Title

Effect of semaglutide on coronary atherosclerosis progression in patients with type II diabetes: rationale and design of the semaglutide treatment on coronary progression trial.

Journal

Coronary Artery Disease, 31(3)

ISSN

0954-6928

Authors

Hamal, Sajad
Cherukuri, Lavanya
Shaikh, Kashif
et al.

Publication Date

2020-05-01

DOI

10.1097/mca.0000000000000830

Peer reviewed

Effect of Semaglutide on Coronary Atherosclerosis Progression in patients with type II diabetes: Rationale and design of the STOP (Semaglutide Treatment On coronary Progression) ~~study~~Trial

Sajad Hamal, Lavanya Cherukuri, Kashif Shaikh, Matthew J Budoff

Corresponding Author:

Matthew J Budoff MD

Los Angeles Biomedical Research Institute

1124 W Carson Street

Torrance CA 90502

(310) 222 4107

Fax (310) 782-9852

mbudoff@labiomed.org

Abstract:

Cardiovascular morbidity and mortality is a major burden in patients type 2 diabetic mellitus (T2DM). In a landmark study, semaglutide (an injectable GLP-1 receptor (GLP-1R) agonist) has been shown to significantly reduce cardiovascular (CV) events, however the mechanism of benefit is still unknown. ~~FDA regulated that all the diabetic medications have a cardiovascular (CV) trial to assess the safety. Semaglutide has been shown to reduce CV events.~~ The objective of this randomized, double-blind, placebo-controlled study is to evaluate the effect of semaglutide on coronary atherosclerotic plaque progression. The primary endpoint of the study is to assess the quantitative change in non-calcified plaque volume measured by multidetector computed tomography angiography over 1 year. Secondary endpoints include quantitative changes in different coronary plaque types and morphology in type 2 diabetes mellitus (T2DM)~~ics~~. Furthermore, we will evaluate the relationship

between plaque changes and atherosclerotic burden and plaque vulnerability over the course of 1 year in persons with T2DM.

Introduction:

Cardiovascular disease (CVD) is the principal cause of morbidity and mortality in type 2 diabetes. According to the American College of Cardiology, adults with diabetes are two to four times more likely to have heart disease or a stroke than adults without diabetes (1). Treatment of this disease is challenging and expensive, involving multiple classes of antidiabetic medications. The most recent Centers of Disease Control and Prevention (CDC) data report states that there are 30.3 million Americans with type 2 diabetes (T2DM), with 7.2 million underdiagnosed (2). This disease costs more than $327 billion per year with $237 billion in medical costs and $90 billion in lost productivity. (3).

ADOPT (A Diabetes Outcome Progression Trial) trial evaluated the A1c changes over a 5yrs period using monotherapy with Metformin, Glyburide or Rosiglitazone. (4) The increased risk of CV events with Rosiglitazone after the ADOPT Trial ~~made~~ led to changes in policy with the Food and Drug Administration (FDA) to regulate that all diabetic medications have a cardiovascular trial to assess their safety. (5)

There are multiple classes of medications available to treat type 2 diabetes with the goal of achieving an optimal hemoglobin A1C. However, very little is known concerning the relative effectiveness of the different classes of antidiabetic medications to promote or retard the progression of atherosclerosis in type 2 diabetes. This information is critical if physicians are to reduce the primary cause of death in diabetic patients. Recent trials have shown that liraglutide (glucagon like peptide 1 analogue) and empagliflozin (selective inhibitor of sodium- glucose cotransporter 2) significantly reduced~~tion of CV~~ deaths ~~from cardiovascular causes~~ in patients with T2DM ~~type 2 diabetes mellitus~~ who were at risk of cardiovascular events. (8,6)

