#AHA22

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

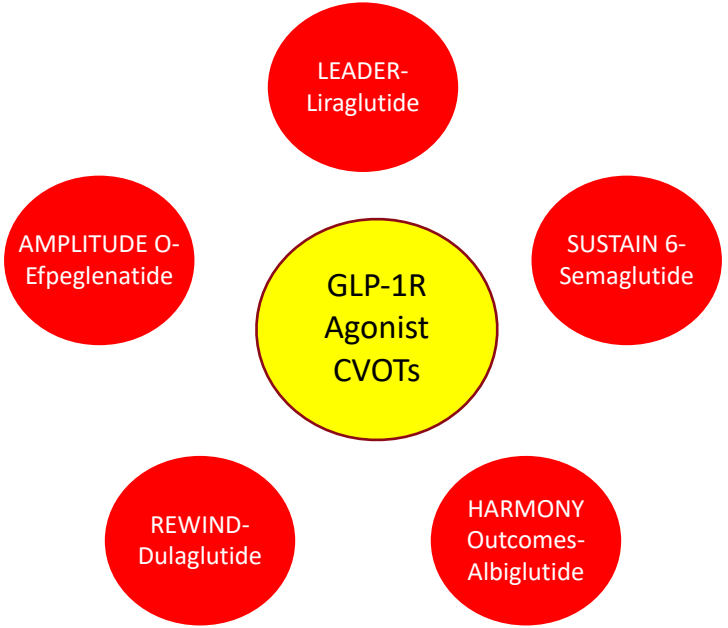
American Heart Association.

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

- 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.

STOP

Randomized Controlled Trial

THE LUNDQUIST INSTITUTE
Research with reach.

Harbor-UCLA MEDICAL CENTER

Sponsored by novo nordisk®

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

Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes STOP

STUDY DESIGN

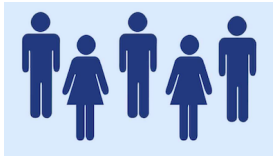
SUBJECT ENROLLMENT

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

THE LUNDQUIST INSTITUTE
Research with reach.

Harbor-UCLA MEDICAL CENTER

Sponsored by novo nordisk®

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

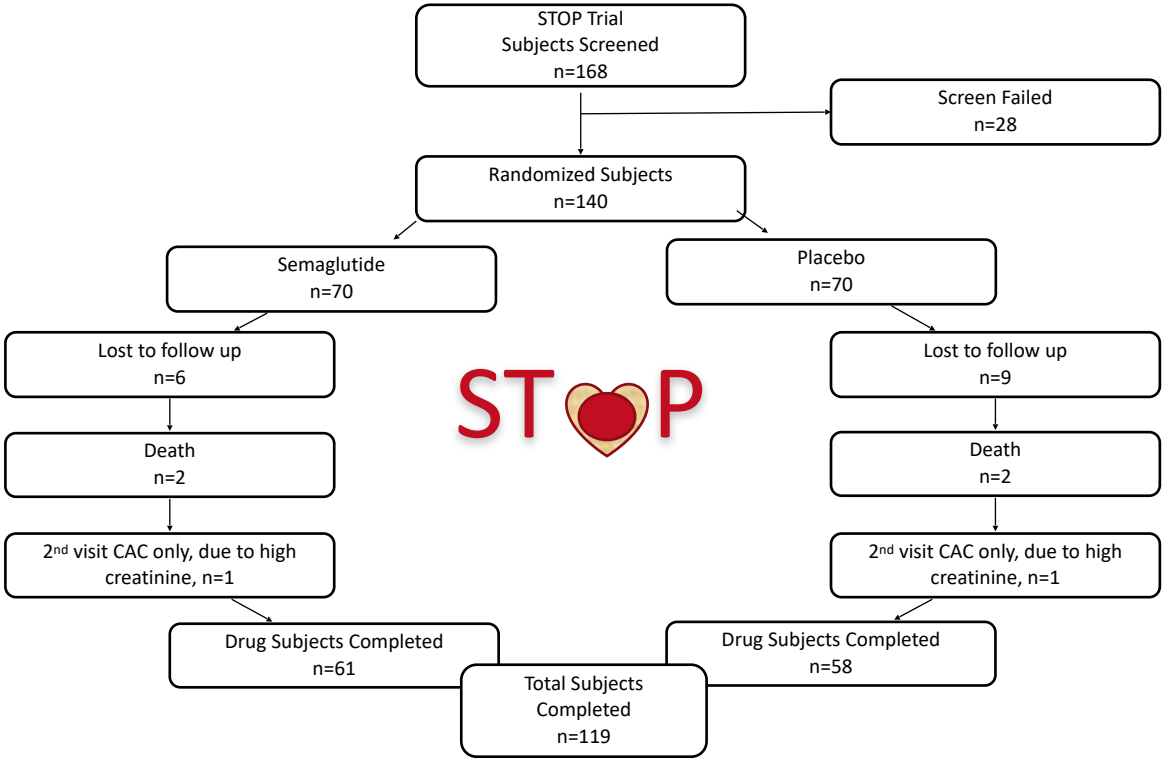
Power Calculation

- 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 STOP

American Heart Association.

