Long-Term Effects of an Intensive Lifestyle Intervention on Electrocardiographic Evidence of Left Ventricular Hypertrophy: The Action for Health in Diabetes (Look AHEAD) Trial

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FINANCIAL DISCLOSURE:
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Introduction – LV Hypertrophy (LVH)

• A marker of subclinical cardiac damage
• Characterized by enlargement and thickening of the LV
• Measured by echocardiography, MRI, ECG
  • Differences in sensitivity, availability, cost
• ECG-LVH is an important clinical tool
  • Strong predictor of future cardiovascular events
  • Regression is associated with reduced risk
  • Useful for assessing changes in CV risk over time
Introduction – LVH and Lifestyle

• LVH is prevalent in obesity and type 2 diabetes

• Exercise and weight loss are recommended to lower cardiovascular disease risk

• Some evidence of a benefit from therapeutic lifestyle changes
  • Pharmacological intervention
  • Diet/exercise interventions

• There are no RCT on long-term effects of weight loss on ECG-LVH
Purpose

To determine whether an intensive lifestyle intervention targeting weight loss reduces the incidence of ECG-LVH in overweight and obese adults with type 2 diabetes
Methods: Look AHEAD

- Multi-center randomized clinical trial
- 5,145 study participants
- 10-year intensive lifestyle intervention (ILI) or diabetes support and education (DSE)
  - ILI: 7% weight loss; 1200-1800 kcal/day; 175 min/week of physical activity
  - DSE: education, social support
Methods: Study Population

• Age: 45 to 76 years
• Overweight or obese (BMI $\geq 25$ kg/m$^2$ or $\geq 27$ kg/m$^2$ if taking insulin)
• Type 2 diabetes
• Excluded prevalent ECG-LVH (5%)
Methods: Electrocardiography

• Resting ECGs were performed every 2 years

• Outcomes of Interest

1) ECG-LVH (Cornell voltage)
   • RaVL + SV3 >2800 µV in men and >2000 µV in women

2) Continuous Cornell voltage
Statistical Analyses (n=4,548)

- Proportional hazards regression was used to compare the incidence of ECG-LVH (defined as time to first occurrence)
- Mixed models were used to compare changes in absolute Cornell voltage over time
- Tests of interactions by sex, race/ethnicity and baseline CVD status
- Analyses were performed according to the intention-to-treat principle
- All available follow-up data were included
# Results: Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>DSE</th>
<th>ILI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=4,548</td>
<td>N=2,261</td>
<td>N=2,287</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>58.7±6.8</td>
<td>58.9±6.9</td>
<td>58.5±6.8</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>2641 (58.1)</td>
<td>1318 (58.3)</td>
<td>1323 (57.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Men</td>
<td>1907 (41.9)</td>
<td>943 (41.7)</td>
<td>964 (42.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>676 (14.9)</td>
<td>340 (15.0)</td>
<td>336 (14.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Native American</td>
<td>230 (5.1)</td>
<td>114 (5.0)</td>
<td>116 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>575 (12.7)</td>
<td>284 (12.6)</td>
<td>291 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>2933 (64.5)</td>
<td>1459 (64.5)</td>
<td>1474 (64.5)</td>
<td></td>
</tr>
<tr>
<td>Other/Mixed</td>
<td>133 (2.9)</td>
<td>64 (2.8)</td>
<td>69 (3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>History of CVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>615 (13.5)</td>
<td>293 (13.0)</td>
<td>322 (14.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>No</td>
<td>3933 (86.5)</td>
<td>1968 (87.0)</td>
<td>1965 (85.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of antihypertensive agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3214 (71.7)</td>
<td>1580 (71.2)</td>
<td>1634 (72.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>No</td>
<td>1268 (28.3)</td>
<td>638 (28.8)</td>
<td>630 (27.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.3±17.0</td>
<td>129.0±16.9</td>
<td>127.6±17.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70.0±9.5</td>
<td>70.2±9.6</td>
<td>69.8±9.5</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Results: Main Intervention Effects

Results: Overall Incident ECG-LVH

Incidence rates: 7.1% vs. 8.0%

HR = 0.88 (0.71-1.08) p=0.22

Interaction:
Sex: p=0.74
Prior CVD: p=0.53
Race: p=0.046
Results: ECG-LVH in Whites

Incidence rate: 6.0%

HR = 1.07 (0.80-1.44); p=0.22
Results: ECG-LVH in Hispanics

Incidence rate: 6.3%

HR = 1.05 (0.55-2.02); p=0.88
Results: ECG-LVH in Native Americans

Incidence rate: 16.1%

HR = 0.56 (0.29-1.09); p=0.09
Results: ECG-LVH in African Americans

Incidence rate: 12.9%

HR = 0.59 (0.39-0.92); p=0.02
## Results: Sensitivity Analysis

<table>
<thead>
<tr>
<th>Race / Ethnicity</th>
<th>Hazard Ratios for ILI vs DSE adjusted for treatment arm, race, arm x race*</th>
<th>Hazard Ratios for ILI vs DSE further adjusted for change in SBP and BP drug use**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>White</td>
<td>1.07</td>
<td>0.79 - 1.44</td>
</tr>
<tr>
<td>African American</td>
<td>0.57</td>
<td>0.37 - 0.88</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.12</td>
<td>0.58 - 2.16</td>
</tr>
<tr>
<td>Native American</td>
<td>0.56</td>
<td>0.29 - 1.09</td>
</tr>
<tr>
<td>Other/Mixed</td>
<td>4.10</td>
<td>0.48 - 35.7</td>
</tr>
</tbody>
</table>

*Interaction p-value = 0.046
**Interaction p-value = 0.065
Results: Cornell Voltage (CV)

Intervention by year interaction: $p = 0.63$
Average intervention difference over time: $12.48 \mu V$ (95%CI: -1.79 to 26.74), $p = 0.09$

Change in Adjusted Mean CV ($\mu V$) Years after randomization

Interactions:
- Sex: $p=0.70$
- Prior CVD: $p=0.56$
- Race: $p=0.70$
Summary

• A long-term intensive lifestyle intervention in overweight and obese adults with type 2 diabetes does not significantly lower overall incident ECG-LVH

• The protective effect of the lifestyle intervention observed in African Americans, however, warrants further investigation
Strengths and Limitations

Limitations

• Limited generalizability (T2DM, volunteer)
• Indirect measure of LVH
• Several different criteria for ECG-LVH

Strengths

• Large, well-characterized cohort
• Good retention
• Many years of follow-up
Future Analyses

• Identify possible mechanisms for race-specific findings

• Explore other relevant factors
  • Fitness vs. Fatness
  • Glycemic control, statin use

• Examine regression of ECG-LVH (5.1% prevalence at baseline)
## Acknowledgements

<table>
<thead>
<tr>
<th>Coauthors</th>
<th>Funding Support for Look AHEAD</th>
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