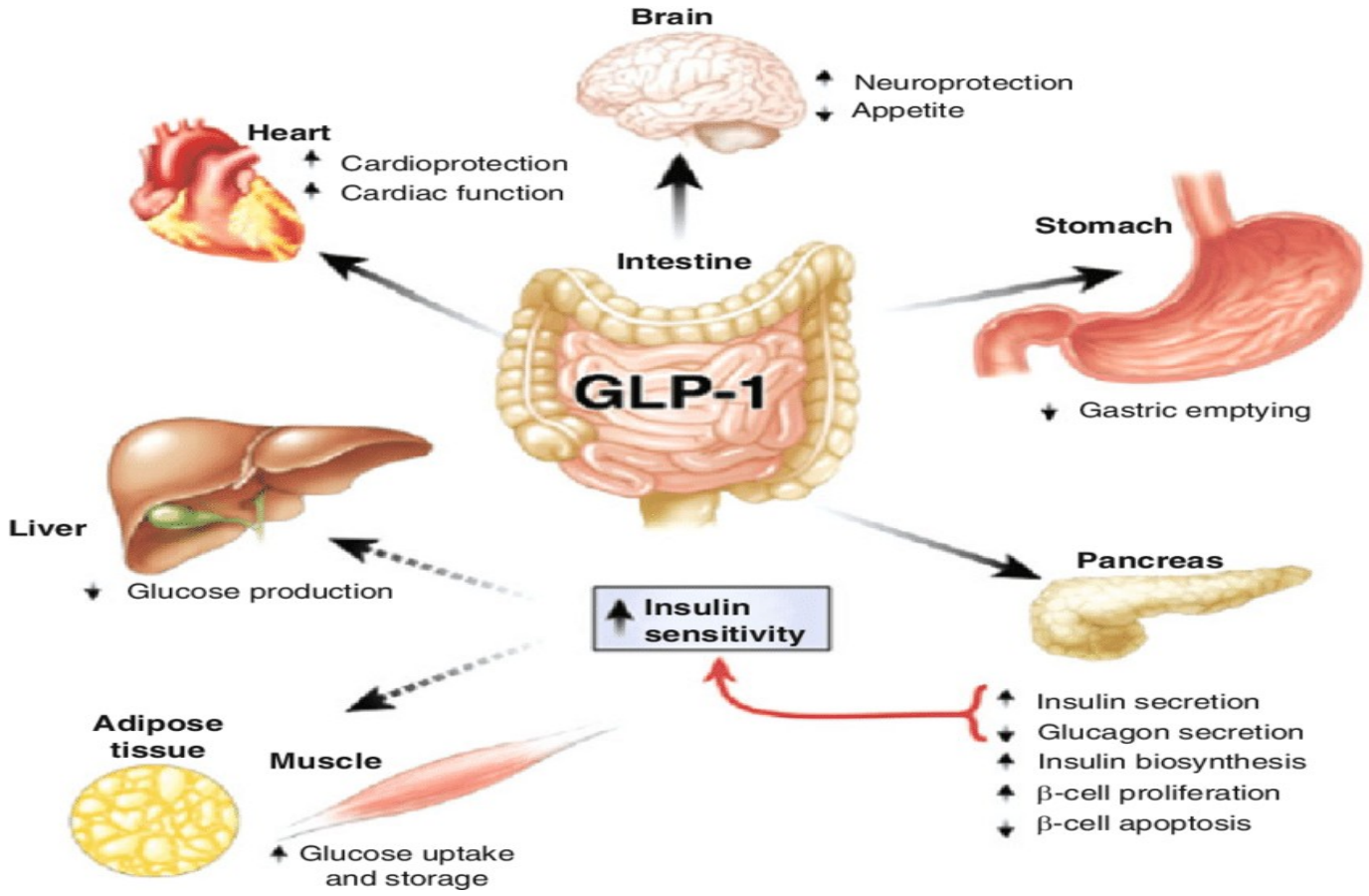


Figure 1: Effects of GLP-1 on specific tissues.

Injectable GLP-1 receptor (GLP-1R) agonists mimic endogenous GLP-1 by stimulating pancreatic insulin secretion with a low risk of hypoglycemia and cause significant weight loss by reducing appetite (figure 1). (7,10) Semaglutide, a newer GLP1 analogue, which has an extended half-life of 1 week, has proven to reduces the cardiovascular mortality in ~~diabetics~~ T2DM by SUSTAIN-6 (semaglutide and cardiovascular outcomes in patients with T2DM) trial. (6) Limited preliminary data suggest a marked difference in the rate of coronary atherosclerosis progression with different classes of

antidiabetic medications (9), but no randomized ~~comparison~~ clinical trials have been reported with the ~~most commonly prescribed~~ newest classes of antidiabetic medications. This information is critical for both the type 2 diabetic patients and their physicians if the treatment is to be optimized to reduce cardiovascular morbidity and mortality. Our study will provide this needed mechanistic information to better understand the CV benefits, which will have a major impact on the diabetes care of millions of Americans.