TRIAL PROFILE



THE LUNDQUIST INSTITUTE
Research with reach.

Harbor-UCLA MEDICAL CENTER

Sponsored by

novo nordisk®

Baseline Characteristics at Randomization

	Semaglutide	Placebo	P- value
Demographics	n=61	n=58	
Age (years)	58.1 ± 8.5	56.7 ± 7.7	0.341
Body Mass Index (kg/m²)	30.3 ± 5.7	34.0 ± 7.4	0.002
Male (%)	39 (64)	35 (60)	0.687
Hispanic / Latino	36 (59)	37 (64)	0.593
Race			0.483
White (%)	44 (72)	43 (74)	
Asian (%)	11 (18)	9 (16)	
Black or African American (%)	5 (8)	5 (9)	
Other (%)	1 (2)	1 (2)	
Follow-up Time (years)+	1.1 ± 0.5	1.1 ± 0.5	0.848

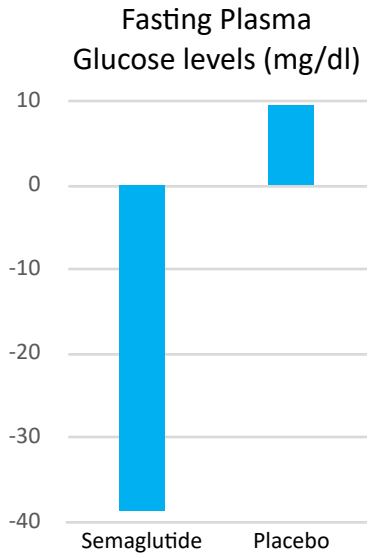
Baseline Characteristics at Randomization

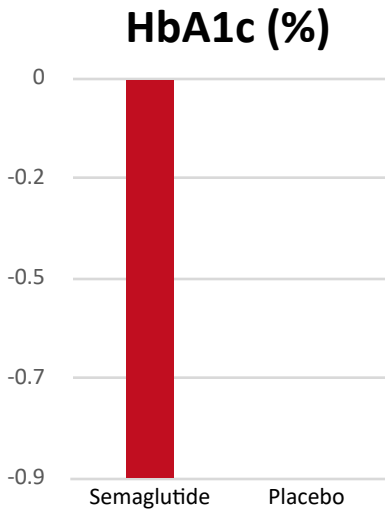
Risk Factors	Semaglutide	Placebo	P- value
Hypertension (%)	43 (70)	45 (78)	0.378
Hyperlipidemia (%)	52 (85)	45 (78)	0.282
Family History of CAD (%)	13 (21)	14 (24)	0.675
Current smoker (%)	8 (13)	8 (14)	0.914
Past Smoker (%)	22 (36)	27 (47)	0.245

