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# Intensive vs. Standard Lipid Management in Intermediate Framingham risk patients with Elevated Coronary calcium scores(ISLAND-CCS Trial)

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# **I**ntensive vs. **S**tandard **L**ipid M**an**agement in Interme**d**iate Framingham risk patients with Elevated **C**oronary **c**alcium **s**cores(ISLAND-CCS Trial)

1. Study Purpose and Rationale.
   - Approximately 650,000 assymptomatic persons/year present with ACS as their first manifestation of CAD[1]. Additionally, 68% of all ACS events occur at locations that were previously without significant obstruction.[2] This information has established the need for accurate predictors of CHD risk. To date, the Framingham risk score has been the most clinically useful predictor of CHD risk, and has provided the basis for ATPIII guidelines for CHD prevention using lipid lowering therapy[3]. However, a number of patients presenting with ACS would not meet criteria for lipid lowering therapy based on their Framingham risk score, and a number of patients who are treated based on ATPIII guidelines still present with CHD events. This creates the need for a more accurate prediction model to guide therapy.[4]
   - Calcium scoring by Electron beam CT scanning and multislice detector ct scanning has been shown to be predictive of future cardiovascular events in asymptomatic individuals, above conventional risk factors[5-10]. One of which was the St. Francis heart study where CACS was an independent predictor of future CHD events within 4.3years of follow up, as well as predicted CHD events more accurately than traditional Framingham risk alone[11]. It has been noted by hecht that CACS is most useful in patients with intermediate cardiovascular risk[12]. Accordingly, CACS has been incorporated into the European guidelines on cardiovascular disease for those with medium risk, as well as into the AHA guidelines for CHD prevention in women[13]. This has based on a number of studies that have shown that risk for future CHD events change most with CACS in intermediate risk patients, as seen most recently in a recent publication of the MESA group where the greatest reclassification of risk of future cardiac events was seen in this group as measured by the net reclassification index.[14] Thus, it has been proposed that CACS may be most clinically useful in altering lipid management in those with intermediate Framingham risk.[12]
   - To date, there is a lack of evidence to confirm CACS based modifications to ATP-III guidelines. Currently, treatment with the

knowledge of CACS relies solely on extrapolation of risk from previous studies and clinical experience alone. We propose to study the effect of change to current ATP-III guidelines in lipid lowering therapy based on the combination of Framingham and CACS risk.

Study Design and statistical analysis

- Study aim: The study will evaluate benefit of aggressive lipid control in reducing risk of cardiovascular events in patients with intermediate Framingham risk but elevated CACS
- Study Design- Prospective Randomized controlled multiple center study
- Study arms
    i. Intensive lipid management group: Goal LDL< 100, Non HDL <130
    ii. Standard lipid management group: Goal LDL <130 Non HDL <160
- Study entrance and randomization
    i. Subjects will undergo Framingham risk stratification by initial evaluation of risk factors and blood pressure measurement. Patients who are determined to be at either low(0-1risk factor) or high risk(CHD and CHD risk equivalent) will be excluded from the study and follow up with their primary care doctors. Eligible subjects(intermediate risk 2+risk factors w/o known coronary disease) will subsequently obtain a Cardiac CT for Coronary calcium scoring. Those with an elevated CACS, as defined by agatson score>400 will be eligible for study participation. Those with Agatson score <400 will be excluded. Eligible subjects will subsequently be randomized to intensive vs. standard lipid control arms and participate in trial. Randomization will be performed to match baseline characteristics such as age, gender, baseline LDL, Baseline HDL, Baseline triglycerides, Baseline total cholesterol, baseline ASA use, smoking status, family history