The objective of the study is to evaluate the effects of Semaglutide on reducing the progression of atherosclerotic plaque, measured by multidetector computed tomography angiography (MDCTA) over 1 year. With its ~~volumetric~~ quantitative nature, MDCTA well suited to evaluate the presence, extent, and severity of coronary atherosclerotic plaque burden and progression. We will evaluate this effect in the context of statin use, glycemic control, microvascular disease and cardiovascular risk factors.

Methods:

Study Design:

This study is a single centered, randomized, double-blinded, placebo-controlled trial being conducted at Los Angeles Biomedical Research Institute, California in the United States (NCT……). Eligible patients will be randomly assigned to semaglutide 2mg/1.5 ml (1.34 mg/ml) prefilled pen for SC injection or placebo

1.5 ml, pen-injector for SC injection in a 1:1 fashion as an add-on to their standard of care. Patients will be followed for 12 months, with a phone call 30 days after medication discontinuation.

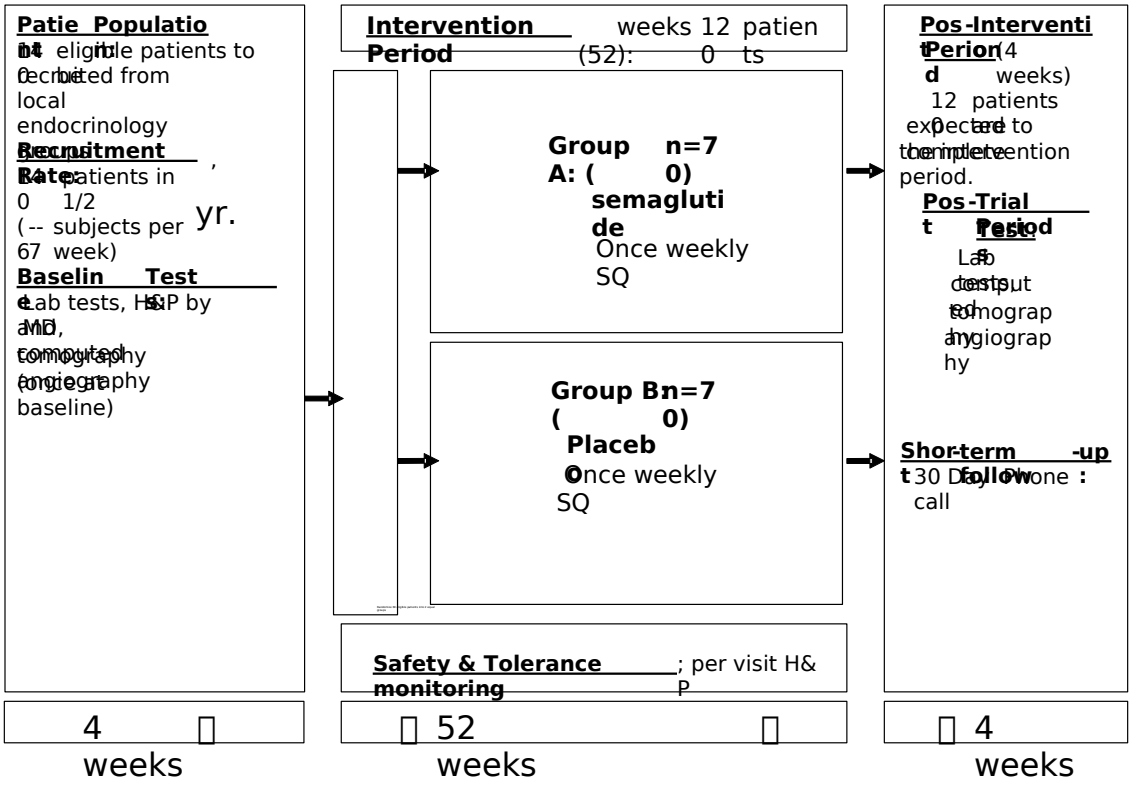
After randomization, semaglutide or placebo will be introduced at a dose of 0.25 mg/weekly. A fixed dose-escalation procedure will be used, with a starting dose of 0.25 mg for 1 month that is escalated to 0.5 mg as per protocol in SUSTAIN-6. After an additional 4 weeks, the dosage will be increased to 1 mg once weekly. Dose increase period can be extended based on the subject's tolerance to the trial product. If the maximum dose of 1 mg once weekly is not tolerated or otherwise associated with unacceptable adverse events, reduction in the dose to 0.5 mg/week is allowed at the investigator's discretion. Subjects unable to tolerate 0.5 mg/week will be dropped from the study. Injection can be done at any time of the day and irrespective of meals. It will be recommended that the time of injection is consistent from one injection to another.

