Health Status and Depression Remission in Patients With Chronic Heart Failure
Patient-Reported Outcomes From the SADHART-CHF Trial

Glen L. Xiong, MD; Mona Fiuzat, PharmD; Maragatha Kuchibhatla, PhD; Ranga Krishnan, MD; Christopher M. O’Connor, MD; Wei Jiang, MD; on behalf of the SADHART-CHF Investigators

Background—Depression is a common comorbidity in heart failure and is strongly associated with increased mortality, morbidity, and reduced health status. Whether depression treatment may result in improvement of health status in heart failure patients with comorbid depression remains unknown.

Methods and Results—The Sertraline Against Depression and Heart Disease in Chronic Heart Failure study randomized 469 participants with chronic heart failure (left ventricular ejection fraction ≤45% and New York Heart Association class II) and major depressive disorder based on Diagnostic Statistics Manual fourth edition criteria to sertraline or placebo for 12 weeks. The Kansas City Cardiomyopathy Questionnaire, 36-Item Short-Form Health Survey, and 6-minute walk test were used to assess health status. Health status changes between treatment arms and remission status were evaluated adjusting for baseline variables and treatment assignment. The final Hamilton Depression Rating Scale scores were 3.50±2.08 and 12.97±4.33 in the remission and nonremission groups, respectively (P value=0.0001). Of 469 total participants, 378 (80.6%) completed the 6-minute walk test and 285 (70.1%) completed Kansas city cardiomyopathy questionnaire and 36-item short-form health survey, at baseline and at week 12. Depression remission was significantly associated with higher improvements in Kansas City Cardiomyopathy Questionnaire subscale scores (P<0.001) except on the Self-Efficacy (P=0.18) and Symptom Stability (P=0.91). On the 36-Item Short-Form Health Survey, depression remission was associated with significant improvement in subscales of the physical and mental component summary except the Pain Index (P=0.34). The 6-minute walk test improved more in depression remission compared with nonremission group (difference from baseline: 63.51±238.78 versus 16.24±115.70 m, P=0.03).

Conclusions—Patients with heart failure whose depressive symptoms remitted had significantly greater improvement in functional disability and lower quality-of-life. In HF, the prevalence of depression is at least 20%.

Key Words: heart failure ▪ depression ▪ health status ▪ Kansas City Cardiomyopathy Questionnaire ▪ 6-minute walk test

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by the institutional review board for each center. The study recruited 469 participants (N=234 sertraline, N=235 placebo), from 3 centers in the United States between August 13, 2003, and March 3, 2008. Participants were ≥45 years of age with left ventricular ejection fraction ≤45% (within the previous 6 months), New York Heart Association class II–IV HF symptoms, and had major depressive disorder based on Diagnostic Statistics Manual 4th edition criteria. The intervention was sertraline versus matched placebo for 12 weeks. Additionally, all participants received nurse-facilitated support that was to build rapport and trust with the study participants, ascertain compliance with the study protocol, re-evaluate depression status, monitor suicidal ideation, and consult with study physicians on appropriate patient management. Trial intervention was terminated after week 12.13,14 For the primary outcome of depression remission, sertraline treatment did not significantly differ from placebo. Of 469 participants, 208 (44.3%) achieved remission, 194 (41.4%) remained depressed, and 67 (14.3%) dropped out or died without any repeat Hamilton Depression Rating Scale (HDRS) assessment.14

**Depression Measurement and Comparison**

The 17-item HDRS was completed at baseline and at 2-week intervals during the 12-week treatment phase and at the end of the 12-week intervention. Depression remission was defined as HDRS<8 during the last depression assessment. Patients whose HDRS remained ≥8 were considered nonremission. Participants (n=67, 14.3%) who dropped out without having a repeat HDRS were excluded.