Baseline Characteristics at Randomization

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

Results- Mean Change in Glucose and HbA1c



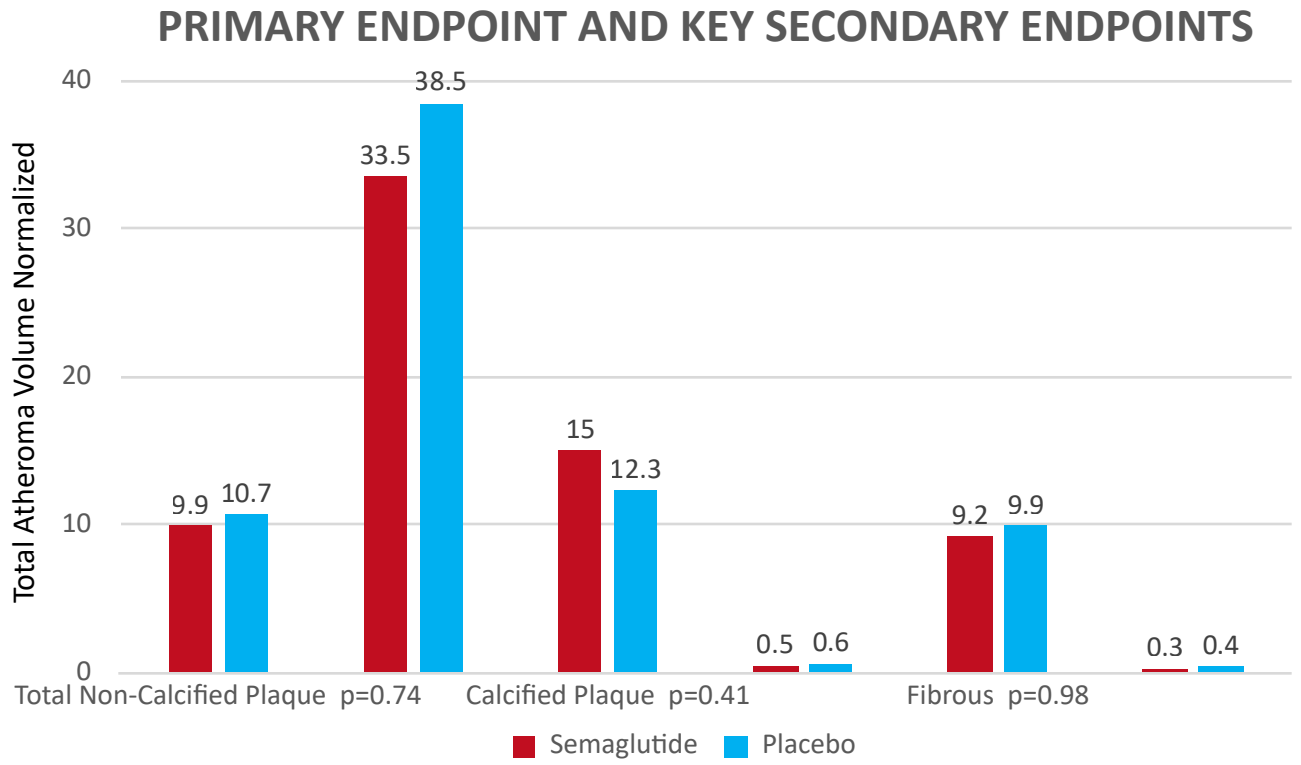


Semaglutide Placebo

Semaglutide Treatment Effect on Atherosclerosis Progression in Diabetes

ST P

American Heart Association.



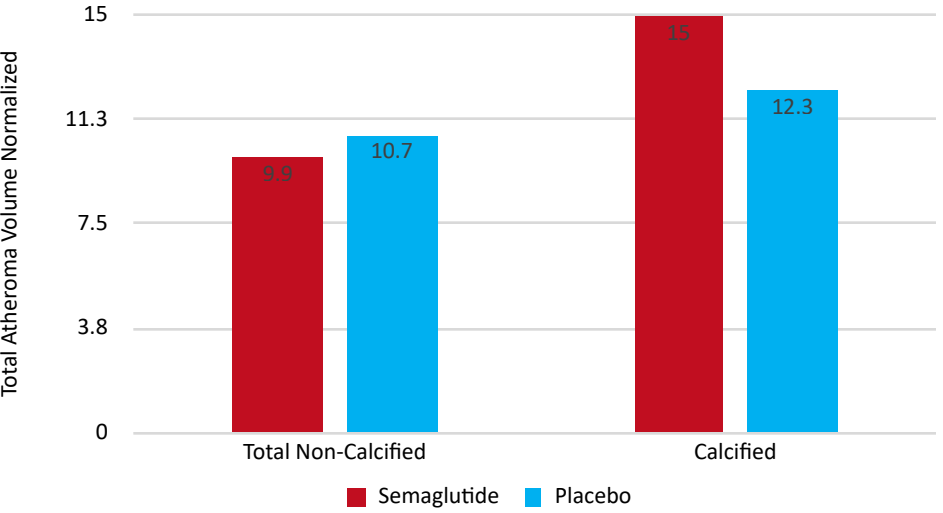
THE LUNDQUIST INSTITUTE
Research with reach.

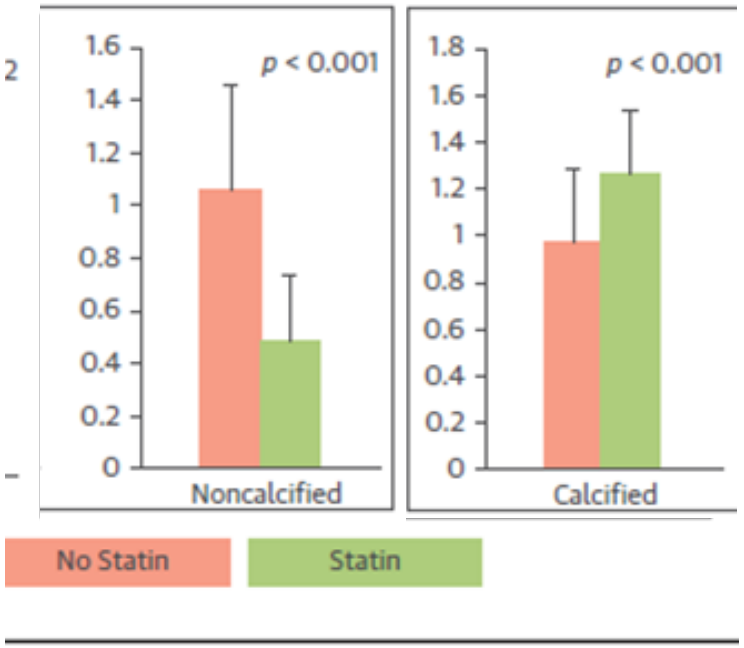
Harbor-UCLA MEDICAL CENTER

Sponsored by

novo nordisk®

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





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

Sponsored by

THE LUNDQUIST INSTITUTE
Research with reach.

Harbor-UCLA MEDICAL CENTER

THANK YOU

American Heart Association.

Scientific Sessions

#AHA22