If a subject misses a dose of investigational product during the trial, they will be instructed to take it as soon as possible within 5 days after the missed dose. If more than 5 days have passed, they will be instructed to skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. Subjects should be instructed not to "make-up" for the missed dose by taking a double dose at the same time. The day of weekly administration can be

changed if necessary, as long as the time between two doses is at least 2 days (> 48 hours).

Baseline examination will include the results of their demographics, physical examination and an evaluation of blood pressure, height, weight and laboratory blood testing. All participants will be educated on an ADA diet at entry to the study. Baseline information regarding risk factors for atherosclerotic cardiovascular disease (cigarette smoking status, systemic hypertension, family history of premature atherosclerosis, menopausal and hormone replacement status in women, sedentary lifestyle, current medications, chest pain questionnaire and measures of obesity) will be determined. CCTA, using state-of-the-art MDCTA technology, will be used to evaluate coronary plaque volume/composition. The evaluations of plaque using CCTA will be repeated at month 12. Adverse events will be monitored throughout the study. The study schematic is shown in Figure **2**.

Figure 2: Study Schematic



Study population:

Inclusion and exclusion criteria were included in Table 1. The eligible patients will be age ≥ 40yrs with HbA1c ≥ 7 or more and coronary atherosclerosis (narrowing ≥ 20% in 1 coronary artery) by Cardiac Computed Tomography Angiography (CCTA).

Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria
• Men or women with type 2 diabetes with a glycated hemoglobin level of 7.0% or more drug naïve or treated with oral agents and/or basal insulin. For patients on basal insulin at entry, the PI will consider dose reduction of basal insulin according to A1c and risk for hypoglycemia. Patients on SGLT-2 inhibitors may be screened but the agents must be discontinued at least 30 days prior to randomization. • Age $\geq$ 40 years of age • Patients with a 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 (prior stroke, TIA, claudication, coronary artery disease) • Written informed consent
Exclusion Criteria
• History of type 1 diabetes mellitus • History of ketoacidosis. • Current use of GLP-1–receptor agonists or use of a GLP-1 receptor agonist within 3 months of screening • Current Use of SGLT-2 inhibitors within 30 days of screening • Patients on prandial insulin or using an insulin pump or pramlintide. • History of one or more severe hypoglycemic episodes within 6 months of Screening (V1) or a severe hypoglycemic episode occurring during the interval between the Screening visit (V1) and randomization. • Patients experiencing a cardiovascular event (e.g., myocardial infarction or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit (V1) and randomization. • Recent ASCVD Event (stroke, heart attack, ACS or revascularization) within 3 months (90 days) of the screening visit (VI). • Undergoing any cardiovascular surgery (e.g., valvular surgery) within 3 months (90 days) of the Screening visit (V1). • Any planned coronary revascularization or peripheral intervention procedure or other cardiovascular surgery. • History of New York Heart Association (NYHA) Class III or IV heart failure at the Screening visit (V1). • Renal insufficiency (calculated creatinine clearance of <50 ml per minute, MDRD equation). • AST or ALT >2 X the upper limit of normal (ULN) at the Screening visit (V1), or a total bilirubin >1.5 X the ULN unless the subject has a history of Gilbert's. • Weight in excess of 325 pounds • Resting hypotension (systolic blood pressure of <90mmHg) or resting hypertension (systolic blood pressure of >170mmHg or diastolic blood pressure of >110 mmHg) • History of malignancy ≤5 years prior to signing informed consent • Pregnancy • Currently enrolled in another placebo-controlled trial. • Family or history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC) • History of non-familial medullary thyroid carcinoma. • Known or suspected hypersensitivity to trial products.