**Patient-Reported Outcomes for Health Status**

In addition to the primary outcome of depression remission, a priori outcome measurements included patient-reported health status outcomes.11 The health status outcomes were ascertained at baseline prior to randomization and the end of 12-week intervention via the KCCQ, total and subscale scores, the Medical Outcomes Study SF-36 Mental and Physical Component Summary scores, and 6MWT. KCCQ is a 23-item self-administered disease specific questionnaire, scored from 0 to 100 with higher scores corresponding to better health status. In addition to the overall summary score, we also examined score from the subscales for Social Limitation, Quality-Of-Life, Symptom Frequency, Total Symptom Score, and Clinical Summary. A 5-point change in the KCCQ summary score had been previously used to correspond to minimal clinical significance.17,18 The SF-36 was designed to measure general health status with high scores indicating a better health state. The results are expressed in terms of 8 subscores. The Physical Component Summary consists of a 10-item Physical Functioning, 4-item Role Physical, 2-item Pain index, and 5-item General Health Perception.18 Mental Component Summary consists of 4-item Vitality, 2-item Social Functioning, 3-item Emotional Role, and 5-item Mental Health Index.19,20 The 6MWT reflects a global and integrated response of the body systems to exercise testing and closely mimics everyday activity. It examines overall functional capacity and serves as a simple prognosticator.21–24

**Statistical Analysis**

Statistical analyses were performed using SAS, version 9.1 (SAS Inc. Cary, NC). Descriptive statistics were reported for the depression remission and nonremission groups. Differences of depression treatment and remission on health status scores with categorical variables (eg, sex, race, etc) were examined using χ² test, whereas for the continuous variables Wilcoxon test was used. Linear regression models with model based standard errors were used to test if the changes scores (final minus baseline) of health status between groups were associated with or without covariates including age, sex, race, history of depression, baseline Hasegawa’s Dementia Rating Scale Revised score, New York Heart Association class, ejection fraction, history of depression, ischemia, coronary artery disease, history of coronary artery bypass grafting surgery, implanted cardioverter defibrillator, angina, myocardial infarction, arrhythmia, hypertension, diabetes mellitus, and baseline medications ace inhibitors, statins, beta-blockers, and loop diuretics. Judging by standard models of fit, there was no empirical evidence to support any nonlinear relationships with the outcomes; hence, we used linear regression models. Prior to fitting the final model, we looked for multicollinearity as well as for extreme values using the standard techniques.25 The change scores are obtained from participants who completed both baseline and final measurements. Treatment assignment (sertraline versus placebo) was additionally added as a covariate to examine the effects of depression remission versus nonremission. Because a total of 10 KCCQ and 8 SF-36 outcomes were examined, a P value<0.001 was set as statistical significance to account for examination of multiple dependent variables. Statistical significance for 6MWT was set at P<0.05 because that was the only outcome examined in this category.

**Results**

**Participant Characteristics**

A total of 469 participants were enrolled, and 402 (85.7%) had at least 1 HDRS evaluation during the trial intervention phase. Of them, a total of 378 (80.6%) participants completed the 6MWT at baseline and at week 12, and 285 (70.1%) completed baseline, 12-week KCCQ, and SF-36. Of the participants who completed both the KCCQ and SF-36, 73 (54.1%) of 135 participants received sertraline and achieved remission, whereas 80 (53.3%) of 150 received placebo and achieved remission (P=0.91). Treatment with sertraline versus placebo did not correspond to a difference in KCCQ, SF-36 subscale scores (for KCCQ overall summary, P=0.88; KCCQ Quality-Of-Life, P=0.83; SF-36 physical function, P=0.40; and 6MWT, P=0.53).

Table 1 displays the baseline characteristics between the remission and nonremission groups who completed both baseline and 12-week KCCQ and SF-36 measurements (n=285). The final HDRS scores were 3.50±2.08 and 12.97±4.33 in the remission and nonremission groups, respectively (P value<0.001). For KCCQ changes at week 12 from baseline (Table 2), depression remission was significantly associated with higher score improvements in social limitation (P<0.001), physical limitation (P<0.001), quality-of-life (P<0.001), symptom frequency (P<0.001), total symptom (P<0.001), clinical summary (P<0.001), and overall summary (P<0.001) scores. Depression remission was not associated with improvements in self-efficacy and (P=0.18) symptom stability (P=0.91) measurements.

