < .05$.

Table 4

Estimation of Minimally Important Change in KCCQ Overall Score at 12 Months

Functional Capacity Variable	Parameter Estimate*	Change Corresponding to 5-Point Change in KCCQ (95% CI)
Peak VO_2	2.00	2.50 (2.21–2.86)
6-minute walk distance	0.04	111.69 (95.91–133.67)

Abbreviation: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire.

* From ordinary least squares regression model in which KCCQ overall score was regressed on the functional capacity variable, adjusted for all patient characteristics and their significant interactions.