Study endpoints

Primary Endpoint

- The primary objective of study is to assess the quantitative change in non-calcified plaque volume over 1 year.

Secondary Endpoints

- Assess incident plaque rates and quantitative changes in different plaque types including calcified and different forms of non-calcified atherosclerosis including fibrous, fibrous-fatty, and low attenuation plaque in patients with type 2 diabetes who are on a standard of care regimen receiving once-weekly semaglutide or placebo with CCTA, 12 months after an initial evaluation.
- Evaluation of plaque progression rates and incident plaque rates in subjects treated with semaglutide and placebo. In that context, we will determine whether subjects treated with semaglutide display slower rates of progression compared to placebo treated subjects, after control for all CV risk factors, diabetes control, concomitant medications and demographics

Statistical Design and Analysis

The primary outcome will be the intention to treat per-subject rate of change in the coronary atherosclerotic burden. CCTA outcomes obtained at the end-of-treatment will be compared between treatment groups as described above: 1) primary CCTA measures – non-calcified plaque volume change over time; and, 2) secondary CCTA measures – individual components of plaque including low attenuation, fibro-fatty, fibrous and calcified plaques. CAC measures, as a secondary outcome, will include presence of any CAC (dichotomous variable) and CAC score, as well as changes in LV mass between assignment groups. General linear models (GLM) will be used, specifying these CCTA and CAC measures as dependent variables. The baseline measures of the same outcomes (CAC and CCTA outcomes) will be included as covariates. To account for the fact that the end-of-treatment visit will differ across subjects, indicator variables for the study visit at which the CAC and CCTA measures were obtained will also be included as covariates

The primary analysis will compare the semaglutide group to placebo group (Objective 1). Accounting for the comparison, conservative sample size calculations can be obtained at the nominal two-sided alpha level of 0.05.

For sample size determination, the following assumptions on the efficacy variable of the changes in non-calcified plaque from baseline are considered:

- A standard deviation of 6 mm^3 for the primary variable
- A treatment difference of at least 12 mm^3 in non-calcified plaque in favor of semaglutide vs. placebo

Allowing for 15% dropouts, a total sample size of 140 participants (120 after dropout), consisting of final of 60 subjects each in the semaglutide and placebo group, provides 0.898% power at level 0.05.

In the field of atherosclerosis progression imaging (with intravascular ultrasound, computed tomographic angiography or coronary artery calcification), the primary outcome is a statistical difference between groups, suggesting that the intervention slows atherosclerosis compared to the control arm. Prior studies using CCTA have ranged in size from 40 to 140 participants, each showing significant differences between arms. Studies have included statins (40 and 100 persons), anti-inflammatories (54 persons), garlic therapy (55 persons) and testosterone (140 persons) (6, 8-10). New studies with novel oral anti-coagulants have each shown differences in randomized studies performed by the core lab at LA BIOMED, with total sample sizes of 66 and 120 respectively, each demonstrating significant differences between active agent and placebo. Each study demonstrated a statistically significant difference between groups, and the effect size varied from 24-40 mm^3. Thus, to be conservative, we are powering this study with an effect size of 12 mm^3, to ensure that if differences in rates of progression are occurring, we will be well powered to visualize those changes.

Compliance

After randomization, participants will return at 1 month for titration of medication, then quarterly (months 3, 6, 9 and 12 months to assess compliance with medication, and receive an additional supply of medicine. Between 3-month visits, we will have an inter-trial phone visit to ensure improved study medication adherence and compliance during dose escalation and maintenance.

