The Heart Outcomes Prevention Evaluation (HOPE) – 3 Trial: Cognitive & Functional Outcomes

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Rationale

• Cognitive impairment & dementia affect 5-7% of those over 60 years
• Elevated BP associated with cognitive impairment
• Statins linked to short term memory loss in observational studies, but not RCTs
• The HOPE-3 study evaluated BP lowering & rosuvastatin use in 12,705 intermediate CV risk:
  – Statin reduced CV events by 25% in all
  – BP lowering reduced CV events by 24% only in those with hypertension
• We evaluated the effect of these interventions on cognitive & functional decline
Cognitive Questionnaire Completion (Primary Outcome)

Participants 70 years+ invited to complete questionnaires

12,705 Randomized

3,086 ≥ 70 years

2,361 Completed baseline questionnaire

219 Died

2,142 Alive at study end

1,626 Completed baseline & study end questionnaire (76%)
Pre-Stated Outcomes: Cognitive & Functional

• Primary Outcome: Decline in processing speed (Digit Symbol Substitution Test [DSST])

• Secondary Outcomes
  • Decline in executive function (modified Montreal Cognitive Assessment [mMoCA])
  • Increase in psychomotor speed (Trail Making Test Part B [TMT-B])

• Other Outcomes
  – Change in function (functional questions [EQ 5D])
  – Study end: Standard Assessment of Global Activities in the Elderly [SAGE])
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline + Study End</th>
<th>Baseline Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, SD)</td>
<td>74 (±3.5)</td>
<td>75 (±4.1)</td>
</tr>
<tr>
<td>Female</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>140/79</td>
<td>139/79</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dL)</td>
<td>127</td>
<td>128</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Education &gt;12 years</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Caucasian</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Latin American</td>
<td>36%</td>
<td>54%</td>
</tr>
<tr>
<td>Chinese</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>Other Asian</td>
<td>13%</td>
<td>10%</td>
</tr>
</tbody>
</table>
SBP and LDL Changes by Treatment Group

**Placebo**

- Mean Δ BP = 6/2.9 mmHg

**Candesartan/HCTZ**

**Rosuvastatin**

- Mean Δ 24.9 mg/dl
Sensitivity analysis demonstrated similar results.
Change in Cognitive Outcome by Treatment Group

BP Lowering

- **DSST**
  - Baseline vs. Study End BP
  - Plots show decrease in scores
  - BP vs. Pla comparison

- **mMoCA**
  - Baseline vs. Study End BP
  - Plots show decrease in scores
  - BP vs. Pla comparison

- **TMT-B**
  - Baseline vs. Study End BP
  - Plots show increase in scores
  - BP vs. Pla comparison

Cholesterol Lowering

- **DSST**
  - Baseline vs. Study End BP
  - Plots show decrease in scores
  - Rosu vs. Pla comparison

- **mMoCA**
  - Baseline vs. Study End BP
  - Plots show decrease in scores
  - Rosu vs. Pla comparison

- **TMT-B**
  - Baseline vs. Study End BP
  - Plots show increase in scores
  - Rosu vs. Pla comparison
BP Lowering in Key Subgroups

Overall

Age-years

<=72 (Mean=71.0)
72-75 (Mean=73.3)
>75 (Mean=78.1)

P Trend

0.970

SBP-mmHg

<=133.0 (Mean=123.8)
133.0-145.0 (Mean=139.1)
>145.0 (Mean=156.3)

0.078
Rosuvastatin in Key Subgroups

Mean $\Delta$ DSST for Combination Treatment: High SBP and High HDL

<table>
<thead>
<tr>
<th></th>
<th>Double Active</th>
<th>Double Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SBP/High LDL</td>
<td>-4.7 (22.6)</td>
<td>-11.8 (16.5)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Overall

Age-years
- $\leq 72$ (Mean=71.0)
- 72-75 (Mean=73.3)
- $>75$ (Mean=78.1)

LDL-mg/dl
- $\leq 112$ (Mean=88.7)
- 112-140 (Mean=125.7)
- $>140$ (Mean=164.9)
## Treatment Effect by Length of Intervention

### BP Lowering

<table>
<thead>
<tr>
<th>Duration</th>
<th>Active Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>Difference Mean (95% CI)</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yrs</td>
<td>-5.9 (19.8)</td>
<td>-3.2 (18.0)</td>
<td>-2.7 (-6.4, 0.98)</td>
<td></td>
</tr>
<tr>
<td>5-5.5 yrs</td>
<td>-9.7 (19.0)</td>
<td>-6.7 (17.8)</td>
<td>-3.0 (-6.6, 0.63)</td>
<td></td>
</tr>
<tr>
<td>5.5-6.2 yrs</td>
<td>-3.4 (19.3)</td>
<td>-3.6 (21.1)</td>
<td>0.17 (-3.8, 4.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;6.2 yrs</td>
<td>-4.4 (14.4)</td>
<td>-6.3 (15.7)</td>
<td>1.9 (-1.1, 4.8)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

No significant difference in effects of rosuvastatin by duration of treatment
### Functional Outcomes by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>BP</th>
<th>Pla</th>
<th>P</th>
<th>Ros</th>
<th>Pla</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>New functional impairment (EQ-5D)</td>
<td>22%</td>
<td>22%</td>
<td>0.96</td>
<td>21%</td>
<td>23%</td>
<td>0.46</td>
</tr>
<tr>
<td>Overall function at study end (SAGE)</td>
<td>59%</td>
<td>56%</td>
<td>0.19</td>
<td>57%</td>
<td>59%</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Conclusions

- HOPE-3 participants experienced cognitive and function decline over 5.6 years
- BP lowering and rosuvastatin use did not significantly prevent cognitive or functional decline
- Rosuvastatin had no adverse effect on cognitive function
- Subgroup analyses:
  - Trend for benefit in those with highest baseline BP and LDL
  - Longer duration of blood pressure lowering associated with less cognitive decline
  - Both findings require further confirmation
Acknowlegdements


- **Data and Safety Monitoring Board**: D. Sackett (Chair)*, D. DeMets (Chair), C. Baigent, C. Hennekens, J. Mancini


* Deceased

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We thank all participants for their selfless dedication