Semaglutide Treatment Effect On Coronary Atherosclerosis Progression In Diabetes: STOP Randomized Control Trial

Matthew J Budoff MD
Professor of Medicine, UCLA
Endowed Chair of Preventive Cardiology
Los Angeles, California, USA
BACKGROUND

➢ GLP1 receptor agonists have shown significant cardiovascular (CV) risk reduction in type 2 diabetes.

➢ In preclinical studies, mouse models have demonstrated the favorable effect of GLP1R agonists on atherosclerosis.

➢ Reaven et al demonstrated no slowing of carotid atherosclerosis in an in-vivo model using exenatide vs placebo over 18 months.
CARDIOVASCULAR OUTCOME TRIALS

- Beneficial effects of GLP1 receptor agonists has been demonstrated in multiple cardiovascular outcome trials in patients with type 2 diabetes, including two with semaglutide
  - SUSTAIN 6
  - PIONEER 6
Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes

➢ STOP study evaluated the effect of semaglutide on atherosclerosis in type 2 diabetes utilizing coronary computed tomography angiography (CCTA)

HYPOTHESIS

➢ Semaglutide will reduce progression of non-calcified coronary atherosclerotic plaque volume as measured by serial coronary CTA as compared to placebo in persons with diabetes.
Major Inclusion Criteria

- Age ≥40 years of age at the time of the initial screening visit.

- Men or women with type 2 diabetes with a glycated hemoglobin level of 7.0% or more.

- Diagnosis of T2DM in accordance with American Diabetes Association (ADA) guidelines and with at least one cardiovascular risk factor (hypertension, high cholesterol, family history of premature heart disease or past/current smoking) or prior ASCVD.

Major Exclusion Criteria

- History of type 1 diabetes mellitus.

- Recent ASCVD Event (stroke, heart attack, ACS or revascularization) within 3 months (90 days) of the screening visit.

- Renal insufficiency (calculated creatinine clearance of <50 ml per minute).
Primary Outcome

• The primary endpoint is the rate of change in the volume of total noncalcified plaque as evaluated by CCTA.

Secondary Outcome

• Rate of change in volume of various plaque components, including total plaque volume, calcified plaque, fibrofatty plaque, fibrous plaque and low attenuation plaque
**STUDY DESIGN**

**SUBJECT ENROLLMENT**

Endocrinology & Cardiology Clinics

Patients with type 2 diabetes with at least 1 CV risk factor or prior ASCVD

Visit 1

- Consent
- Screening
- H&P
- Baseline blood tests

**1:1 RANDOMIZATION**

Semaglutide SQ

**Versus**

Placebo SQ

**BASELINE CCTA**

52 Weeks Follow up

**FOLLOW UP CCTA**

**POST -Trial PERIOD**

- Blood tests
- Quantitative plaque analysis
- 30 days phone follow up

*Hamal et al Cor Art Dis 2020*
Statistical Analysis

- Univariable analysis and multiple linear regression were used to examine the change in plaque volumes between the cohorts.
- Multivariable analysis, after adjustment for baseline plaque and cardiovascular (CV) risk factors, was performed.

Power Calculation

- Assuming an average of 1.7 measurable plaques per patient, with intra-patient plaque correlation of 0.24, 110 patients would provide power of 0.80 and a two-sided type 1 error of 0.048 to detect an 8% difference in plaque volume between the active and placebo groups.
**Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes**

**TRIAL PROFILE**

- **STOP Trial**
  - Subjects Screened: n=168
  - Screen Failed: n=28
  - Randomized Subjects: n=140

- **Semaglutide**
  - n=70
    - Lost to follow up: n=6
      - Death: n=2
      - 2nd visit CAC only, due to high creatinine, n=1
  - Drug Subjects Completed: n=61

- **Placebo**
  - n=70
    - Lost to follow up: n=9
      - Death: n=2
    - 2nd visit CAC only, due to high creatinine, n=1
  - Drug Subjects Completed: n=58

- Total Subjects Completed: n=119

**Sponsored by**

- **Harbor-UCLA Medical Center**
- **The Lundquist Institute**
- **Novo Nordisk**
Baseline Characteristics at Randomization