Ethical considerations and study organization

The current study is being conducted in compliance with Institutional Review Boards (IRB)/Institutional Ethics Committees (IEC), the principles of the Declaration of Helsinki, the International Conference on Harmonisation (ICH), Good Clinical Practice guidelines (GCP), Code of Federal Regulations (CFR) and relevant local laws and regulations. All patients will provide written informed consent. The Data Safety Monitoring Board will meet at 6-month intervals to monitor study progress, safety, and efficacy. All personnel will follow our institution standard operations Procedure “SOP: Informed Consent Process for Research (HRP-090)”

Study status

As of June 2019, t~~T~~**he study was approximately 30% enrolled with an estimated** ~~study~~ enrollment **completion by first quarter of 2020**, and end of study by first quarter 2021**.**

Discussion

Our study protocol is a natural extension of the results of LEADER (liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results) and SUSTAIN 6. This study provides an opportunity to evaluate the anti-atherogenic potential of semaglutide, providing a mechanism of CV benefit. We will randomize patients with type 2 diabetes who are on a standard of care regimen (similar to LEADER and SUSTAIN 6, table 2) to receive once weekly semaglutide or placebo. This is crucial to our understanding of DM treatment and CVD, since plaque progression portends worse outcomes in these populations. (1,9) While CVD represents a critical source of morbidity and mortality, there exist few data to support the preference of any specific glucose-lowering regimen to prevent these complications. Furthermore, proof of slowing atherosclerosis could have specific applications for certain regimens in those persons with co-existent ASCVD and DM. The focus on individual demographic, clinical, and plaque factors that may influence a differential coronary plaque response to medications will add to our understanding of therapy for T2DM. The major aim of this study is to assess the impact of semaglutide on coronary artery atherosclerosis progression.

	Treatment / Guideline
Blood glucose	HbA1c ≤7.0% (individualized depending on patient) If >7.0%, additional HbA1c measurement after 3m. If HbA1c still >7.0%, treatment should be intensified to achieve target if appropriate
Therapy	Lifestyle modifications and metformin are considered foundational therapy in most countries Add-on therapy: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed) Insulin therapy: should be based on local practice, including basal, basal/bolus, premix, and mealtime bolus
Blood pressure	Target: 130/80 mm Hg
Antihypertensive therapy	First line: ACE inhibitors or ARBs Based on individual patient needs: Ca2+ blockers, diuretics, others
Lipids	Target LDL: <100 mg/dL (<70 mg/dL in patients with previous cardiovascular events) Statins: recommended for all patients Second-line therapy: investigator discretion
Antiplatelet therapy	Aspirin or clopidogrel (if aspirin intolerant) for patients with prior cardiovascular events (MI, CVA, or revascularization)

HbA1c: glycated hemoglobin; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; MI: myocardial infarction; CVA: cerebrovascular accident

Table 2. Standard of Care Regimen

In the LEADER trial, 9340 patients with type 2 diabetes at high CV risk were randomized to receive the longer-acting drug liraglutide 1.8 mg (or maximum tolerated dose) or matching placebo once daily and followed for a median of 3.8 years.(11) There was a 13% statistically significant ($P < 0.001$ for noninferiority, $P < 0.01$ for superiority) reduction in the primary end point, including a 22% reduction cardiovascular mortality ($P = 0.007$) and 15% reduction in total mortality ($P = 0.02$). (11) Other evaluations of longer-acting GLP-1R agonists include semaglutide, once-weekly exenatide, and dulaglutide. (12) The long-term cardiovascular outcomes of semaglutide were investigated in the SUSTAIN-6 trial, which recruited 3297 patients with type 2 diabetes, of whom 83% had established CVD. Two

dosage levels of 0.5 and 1.0 mg of semaglutide and placebo once weekly were compared in addition to conventional therapy. (13,14) During a 2.1-year median follow-up, the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke occurred in 6.6% of patients in the semaglutide group and in 8.9% in the placebo group (HR = 0.74; 95% CI, 0.58–0.95; P < 0.001 for noninferiority, P = 0.02 for superiority). (15)

The US Food and Drug Administration (FDA) has approved Victoza® (liraglutide) injection 1.2 mg or 1.8 mg to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established CVD. (16,17) There is also robust myocardial infarction and stroke reduction seen in SUSTAIN-6 (26 and 39% respectively) that further enhances the likelihood that this effect is likely related to effects on atherosclerosis. Recently, the FDA approved Ozempic® (semaglutide) as well to improve the cardiovascular outcomes in T2DM. (6,18) The clear reduction in end points in the LEADER and SUSTAIN trials, may represent an anti-atherosclerotic effect of the GLP-1R agonists, liraglutide and semaglutide. (19,20) To further elucidate the mechanism of hypothesized anti-atherosclerotic effect of semaglutide, our current study will evaluate the association between pre and post treatment MDCTA (changes in plaque components, stenosis and coronary calcium) and distinct biomarkers.

