Impact of Plant Sterol Supplement on LDL-C Lowering in Low-to-Moderate Risk South Asian Patients Participating in a Cardiovascular Disease Prevention Program

Study Protocol and Statistical Analysis Plan

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Title: Impact of Plant Sterol Supplement on LDL-C Lowering in Low-to-Moderate Risk South Asian Patients Participating in a Cardiovascular Disease Prevention Program

PI: Rajesh Dash, MD PhD
Asst Prof, Stanford University Medical Center
Medical & Scientific Director, SSATHI Clinic
Medical Director, CardioClick Telemedicine Clinic

Sites (2):
- Stanford SSATHI Clinic, 3260 Alpine Road, Portola Valley, CA
- Main Cardiology Clinic, 300 Pasteur Drive, Stanford, CA 94305

Purpose:
The purpose of this study is to measure the effectiveness of a twice daily plant sterol supplement, which is in a gummy format and packaged with health insights, in a population of South Asian patients who have low to moderate cardiovascular disease (CVD) risk by traditional risk scoring. Defined as a 10-year cardiovascular risk score (ASCVD Score) of < 7.5%, and a LDL-C level of 120-189mg/dl, these individuals do not meet guideline-based criteria (2018 ACC/AHA Lipid Guidelines) for medical lowering of their LDL-C with an HMG CoA reductase inhibitor (statin) drug, and they are recommended to improve their lipid-risk profile through diet and exercise primarily. Additional lipid lowering is routinely desired yet often never achieved solely through a lifestyle approach. In addition, patients who may qualify for statin therapy, those with ASCVD score > 7.5% or LDL > 189 mg/dl, but are deemed to be intolerant of statins or who refused lipid lowering medication may also qualify. While the safety and benefits of plant sterol supplements have been established and are incorporated into many lipid lowering guidelines, their effects have not been measured in the highest CVD risk population in the world, namely South Asians. In this study, we aim to measure the LDL-C reducing impact of regular plant sterol supplementation for these low-to-moderate risk South Asians.

The Clinic
Founded in 2014, the Stanford South Asian Translational Heart Initiative (SSATHI) is the only preventive cardiology clinic in the U.S. dedicated to exclusively treating South Asian patients for both traditional and non-traditional cardiovascular risk factors. The clinic includes an intensive program combining physician visits and serial laboratory testing. The patients also benefit from frequent dietitian/health coach visits during the program, all of which are conducted virtually through SSATHI's telehealth arm, CardioClick. Typically, lipid lowering effects from lifestyle changes are manifest within 3 months. In this proposal, the study length will be 3 months for each enrolled subject.

Study Design
This single arm study will include one in-person or video baseline visit, with a virtual follow up visit with the treating physician.

At the baseline visit, subjects will complete informed consent, a medical history, and clinic visit procedures, inclusion/exclusion criteria, medication review, measurement of morphometrics (body weight, height, BMI, hip and waist circumference, blood pressure, heart rate). A fasting blood draw for baseline labs will be performed within 8 weeks of start date. Women under 60 years will receive a urine pregnancy test. We are washing out any lipid lowering non prescription medications.

There will also be focused patient engagement questionnaires administered at the end of the study.

Intervention
Enrolled subjects, upon completion of the baseline clinical and laboratory assessment, will be given a 90 day supply of gummy plant sterol supplements in daily packets, totaling 1400 mg of daily plant sterol to be ingested in two daily doses. During the 90 day treatment, subjects will be contacted weekly through Twilio or SMS messaging by the research team to assess compliance which requires a single digit response from each subject to report compliance with the gummy sterol treatment. At the end of the study, a virtual clinical visit and laboratory test, along with post-study surveys, will be administered.