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Semaglutide</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1 ± 8.5</td>
<td>56.7 ± 7.7</td>
<td>0.341</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>30.3 ± 5.7</td>
<td>34.0 ± 7.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Male (%)</td>
<td>39 (64)</td>
<td>35 (60)</td>
<td>0.687</td>
</tr>
<tr>
<td>Hispanic / Latino</td>
<td>36 (59)</td>
<td>37 (64)</td>
<td>0.593</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.483</td>
</tr>
<tr>
<td>White (%)</td>
<td>44 (72)</td>
<td>43 (74)</td>
<td></td>
</tr>
<tr>
<td>Asian (%)</td>
<td>11 (18)</td>
<td>9 (16)</td>
<td></td>
</tr>
<tr>
<td>Black or African American (%)</td>
<td>5 (8)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Time (years)+</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.5</td>
<td>0.848</td>
</tr>
</tbody>
</table>
Baseline Characteristics at Randomization

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Semaglutide</th>
<th>Placebo</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>43 (70)</td>
<td>45 (78)</td>
<td>0.378</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>52 (85)</td>
<td>45 (78)</td>
<td>0.282</td>
</tr>
<tr>
<td>Family History of CAD (%)</td>
<td>13 (21)</td>
<td>14 (24)</td>
<td>0.675</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>8 (13)</td>
<td>8 (14)</td>
<td>0.914</td>
</tr>
<tr>
<td>Past Smoker (%)</td>
<td>22 (36)</td>
<td>27 (47)</td>
<td>0.245</td>
</tr>
</tbody>
</table>
### Baseline Characteristics at Randomization

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Semaglutide</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Plasma Glucose, mg/dL</td>
<td>198.4 ± 56.5</td>
<td>212.2 ± 60.1</td>
<td>0.199</td>
</tr>
<tr>
<td>Hemoglobin A1C %</td>
<td>8.5 ± 1.8</td>
<td>9.0 ± 2.1</td>
<td>0.197</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>146.3 ± 68.5</td>
<td>135.6 ± 63.0</td>
<td>0.956</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>39.6 ± 10.6</td>
<td>39.2 ± 10.5</td>
<td>0.864</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>73.9 ± 32.5</td>
<td>78.6 ± 30.8</td>
<td>0.422</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.6 (0.6, 5.4)</td>
<td>2.3 (0.9, 4.3)</td>
<td>0.299</td>
</tr>
</tbody>
</table>
Results- Mean Change in Glucose and HbA1c

- Fasting Plasma Glucose levels (mg/dl)
  - Semaglutide: -40, Placebo: 0
  - Semaglutide: -30, Placebo: 0
  - Semaglutide: -20, Placebo: 0
  - Semaglutide: -10, Placebo: 0
  - Semaglutide: 0, Placebo: 0

- HbA1c (%)
  - Semaglutide: -0.9, Placebo: -0.7
  - Semaglutide: -0.5, Placebo: -0.2
  - Semaglutide: 0, Placebo: 0
  - Semaglutide: -0.9, Placebo: -0.7

Sponsored by

- Semaglutide
- Placebo
Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes

**PRIMARY ENDPOINT AND KEY SECONDARY ENDPOINTS**

<table>
<thead>
<tr>
<th>Component</th>
<th>Semaglutide</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Non-Calcified Plaque</td>
<td>9.9</td>
<td>10.7</td>
<td>0.74</td>
</tr>
<tr>
<td>Calcified Plaque</td>
<td>15</td>
<td>12.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Fibrous</td>
<td>9.2</td>
<td>9.9</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Sponsored by

**Sponsored by**
Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes

Results - Conversion of Plaque from Non-Calcified to Calcified?

<table>
<thead>
<tr>
<th></th>
<th>Semaglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Non-Calcified</td>
<td>9.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Calcified</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

No Statin | Statin

\[ p < 0.001 \]
CONCLUSIONS

• Semaglutide was not associated with significant reduction in plaque volumes as compared to placebo over 1 year

• It is possible the effect size is smaller than anticipated and thus the trial was underpowered

• In exploratory analysis, there was a greater conversion from non-calcified to calcified plaque, which may represent ‘stabilization’, which has been shown to be a mechanism of benefit of such therapies such as statins

• Further pre-specified analyses for: Advanced Plaque Metrics, LV mass, liver fat, bone density and epicardial fat are ongoing
ACKNOWLEDGEMENTS

The Study Team
THANK YOU