“First Stroke Reduced 44 Percent by Well Tolerated Medication”

Stroke Outcomes From the Heart Outcomes Prevention Evaluation 3 Study

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Presenter Disclosure Information

Jackie Bosch, PhD
Stroke Outcomes From HOPE-3

FINANCIAL DISCLOSURE:
The study was funded by Unrestricted grants from the Canadian Institutes of Health Research and AstraZeneca

UNLABELED/UNAPPROVED USES DISCLOSURE:
Use of candesartan/HCTZ or rosvastatin for primary stroke prevention
Strategies to reduce the burden of stroke

• >76% are first strokes, often result in permanent disability or death
• To decrease burden, must focus on primary prevention
• BP lowering & statins recommended for those at high-risk; data uncertain for those at moderate or low risk
• Interventions must be safe, easy to administer and monitor and effective
HOPE- 3 Objectives

In an intermediate-risk population without CVD, to evaluate the effects on CV events of:

1. BP lowering with a fixed dose combination of Candesartan 16 mg and HCTZ 12.5 mg daily
2. Cholesterol lowering with Rosuvastatin 10 mg daily
3. Combined BP and cholesterol lowering

Participants received lifestyle advice and necessary therapies
Intermediate-Risk Population

Inclusion Criteria (Target Risk 1.0%/yr)

<table>
<thead>
<tr>
<th>Women ≥ 60 yrs, men ≥ 55 yrs with at least one additional Risk Factor</th>
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</thead>
<tbody>
<tr>
<td>• Increased WHR</td>
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<tr>
<td>• Smoking</td>
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<tr>
<td>• Low HDL-C</td>
</tr>
<tr>
<td>• Dysglycemia</td>
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<tr>
<td>• Mild renal dysfunction</td>
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<tr>
<td>• Family history of CHD</td>
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</tbody>
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Exclusion Criteria:

- CVD or indication(s) or contraindication(s) to study drugs

No strict BP or LDL-C criteria for entry

Uncertainty principle
The HOPE-3 Trial

228 centers in 21 countries
Coordinated by PHRI, Hamilton, Canada

Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, United Kingdom, Ukraine

www.phri.ca
2 by 2 Factorial Design

14,682 Entered Single-blind 4 week Active Run-in
12,705 (87%) Randomized

- **Candesartan 16 mg + HCTZ 12.5 mg**
  - Rosuvastatin
  - Cand+HCTZ
  - Placebo
  - Double Placebo
  - n = 6,356
  - n = 6,349
  - n = 3,180
  - n = 3,176
  - n = 3,168

Simple follow-up and few blood tests
BP Lowering vs. Placebo: SBP Changes

Δ BP = 6.0/3.0 mmHg

Systolic Blood Pressure (mmHg)

<table>
<thead>
<tr>
<th>Years</th>
<th>Cand+HCTZ</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6356</td>
<td>6347</td>
</tr>
<tr>
<td>1</td>
<td>5907</td>
<td>5879</td>
</tr>
<tr>
<td>2</td>
<td>5667</td>
<td>5623</td>
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<tr>
<td>3</td>
<td>5446</td>
<td>5442</td>
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<tr>
<td>4</td>
<td>5213</td>
<td>5186</td>
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<tr>
<td>5</td>
<td>3862</td>
<td>3822</td>
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<tr>
<td>6</td>
<td>1437</td>
<td>1424</td>
</tr>
<tr>
<td>7</td>
<td>350</td>
<td>334</td>
</tr>
</tbody>
</table>
Effects of BP Lowering on Stroke

MI/stroke/CV death: HR (95% CI), 0.93 (0.79-1.10); p=0.40
stroke: HR (95% CI), 0.80 (0.59-1.08); p=0.14

No. at Risk
Candesartan/HCTZ 6356  6292  6235  6155  6038  5042  2111  534
Placebo  6349  6291  6234  6147  6041  5045  2115  505
Effects of BP Lowering on Stroke

**Ischemic**

HR (95% CI), 0.82 (0.59-1.14); p=0.24

**Hemorrhagic**

HR (95% CI), 0.69 (0.32-1.48); p=0.34
Cholesterol Lowering Arm: Change in LDL-C, Apo-B, and CRP

LDL-C (mg/dL)

Placebo
mean Δ 34.6 mg/dl*
Rosuvastatin

APO B (g/L)

Placebo
mean Δ 0.23 g/l*
Rosuvastatin

* P< 0.001
Effects of Rosuvastatin on Stroke

MI/stroke/CV death: HR (95% CI), 0.76 (0.64-0.91); p=0.002
stroke: HR (95% CI), 0.70 (0.52-0.95); p=0.02

Cumulative Hazard Rates

No. at Risk
Rosuv  6361  6308  6259  6176  6069  5074  2132  534
Placebo 6344  6275  6210  6126  6010  5013  2094  505

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE
Effects of Rosuvastatin on Stroke

Ischemic
HR (95% CI), 0.63 (0.45-0.88); p=0.006

Hemorrhagic
HR (95% CI), 1.24 (0.58-2.65); p=0.57
Effects of Combination on Stroke

MI/stroke/CV death: HR (95% CI), 0.71 (0.56-0.90); p=0.005
stroke: HR (95% CI), 0.56 (0.36-0.87); p=0.02

Fatal or disabling stroke: HR (95% CI), 0.55 (0.32-0.95); p=0.03
Effects of Combination on Stroke

**Ischemic**
HR (95% CI), 0.53 (0.33-0.85); p=0.008

**Hemorrhagic**
HR (95% CI), 0.83 (0.25-2.72); p=0.75
HOPE-3 Stroke Results

1. No statistically significant effect of candesartan 16 mg + HCTZ 12.5 mg daily
   - Trend for fewer events for both ischemic and hemorrhagic

2. 30% stroke reduction with rosuvastatin 10 mg daily
   - Larger effect than expected
   - Differed for ischemic vs. hemorrhagic strokes

3. 44% stroke reduction with combination
   - NNT for 1 year to prevent 1 stroke = 714
HOPE-3 Stroke Conclusions

- Use of these well tolerated, simple to implement therapies has the potential to prevent 44% of first strokes

- The Public Health implications will require debate and consideration by guideline writers