A Naturally Randomized Trial Comparing the Effect of Long-Term Exposure to Lower LDL-C, Lower SBP, or Both on the Risk of Cardiovascular Disease

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Background

• Persons with ideal risk factor profiles have low lifetime risk of CVD
  • Fewer 5% of persons are able to maintain ideal risk factor profiles

• Mendelian randomization studies have shown that LDL-C and SBP each have both causal and cumulative effects on the risk of CVD
  • Because their effects are cumulative over time, focusing on promoting the combination both lower LDL-C and lower SBP may be an effective strategy to prevent CVD

• Causal effect of combined exposure to LDL-C and SBP is unknown
  • Prospective epidemiologic studies suggest the effect may be more than additive but less than multiplicative
  • Recent 2x2 factorial randomized trial (HOPE-3) suggested benefit of combined LDL-C and SBP lowering was not greater than LDL lowering with a statin alone

Objectives

• To estimate the causal effect of combined exposure to lower LDL-C and lower SBP on the risk of cardiovascular events using a 2x2 factorial Mendelian randomization study design

• To estimate the potential clinical benefit of a parsimonious prevention strategy that focuses on promoting long-term exposure to combination of one mmol/L lower LDL-C and 10 mmHg lower SBP
Mendelian Randomization

"Naturally Randomized Trial"

- Eligible Population
- SNP associated with LDL-C (Naturally Random Allocation of Alleles)
  - Lower LDL-C Allele (Treatment Arm)
  - Other Allele (Usual Care Arm)
  - $\Delta$ LDL-C
  - Incident Major Cardiovascular Events

Randomized Controlled Trial

- Eligible Population
- LDL-C Lowering Therapy (Random Allocation of Treatment)
  - Treatment Arm
  - Usual Care Arm
  - $\Delta$ LDL-C
  - Incident Major Cardiovascular Events
Study Population and Exposures

• Study sample: 102,773 persons (age 27 - 100 years)
  • enrolled in one of 14 prospective cohort or case-control studies

• LDL-C genetic score: 46 polymorphisms associated primarily with lower LDL-C at genome-wide level of significance

• SBP genetic score: 33 polymorphisms associated with lower SBP at genome-wide level of significance

• Genetic scores used as both the instrument of randomization and the instrument of exposure
Study Design: 2x2 factorial Mendelian randomization

- LDL-C score
  - Above Median (reference)
  - Below Median (Lower LDL-C)

- SBP score
  - Above Median (reference)
  - Below Median (Lower SBP)

- Reference
  - Lower SBP
  - Lower LDL-C
  - Both Lower LDL-C & lower SBP

Lifetime risk of cardiovascular events
Outcomes

• **Primary Outcome: Major vascular events**
  • First occurrence of CHD death, MI, stroke or coronary revascularization

• **Secondary Outcomes:**
  • Major Coronary Events: first occurrence of CHD death, MI or coronary revascularization
  • CHD: first occurrence of CHD death or MI
  • CHD or stroke

• **Tertiary Outcomes:**
  • Individual components of composite outcomes: CHD death, MI, Stroke, Coronary revascularization
  • All cause mortality
  • Rate of rise in SBP with age; hypertension
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reference Group</th>
<th>LDL-C score below median</th>
<th>SBP score below median</th>
<th>Both LDL-C &amp; SBP scores below median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>25,795</td>
<td>25,283</td>
<td>26,106</td>
<td>25,589</td>
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</tr>
</tbody>
</table>

Genetic score related lipid and blood pressure baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reference Group</th>
<th>LDL-C, mg/dl (SD)</th>
<th>SBP, mmHg (SD)</th>
<th>DBP, mmHg (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, mg/dl (SD)</td>
<td>134.4 (31.8)</td>
<td>122.3 (33.1)</td>
<td>125.1 (16.5)</td>
<td>7.2x10^{-6}</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dl (SD)</td>
<td>51.5 (14.7)</td>
<td>53.8 (14.8)</td>
<td>125.0 (16.9)</td>
<td>2.1x10^{-74}</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C, mg/dl (SD)</td>
<td>162.0 (36.8)</td>
<td>148.5 (35.1)</td>
<td>125.0 (16.9)</td>
<td>6.3x10^{-23}</td>
<td></td>
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<tr>
<td>SBP, mmHg (SD)</td>
<td>128.1 (15.7)</td>
<td>128.3 (17.1)</td>
<td>125.0 (16.9)</td>
<td>4.9x10^{-12}</td>
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<tr>
<td>DBP, mmHg (SD)</td>
<td>74.8 (10.2)</td>
<td>74.9 (11.3)</td>
<td>73.4 (11.3)</td>
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Non-Lipid and non-blood pressure related baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reference Group</th>
<th>Age (SD)</th>
<th>Women (%)</th>
<th>Weight, lbs (SD)</th>
<th>BMI (SD)</th>
<th>Ever Smoker (%)</th>
<th>Genetic randomization score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>60.1 (6.8)</td>
<td>57.9</td>
<td>168.5 (36.5)</td>
<td>27.5 (5.3)</td>
<td>54.1</td>
<td>110</td>
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<td>60.5 (6.3)</td>
<td>58.1</td>
<td>169.2 (37.1)</td>
<td>27.9 (5.6)</td>
<td>54.5</td>
<td>109</td>
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<td>61.2 (5.9)</td>
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p-values indicate statistical significance.
Causal and Cumulative Effect of LDL-C

N = 14,368 Major Vascular Events

LDL-C Genetic Score

LDL-C Effect Size

LDL-C score below median
-12.1 mg/dL

LDL-C score
-1 mmol/L

Meta-analysis of statin trials
-1 mmol/L

ORMVE (95% CI)

