Effect of Exercise Training on Health Related Quality of Life in Patients with Chronic Heart Failure:

An HF-ACTION Substudy

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Case Western Reserve University

on behalf of the
HF-ACTION Steering Committee, Investigators, and Coordinators

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FINANCIAL DISCLOSURE: None

UNLABELED/UNAPPROVED USES DISCLOSURE: None
Background

- Few studies of exercise training in heart failure patients have assessed health status
  - Symptoms
  - Function
  - Quality of life

- The effects of exercise training on health status have been inconsistent

- Exercise training is recommended by guidelines

Limitations of Prior Studies

- Generalizability
  - Selection bias
  - Small sample size
  - Single center

- Short duration of exercise training

- Variability in measurement tools

- Most undertaken prior to current guidelines for beta blockers and ICDs
HF-ACTION: QOL Objective and Hypothesis

- To examine the impact of aerobic exercise training on health status in patients with stable chronic HF (NYHA Class II-IV) due to systolic dysfunction

- Primary hypothesis
  - Exercise training will significantly improve the health status of heart failure patients compared to usual care alone
Chronic heart failure, NYHA Class II-IV, LVEF ≤ 35%, optimal HF medical therapy, capable of exercising

Pre-randomization CPX and ECHO

Randomization 1:1
(Stratified by center and HF etiology)

N=2331

Usual Care
Median Follow-up 2.5 years
Exercise Training

Treatment Groups

■ Usual Care
  ■ Optimized medical treatment
  ■ Patient education
  ■ Phone calls

■ Exercise Training
  ■ Optimized medical treatment
  ■ Patient education
  ■ Phone calls
  ■ Supervised training
  ■ Home training
Summary of Clinical Results

- Exercise training produced a modest decrease in the primary endpoint (all-cause mortality or all-cause hospitalization) and key secondary cardiovascular endpoints.
- Exercise training provided modest improvements in physiologic endpoints.
- Regular exercise training is safe in patients with heart failure and systolic dysfunction.
Health Status Instrument

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - 23 items
    - Subscales
      - Physical Limitations
      - Symptoms
      - Quality of Life
      - Social Limitations
  - Baseline, 3, 6, 9, 12 months, and annually for up to 4 years
  - Scale of 0-100
  - Higher scores = better health status
  - A difference ≥ 5 points considered clinically significant*

Statistical Analysis

- Primary Analysis
  - Intention-to-treat
  - Linear mixed model
    - *Uses all available data*
    - *Averages health status trajectory for each group*
    - *Assumes missing data are missing-at-random*
    - *Included etiology as baseline covariate*

- Sample provided >90% power with 2-sided \( \alpha=0.05 \) to detect a 5 point difference in KCCQ score between groups
Statistical Analysis (continued)

- Secondary Analyses
  - Pre-specified
    - KCCQ Subscales
    - Key subgroups
  - Not pre-specified
    - Percentage with \( \geq 5 \) point improvement at 3 and 12 months
      - Number Needed to Treat

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Exercise Training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1172</td>
<td>N=1159</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>59 (51, 68)</td>
<td>59 (51, 68)</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td><strong>African American, %</strong></td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td><strong>NYHA Class, % II / III / IV</strong></td>
<td>64 / 35 / 1</td>
<td>62 / 36 / 1</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td>25 (20, 30)</td>
<td>25 (20, 30)</td>
</tr>
<tr>
<td><strong>Ischemic etiology, %</strong></td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td><strong>Afib/flutter, %</strong></td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td><strong>History of Stroke, %</strong></td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><strong>BMI, kg/m^2</strong></td>
<td>30 (26, 35)</td>
<td>30 (26, 35)</td>
</tr>
<tr>
<td><strong>Serum Creatinine, mg/dL</strong></td>
<td>1.2 (1.0, 1.5)</td>
<td>1.2 (1.0, 1.5)</td>
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<tr>
<td><strong>Peak VO\textsubscript{2}, mL/min/kg</strong></td>
<td>14.5 (11.6, 17.8)</td>
<td>14.4 (11.3, 17.6)</td>
</tr>
<tr>
<td><strong>CPX duration, minutes</strong></td>
<td>9.7 (7.0, 12.1)</td>
<td>9.5 (6.9, 12.0)</td>
</tr>
</tbody>
</table>