Table 3 displays the SF-36 physical component summary and mental component summary changes in subscale scores between depression remission and nonremission. In the physical component summary subscales, there was significant improvement in the depression remission group on general health perception (P<0.001), physical function (P<0.001), and role physical (P<0.001) but not Pain Index (P=0.34). For the mental component summary subscales, the depression remission group had significant improvement in all 4 subscales including role emotional, mental health index, social functioning, and vitality (Table 3).

Table 4 reports remission and nonremission groups with both baseline and 12-week 6MWT measurements. At baseline, the depression remission group had higher 6MWT compared with depression nonremission group (P=0.007). At the conclusion of the study, the final from baseline change of 6MWT results was higher in the depression remission compared with nonremission group (63.51+238.78 versus 16.24±115.70 m, P=0.03).
The baseline HDRS scores were 16.83±5.33 and 19.51±5.50 in the remission and nonremission groups, respectively (P<0.001). The health status outcomes associated with depression remission were not significantly associated with measured baseline conditions including baseline HDRS score.

Discussion
Depression is considered a major determinant of health status in patients with HF.26,27 However, few studies have examined depression treatment on health status in HF. In a placebo-controlled pilot study (n=28), Gottlieb et al.28 found that paroxetine was associated with higher SF-36 psychological quality-of-life but not with physical quality-of-life. In contrast, the SADHART-CHF study found that sertraline treatment did not differ from placebo in terms of depression remission and health status outcomes, although depression remission was associated with significant improvement in health status.

For the self-reported KCCQ measurements, depression remission was associated with improvement in social limitation, physical limitation, and symptom frequency. A 5-point change in the KCCQ is considered of minimal clinical significance.17 In this study, the KCCQ overall summary score was about 13 point higher in the depression remission group compared to depression nonremission group. The largest difference was observed on the KCCQ quality-of-life and social

Table 1. Baseline Characteristics Between Remission Vs Nonremission Groups

<table>
<thead>
<tr>
<th></th>
<th>Remission (n=132)</th>
<th>Nonremission (n=152)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of antidepressant treatment</td>
<td>119 (45.25%)</td>
<td>144 (54.75%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age</td>
<td>60.5±10.1</td>
<td>62.3±8.40</td>
<td>0.10</td>
</tr>
<tr>
<td>Women</td>
<td>58 (43.94%)</td>
<td>51 (33.33%)</td>
<td>0.07</td>
</tr>
<tr>
<td>White</td>
<td>76 (57.58%)</td>
<td>90 (58.82%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Black</td>
<td>56 (42.42%)</td>
<td>63 (41.18%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>90 (68.18%)</td>
<td>103 (67.32%)</td>
<td>0.71</td>
</tr>
<tr>
<td>New York Heart Association classification</td>
<td>3.0±0.8</td>
<td>2.92±0.70</td>
<td>0.39</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>31.2±10.3</td>
<td>30.2±9.56</td>
<td>0.45</td>
</tr>
<tr>
<td>Previous coronary bypass surgery</td>
<td>35 (26.52%)</td>
<td>53 (34.64%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>27 (20.45%)</td>
<td>21 (13.73%)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of angina</td>
<td>82 (62.12%)</td>
<td>79 (51.63%)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>58 (43.94%)</td>
<td>69 (45.10%)</td>
<td>0.91</td>
</tr>
<tr>
<td>History of arrhythmia</td>
<td>51 (38.64%)</td>
<td>62 (40.52%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (84.85%)</td>
<td>136 (88.89%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70 (53.03%)</td>
<td>82 (53.59%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>95 (71.97%)</td>
<td>115 (75.16%)</td>
<td>0.59</td>
</tr>
<tr>
<td>β-blocker</td>
<td>114 (86.36%)</td>
<td>132 (86.27%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>83 (62.88%)</td>
<td>95 (62.50%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Statin</td>
<td>89 (67.42%)</td>
<td>105 (68.63%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Sertraline</td>
<td>62 (46.97%)</td>
<td>73 (47.71%)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Kansas City Cardiomyopathy Questionnaire Base, Final, and Change Scores Between Depression and Remission Groups