Baseline visit

- Informed consent/HIPAA
- Medical history
- Clinic visit
    - Baseline measurements, lab testing
    - Assess prior and current medication/supplement use
    - Review inclusion/exclusion criteria
- Diet assessment
- Fasting Lipid profile
- In-clinic urine pregnancy test for female subjects, if applicable
- Dispense study product
- Provide study instructions

Regular product compliance assessment

- Weekly Twilio or SMS text messaging question with a numeric response to assess product compliance

End of Study Visit

- Assess prior and current medication/supplement use
- Fasting Lipid profile
- Questionnaire
    - SSATHI questionnaire
    - Sponsor questionnaire
- Assess product compliance
- Assess adverse events

Inclusion Criteria

1. Subject is a South Asian male or female, ≥18 years of age
2. Subject has LDL-C ≥120 and <190 mg/dL measured in the past 3 months (or measured at the baseline visit), while not taking cholesterol-lowering medication or cholesterol-lowering supplement for at least 1 month prior, and having a ASCVD Risk score <7.5%.
3. Subjects with LDL-C ≥120 and <190 mg/dL with ASCVD risk scores >7.5% who are known to be intolerant of statin therapy drugs.
4. Subjects with LDL-C > 189 mg/dl or ASCVD > 7.5% who have declined prescription medical therapy.
5. If current smoker, subject does not have any plans to change current smoking status or frequency.
6. Subject is willing to fast (10-14 h, target 12 h, water only) prior to each clinic visit.
7. Subject understands the study procedures and signs forms documenting informed consent to participate in the study and authorization for release of relevant protected health information to the study Investigator and is willing to complete study procedures.
8. Subject is agreeable to receiving clinical care virtually.

Exclusion Criteria

1. Subject has taken a prescription cholesterol-lowering medication in the past 1 month.
2. Subject has a known allergy or sensitivity to soy, corn, or other ingredients in the study product.
3. Subject is taking dietary supplements for cholesterol-lowering such as red yeast rice, niacin >100 mg/d or omega-3 fatty acid supplements providing ≥1000 mg/d eicosapentaenoic acid and/or docosahexaenoic acid. (Stable use of viscous fiber laxative ≤2 teaspoons/d is allowed.)
4. Subject is a female, who is pregnant, planning to be pregnant during the study period, or lactating. Subjects should agree to use contraception during study period to avoid pregnancy.

5. Individual has active angina, stable or unstable, requiring urgent cardiovascular functional risk stratification (stress testing or catheterization) or intervention. Or has congestive heart failure that is not compensated or in which the subject is not euvolemic, as determined by the treating MD.
6. Individual has a condition the Investigator believes would interfere with his or her ability to provide informed consent, comply with the study protocol, which might confound the interpretation of the study results or put the person at undue risk.

Primary Outcome

% change in LDL Direct, or LDL-C if LDL Direct is not available, from baseline at 3 months

Exploratory Outcomes

% changes from baseline to 3 months in following:

- Total cholesterol
- Calculated LDL-C or LDL Direct
- HDL-C
- Non-HDL-C
- Triglycerides
- Fasting Glucose
- Fasting Insulin
- Hba1c
- Lp(a)
- Apoprotein B-100
- Apoprotein A1
- Ratio, ApoB-100/Apo A1
- C-reactive protein

Changes from baseline to 3 months in questionnaire metrics of patient engagement, satisfaction, and outlook on health

Product compliance

Subjects' interest in continuing to use product

Statistical Analysis

Because of the pre-post nature of this single group study, either a paired t-test or a non-parametric paired test will be employed to analyze the statistical significance of any differences at the end of the study. This decision will depend upon the normality of the data set.

Sample Size

A sample size of 50 will be enrolled. Our population exhibits a standard deviation of 25mg/dl in baseline LDL-C, the primary outcome variable. As a result, an evaluable sample of 40 subjects will provide 80% power to detect a difference of 10% based on a paired t-test and a two-sided alpha of 0.05. A larger enrolled sample will allow for subject attrition of up to 20%.

Statistical Analysis

Baseline characteristics will be described using means and standard deviations or medians and interquartile range limits as appropriate based on the distribution for continuous variables. Numbers of subjects and percentages will be used to describe categorical variables. Responses to the intervention will be assessed using paired t-tests for continuous variables. For categorical variables, McNemar's test will be employed to assess differences in frequencies between baseline and end-of-study. All tests of statistical significance will be completed using alpha = 0.05, two-sided.