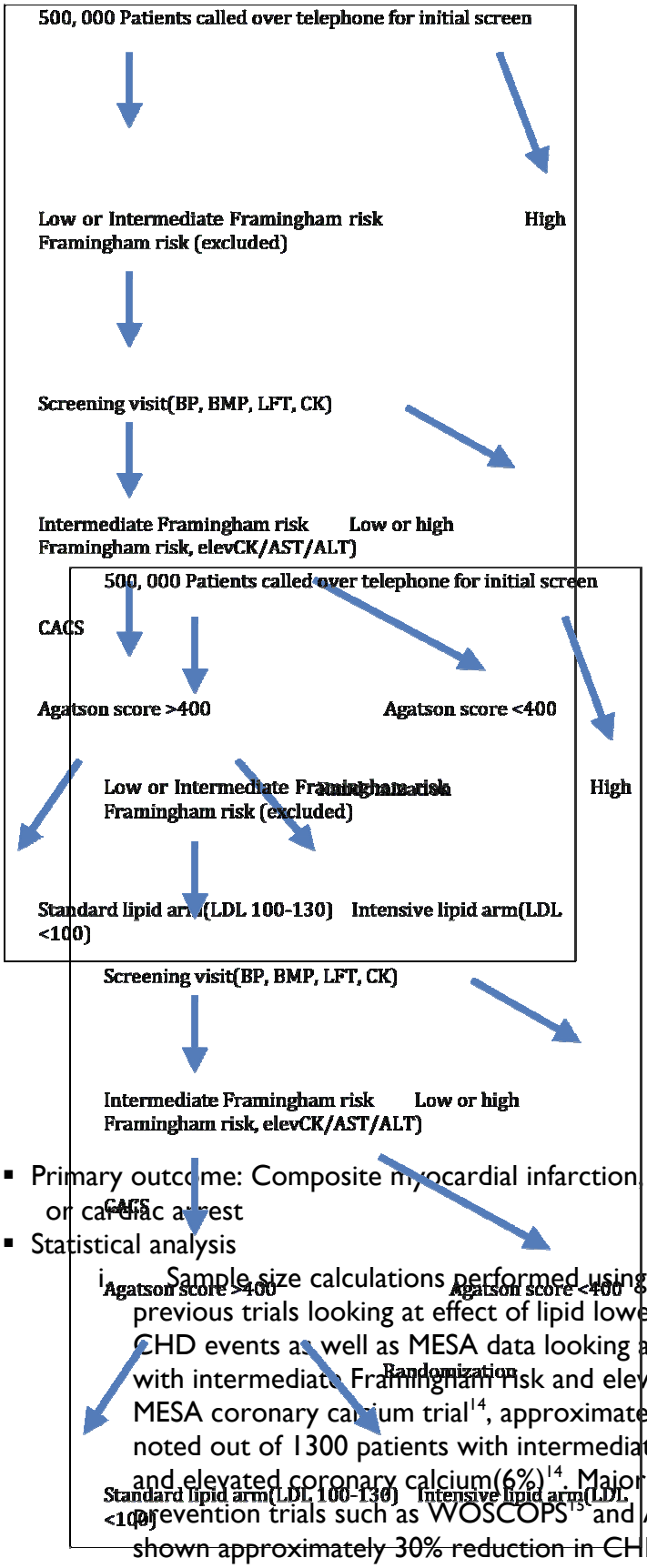


Figure 1

- Primary outcome: Composite myocardial infarction, death from CHD, or cardiac arrest
- Statistical analysis
  - i. Sample size calculations performed using comparison to previous trials looking at effect of lipid lowering therapy on CHD events as well as MESA data looking at events in patients with intermediate Framingham risk and elevated CACS. In the MESA coronary calcium trial[14], approximately 80 events were noted out of 1300 patients with intermediate Framingham risk and elevated coronary calcium(6%)[14]. Major primary prevention trials such as WOSCOPS[15] and AFCAPS[16] have shown approximately 30% reduction in CHD events with lipid

lowering therapy over 5 years of follow up. We therefore predict approximately a 30% reduction in event rates with more aggressive lipid lowering therapy in our study group. Our effect size with therefore be 2%. To achieve 80% power a sample size of 2000 subjects in each group will be needed, total 4000, using chi-square test for power calculation.

2. Study procedure

- Over the phone framingham risk assessment(Age, sex, smoking, known CAD, family hx), those with >20% risk will be excluded
- Those who meet criteria will participate in first study visit, have BP measured, labs drawn for baseline CBC/BMP/CK/LFTs. Elevated CK/LFTs abnormal labs will be notified and excluded/follow up with PMD, framingham risk will be again calculated with BP, only intermediate(2+RF, 10-20% 10 yr risk using online calculator)
- Those who meet criteria will then undergo Multidector CT, a blinded independent cardiologist boarded in CT will evalate CT scans, and calculate agatson score
- Those with agatson scores<400 will be excluded
- Study Visit 1(0weeks): pt will have baseline lipid levels checked.
- Randomization will occur taking into account baseline characteristics including ASA use. Patents will be educated on medication adherence and prescribed and HMG-CoA reductase inhibitor(statin) if their lipid levels are not at the goal for their study arm.
- There will be a 4-6 run in period to assess for adherence to medication regimens
- Study Visit 2(4-6 weeks): pt will have lipid levels checked again, medications will be titrated to achieve goal. They will be informed over the phone of their lab results and will be instructed to increase/decrease statin therapy.
- Study Visit 3(12 weeks): Pts will again have their lipid profile measured. Study procedure will be repeated as per study visit 2.
- Pts will subsequently have follow up visits q6mo where lipid levels will be measured and followed to be sure at goals for specific arm. This process will be repeated until 5 year point achieved.

3. Medical Device
    - Any MCT(Multidector cardiac CT) device
4. Study Questionnaires: Framingham risk questionnaire, ASA use questionnaire
5. Study Subjects
    - Inclusion criteria
        i. Men and women aged 45 to 84 years without known cardiovascular disease.
        ii. Intermediate Framingham risk
        iii. CACS as defined by Agatson score >400
    - Exclusion criteria
        i. High Framingham risk(known CHD or CHD risk equivalent)
        ii. Low Framingham risk(0-1 risk factor)
        iii. Renal disease as defined by cr >1.5
        iv. Liver disease
        v. Rhabdomyolysis
        vi. Hypercalcemia
        vii. Claustrophobia
6. Subject recruitment
    - Subjects will be recruited by posting of campus wide flyers(all sites), Telephone screening will be conducted as described above.
7. Confidentiality of data
    - all data will be strictly confidential
8. Location of study
    - Columbia university medical center
9. Potential conflicts of interest
    - none
10. Potential risks
    - increased side effects of statins
        i. liver dysfunction
        ii. rhabdomyolysis
    - Radiation exposure
11. Potential benefits
    - Improved prevention of cardiac events in those with intermediate risk
12. Alternative therapies
    - none
13. Compensation to subjects
    - TBD
14. Costs to Subject
    - There will be no cost to the subjects.
15. Minors as Research Subjects
    - No minors will be enrolled in the trial; earliest age of enrollment will be 21 years of age

16. Radiation or Radioactive Substances
    - Expected radiation exposure 30–100 mGy.
    - Radiation exposure will be measured in each subject, study will not proceed if greater than expected amount of radiation

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