0.783 (0.755-0.812)  P = 3.0x10^-40

0.458 (0.408-0.514)  P_{total} = 8.0x10^-19

0.781 (0.759-0.801)

Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2010; 376:1670-81
Causal and Cumulative Effect of SBP

N = 14,368 Major Vascular Events

Combined Effect of LDL-C & SBP on Cardiovascular Events

N = 14,368 Major Vascular Events

<table>
<thead>
<tr>
<th>SBP Genetic Score</th>
<th>LDL-C Effect Size</th>
<th>SBP Effect Size</th>
<th>OR_{MVE} (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both LDL-C and SBP scores below median</td>
<td>-12.2 mg/dL</td>
<td>-3.1 mmHg</td>
<td>0.542 (0.509-0.577)</td>
<td>9.6 x 10^{-43}</td>
</tr>
<tr>
<td>LDL-C score below median</td>
<td>-12.1 mg/dl</td>
<td>0.2 mmHg</td>
<td>0.758 (0.715-0.804)</td>
<td>1.4 x 10^{-14}</td>
</tr>
<tr>
<td>SBP score below median</td>
<td>0.3 mg/dL</td>
<td>-3.0 mmHg</td>
<td>0.821 (0.779-0.865)</td>
<td>1.8 x 10^{-23}</td>
</tr>
</tbody>
</table>
Effect of 1 mmol/L lower LDL-C & 10 mmHg lower SBP

$OR_{MVE} = 0.139 (0.114-0.170)$
per 1.0 mmol/l lower LDL-C & 10 mmHg lower SBP

$OR_{MVE} = 0.542 (0.509-0.577)$
per 0.31 mmol/l lower LDL-C & 3.1 mmHg lower SBP
Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Δ LDL-C (mg/dL); Δ SBP (mmHg)</th>
<th>OR_{adj} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-12.1; -3.1</td>
<td>0.542 (0.51-0.58)</td>
</tr>
<tr>
<td>Men</td>
<td>-12.5; -2.9</td>
<td>0.56 (0.49-0.62)</td>
</tr>
<tr>
<td>Women</td>
<td>-11.8; -3.2</td>
<td>0.52 (0.46-0.58)</td>
</tr>
<tr>
<td>Age &lt; 55 years</td>
<td>-12.4; -2.5</td>
<td>0.52 (0.44-0.59)</td>
</tr>
<tr>
<td>Age ≥ 55 years</td>
<td>-11.9; -3.4</td>
<td>0.57 (0.52-0.63)</td>
</tr>
<tr>
<td>Never Smokers</td>
<td>-12.3; -3.2</td>
<td>0.58 (0.48-0.68)</td>
</tr>
<tr>
<td>Ever Smokers</td>
<td>-12.3; -2.7</td>
<td>0.51 (0.44-0.59)</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>-11.9; -3.3</td>
<td>0.53 (0.48-0.58)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-12.4; -2.9</td>
<td>0.60 (0.50-0.70)</td>
</tr>
<tr>
<td>LDL-C &lt; 3.5 mmol/L</td>
<td>-11.9; -3.2</td>
<td>0.55 (0.50-0.60)</td>
</tr>
<tr>
<td>LDL-C ≥ 3.5 mmol/L</td>
<td>-12.3; -3.0</td>
<td>0.53 (0.48-0.59)</td>
</tr>
<tr>
<td>SBP &lt; 120 mmHg</td>
<td>-11.9; -2.8</td>
<td>0.54 (0.48-0.60)</td>
</tr>
<tr>
<td>SBP ≥ 120 mmHg</td>
<td>-12.0; -3.3</td>
<td>0.57 (0.50-0.64)</td>
</tr>
</tbody>
</table>
Effect of 10 mmHg lower SBP on rate of rise in SBP with age & HTN

OR (hypertension): 0.182 (0.114-0.170)
Per 10 mmHg lower SBP
p = 3.0x10^-33

6.17 mmHg increase in SBP per decade
p = 3.5x10^-270

76.9% (72.6-81.3%) slower rate of rise
p = 5.1x10^-35

1.42 mmHg increase in SBP per decade
p = 1.0x10^-137
**External Validation**

**CHD: 22,233 cases, 64,762 controls (CARDioGRAM Consortium)**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Effect Size</th>
<th>$\text{OR}_{\text{CHD}}$ (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C genetic score</td>
<td>1 mmol/L lower LDL-C</td>
<td>0.481 (0.43 - 0.54)</td>
<td>7.6 x10^{-38}</td>
</tr>
<tr>
<td>SBP genetic score</td>
<td>10 mmHg lower SBP</td>
<td>0.576 (0.48 - 0.69)</td>
<td>9.9 x10^{-10}</td>
</tr>
</tbody>
</table>

www.cardiogramplusc4d.org
Limitations

• We evaluated the effect of exposure to lower LDL-C and lower SBP not lowering LDL-C or SBP using medications

• Can not evaluate the risk of LDL-C or SBP lowering medication-induced side-effects

• Genetic scores do not identify persons most likely to benefit from LDL-C or SBP lowering
  • Further research is needed to identify persons who are most vulnerable to LDL-C and SBP to determine who would benefit most from early intervention to lower LDL-C, SBP, or both as strategy to personalize the prevention of cardiovascular disease
Conclusions

• LDL-C and SBP have independent, multiplicative and cumulative causal effects on the risk of cardiovascular events

• Because their effects are multiplicative and cumulative over time, long-term exposure to combination of modestly lower LDL-C and SBP has the potential to dramatically reduce the lifetime risk of cardiovascular disease
  • *Even among persons with apparently normal cholesterol and blood pressure*

• Cardiovascular events are largely preventable: the prevention of cardiovascular disease can be substantially improved and simplified by designing prevention programs that promote long-term exposure to combination of lower LDL-C and lower SBP beginning in early adulthood