<table>
<thead>
<tr>
<th></th>
<th>Remission (n=153)</th>
<th>Nonremission (n=132)</th>
<th>Unadjusted P value</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>Final Mean (SD)</td>
<td>Change* Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Social limitation</td>
<td>40.6 (31.2)</td>
<td>68.5 (28.8)</td>
<td>28.1 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Physical limitation</td>
<td>44.7 (25.5)</td>
<td>60.5 (25.9)</td>
<td>15.7 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Symptom stability</td>
<td>42.3 (33.7)</td>
<td>54.1 (21.4)</td>
<td>11.8 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Quality-of-life</td>
<td>41.7 (25.2)</td>
<td>72.1 (22.5)</td>
<td>30.3 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>79.7 (25.0)</td>
<td>90.1 (16.9)</td>
<td>10.4 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Symptom burden</td>
<td>50.5 (26.3)</td>
<td>74.6 (24.0)</td>
<td>24.1 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Symptom frequency</td>
<td>45.8 (25.9)</td>
<td>71.8 (24.9)</td>
<td>26.9 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Total symptom score</td>
<td>48.1 (24.6)</td>
<td>73.2 (23.4)</td>
<td>25.1 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Clinical summary</td>
<td>46.5 (22.4)</td>
<td>66.9 (22.5)</td>
<td>20.4 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Overall summary</td>
<td>43.9 (22.1)</td>
<td>68.7 (21.5)</td>
<td>24.7 (23.8)</td>
<td></td>
</tr>
</tbody>
</table>

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limitation subscales, where the differences were nearly 20 points between the 2 groups, indicating moderate to large clinical difference. The observed finding on the KCCQ was verified by the SF-36 measurements, in that depression remission was associated with improvements in General Health Perception and Physical Function subscales. On the 6MWT, patients with depression remission were able to walk 47 m more than those patients who continued to have depression (P=0.03). These findings highlight the fact that depression remission was associated with improvements in physical health measurements. However, depression remission was not associated with improvements in KCCQ symptom stability and self efficacy subscales and SF-36 pain index.

The strength of this study includes the use of rigorous instruments (KCCQ, SF-36, and 6MWT) to measure health status in HF, which had been extensively studied to evaluate the health impact of exercise training in HF.29–32 Most of these studies used 1 or 2 of these outcome instruments and not all 3. The observed finding on the KCCQ was confirmed and thus subject to unmeasured confounding effects.

There were limitations to this study, however. First, this study was a secondary analysis where the primary outcome of SADHART-CHF was depression remission. The health status instruments were secondary outcomes. The study was further limited by the low completion rate of KCCQ and SF-36 of 60.1% (n=282), and 6MWT of 80.6% (n=378) in 469 total participants. Therefore, the conclusion of this study may not be generalizable to participants who dropout or who did not complete the health status measurements. Noncompleters were older (64.29 [11.6] versus 61.45 [9.8] P=0.02), had larger incidence of myocardial infarction (40.38 versus 30.88%, P=0.04) and coronary artery bypass grafting (54.5 versus 44.5%, P=0.044). Also, the outcomes were not measured beyond the first 12-weeks during long-term follow-up, therefore whether the improvement persisted after 12 weeks remained unknown. Finally, we did not examine interaction effects between treatments and among independent variables. The conclusions therefore were limited to the variables examined and thus subject to unmeasured confounding effects.

In conclusion, sertraline treatment did not impact health status compared with placebo but depression remission was associated with improved health status in patients with HF and comorbid major depressive disorder. Therefore, it is important that future studies that examine the comorbidity of depression and HF should include health status as an important outcome. Clinically, depression monitoring and treatment of depression in HF to achieve remission has important impacts on physical function and quality-of-life that is beyond just psychological and emotional well-being.

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Disclosures
None.

References


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