*Median (25th, 75th)
## Baseline Health Status

<table>
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<tbody>
<tr>
<td></td>
<td>N=1172</td>
<td>N=1159</td>
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<tr>
<td><strong>KCCQ Overall Summary</strong></td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td><strong>KCCQ Symptom Stability</strong></td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td><strong>KCCQ Physical Limitations</strong></td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td><strong>KCCQ Symptoms</strong></td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td><strong>KCCQ Quality of Life</strong></td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td><strong>KCCQ Social Limitations</strong></td>
<td>63</td>
<td>62</td>
</tr>
</tbody>
</table>
KCCQ Data Collected by Visit*

*The percentage of patients expected at each visit, accounting for death, withdrawn consent, and rolling enrollment into the trial.

Exercise Training
Usual Care

Time in Months

Percent

Duke Clinical Research Institute
Duke University Medical Center
National Institutes of Health
HF Action
Primary Endpoint: Predicted KCCQ Overall Score

- In the exercise arm, patients' health status improved 5 points on average at 3 months, and this was sustained over time.
Primary Endpoint: Predicted KCCQ Overall Score

- Health status for patients in the usual care group also increased 3 points on average at 3 months, and this was sustained over time.
Primary Endpoint: Predicted KCCQ Overall Score

Overall treatment effect $p=0.001$

- **Exercise Training** (Yellow line)
- **Usual Care** (Red dashed line)

KCCQ Score

Time in Months

Duke Clinical Research Institute
Duke University Medical Center
National Institutes of Health
Primary Endpoint: Predicted KCCQ Overall Score

- The 2-point difference in early change was significant

KCCQ Score

- Exercise Training
- Usual Care

Time in Months

Duke Clinical Research Institute
Duke University Medical Center
National Institutes of Health
HF Action
Primary Endpoint: Predicted KCCQ Overall Score

- The difference between the groups in later change (slopes) was not significant.

\[ p = 0.74 \]
More patients had clinically meaningful improvement at 3 months in the exercise arm than usual care.
Predicted Change in KCCQ at 12 Months

More patients had clinically meaningful improvement at 12 months in the exercise arm than usual care.
Percent of Patients with Clinical Improvement

- **3 months:**
  - Exercise Training: 54%
  - Usual Care: 28%
  - NNT = 4

- **12 months:**
  - Exercise Training: 53%
  - Usual Care: 33%
  - NNT = 5

**P < 0.001**
# No Subgroup Interactions

<table>
<thead>
<tr>
<th>Pre-specified analyses</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;=70 vs 71+)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex</td>
<td>0.26</td>
</tr>
<tr>
<td>Race (White vs Black vs Other)</td>
<td>0.97</td>
</tr>
<tr>
<td>NYHA Class (II vs III/IV)</td>
<td>0.61</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.75</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.24</td>
</tr>
<tr>
<td>Perceived Social Support Scale</td>
<td>0.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not pre-specified analyses</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline KCCQ (0-50 vs 50-75 vs 75-100)</td>
<td>0.24</td>
</tr>
<tr>
<td>LVEF (&lt;=25 vs &gt;25)</td>
<td>0.06</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous revascularization (CABG or PCI)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* From overall likelihood ratio tests
Limitations

- Incomplete capture of KCCQ data
- Adherence in the exercise training group and physical activity by the usual care group may have diminished the health status benefit of exercise training
- Blinding of subjects and research personnel not possible
- KCCQ assessment schedule limited after 12 months
Conclusions

- The HF-ACTION Trial is the largest, most comprehensive study of exercise training in heart failure

- Participation in an exercise training program produced a modest but statistically significant improvement in health status compared to usual care
  - Improvement occurred early during supervised exercise training & was sustained during home training
  - Results consistent across subscales and subgroups
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