MDCTA is a new technique and have high reproducibility with <1% variability for non-calcified and calcified plaque volume measure, and < 15 % variability for total plaque volume. (21) MDCTA is a noninvasive procedure which provides an information of plaque composition, volume and severity of coronary vessel stenosis. (22) This technique is now widely used ~~now a days~~ in clinical investigations for the efficacy of therapies on coronary plaque progression including garlic, ~~statins~~testosterone, inflammatory agents, eicosapentaenoic acid (EPA) and ~~various antidiabetic agents~~anti-coagulants. (21-28)

The changes over time seen in the MDCTA scans (plaque volume, severity, and calcification) will assess the anti-atherosclerotic affects of semaglutide, while the biomarkers and assessment of new and existing vulnerable plaque, will assess the potential biological effects on the vasculature (ie – inflammation, plaque stabilization) in our current study. Further, changes over time seen on the CT (ie – soft plaque becoming fibrous or calcified) will inform clinicians relative to the long term stabilization of atherosclerosis that may be seen with Semaglutide during the study.

Conclusion:

Our current study will be the first one to evaluate the effects of semaglutide on atherosclerotic plaque progression measured by MDCTA in T2DM individuals and it will also assess whether these effects correlate with

HbA1c changes and inflammatory markers. This study will provide anti-atherosclerotic mechanism of long acting GLP-1 there by preventing the coronary events in T2DM.

References:

1. Budoff MJ, Raggi P, Beller GA, Berman DS, Druz RS, Malik S, Rigolin VH, Weigold WG, Soman P; Imaging Council of the American College of Cardiology. Noninvasive Cardiovascular Risk Assessment of the Asymptomatic Diabetic Patient: The Imaging Council of the American College of Cardiology. JACC Cardiovasc Imaging. 2016 Feb;9(2):176-92. doi: 10.1016/j.jcmg.2015.11.011. PMID:26846937
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2017.

3. The Cost of Diabetes: American Diabetes Association® [Online]. Available at: http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html [Accessed: 1 April 2019].
4. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, et al. (2007) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 355: 2427–2443.
5. Cherukuri L, Smith MS, Tayek JA. The durability of oral diabetic medications: Time to A1c baseline and a review of common oral medications used by the primary care provider. Endocrinol Diabetes Metab J. 2018;2(3):http://researchopenworld.com/wp-content/uploads/2018/07/EDMJ-2018-105-John-A.-Tayek-USA.pdf.
6. Marso, S.P., Bain, S.C., Consoli, A., et al. 2016. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England Journal of Medicine* 375(19), pp. 1834–1844.
7. Davies, M., Pieber, T.R., Hartoft-Nielsen, M.-L., Hansen, O.K.H., Jabbour, S. and Rosenstock, J. 2017. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: A randomized clinical trial. *The Journal of the American Medical Association* 318(15), pp. 1460–1470
8. Tashiroa Y, Satoa K, Watanabea T, Nohtomib K , Nagashimab M, Hirano T. A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. Peptides 2014; 54 19–26.

9. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochellière R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM; PERISCOPE Investigators. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008 Apr 2;299(13):1561-73. PMID: 18378631

10. **Kalra S, Baruah MP, Sahay RK, Unnikrishnan AG, Uppal S, Adetunji O. Glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes: Past, present, and future. *Indian J Endocrinol Metab*. 2016;20(2):254–267. doi:10.4103/2230-8210.176351**

11. Marso, S.P., Poulter, N.R., Nissen, S.E., et al. 2013. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *American Heart Journal* 166(5), p. 823–30.e5.

12. Htike, Z.Z., Zaccardi, F., Papamargaritis, D., Webb, D.R., Khunti, K. and Davies, M.J. 2017. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes, Obesity & Metabolism* 19(4), pp. 524–536.

13. Doggrell, S.A. 2018. Sgemaglutide in type 2 diabetes - is it the best glucagon-like peptide 1 receptor agonist (GLP-1R agonist)? *Expert Opinion on Drug Metabolism & Toxicology* 14(3), pp. 371–377.

14. Coon, S.A., Crannage, E.F., Kerwin, L.C. and Guyton, J.E. 2018.

Semaglutide once-weekly: improved efficacy with a new safety warning. *Expert review of clinical pharmacology* 11(11), pp. 1061–1072.

15. Li, Y. and Rosenblit, P.D. 2018. Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: Is It a Class Effect? *Current cardiology reports* 20(11), p. 113.

16. Thompson, P.L. and Davis, T.M.E. 2017. Cardiovascular Effects of Glucose-lowering Therapies for Type 2 Diabetes: New Drugs in Perspective. *Clinical Therapeutics* 39(5), pp. 1012–1025.

17. Peterson, G.E. and Pollom, R.D. 2010. Liraglutide in clinical practice: dosing, safety and efficacy. *International Journal of Clinical Practice* 64, pp. 35–43.

18. Dhillon, S. 2018. Semaglutide: first global approval. *Drugs* 78(2), pp. 275–284.

19. Tashiroa Y, Satoa K, Watanabea T, Nohtomib K , Nagashimab M, Hirano T. A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. Peptides 2014; 54 19–26.

20. Vergès, B. and Charbonnel, B. 2017. After the LEADER trial and SUSTAIN-6, how do we explain the cardiovascular benefits of some GLP-1 receptor agonists? *Diabetes & Metabolism* 43 Suppl 1, p. 2S3-2S12.

21. Budoff M, Muhlestein BJ, Le VT, May HT, Roy S, Nelson JR. Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200-499 mg/dL) on statin therapy: Rationale and design of the EVAPORATE study. Clin Cardiol. 2018 Jan;41(1):13-19.

22. Hoffmann, U., Moselewski, F., Nieman, K., et al. 2006. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *Journal of the American College of Cardiology* 47(8), pp. 1655–1662.

23. Nakanishi, K., Fukuda, S., Shimada, K., et al. 2012. Non-obstructive low attenuation coronary plaque predicts three-year acute coronary syndrome events in patients with hypertension: multidetector computed tomographic study. *Journal of Cardiology* 59(2), pp. 167–175.

24. Win TT, Nakanishi R, Osawa K, Li D, Susaria SS, Jayawardena E, Hamal S, Kim M, Broersen A, Kitslaar PH, Dailing C, Budoff MJ. Apixaban versus warfarin in evaluation of progression of atherosclerotic and calcified plaques (prospective randomized trial). Am Heart J. 2019 Jun;212:129-133.

25. Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER 3rd, Wenger NK, Bhasin S, Barrett-Connor E, Swerdloff RS, Stephens-Shields A, Cauley JA, Crandall JP, Cunningham GR, Ensrud KE, Gill TM, Matsumoto AM, Molitch ME, Nakanishi R, Nezarat N, Matsumoto S, Hou X, Basaria S, Diem SJ, Wang C, Cifelli D, Snyder PJ. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017;317(7):708-716.

26. Matsumoto S, Ibrahim R, Grégoire JC, L'Allier PL, Pressacco J, Tardif JC, Budoff MJ. Effect of treatment with 5-lipoxygenase inhibitor VIA-2291 (atreleuton) on coronary plaque progression: a serial CT angiography study. Clin Cardiol. 2017;40(4):210-215.

27. Matsumoto S, Nakanishi R, Li D, Alani A, Rezaeian P, Prabhu S, Abraham J,

Fahmy MA, Dailing C, Flores F, Hamal S, Broersen A, Kitslaar PH, Budoff MJ. Aged Garlic Extract Reduces Low Attenuation Plaque in Coronary Arteries of Patients with Metabolic Syndrome in a Prospective Randomized Double-Blind Study. J Nutr. 2016 Feb;146(2):427S-32S.

28. Lee J, Nakanishi R, Li D, Shaikh K, Shekar C, Osawa K, Nezarat N, Jayawardena E, Blanco M, Chen M, Sieckert M, Nelson E, Billingsley D, Hamal S, Budoff MJ. Randomized trial of rivaroxaban versus warfarin in the evaluation of progression of coronary atherosclerosis. Am Heart J. 2018;206:127-130.