Incidental Coronary Calcification Quality Improvement Project (ICC QI)

March 10, 2021

QUALITY IMPROVEMENT PROJECT SUMMARY

Title	Incidental Coronary Calcification Quality Improvement Project
Project Objectives	Primary objective is to estimate the impact of notification of primary care provider and patient of incidental coronary artery calcification (CAC) on a prior non-gated chest CT on statin prescription rates at 6 months among statin-naïve patients without a clinical history of atherosclerotic cardiovascular disease. Secondary objectives are to evaluate the following at 6 months after notification: - Specific statin medication and dose - Aspirin prescription rates - Change in cardiovascular risk factors (blood cholesterol levels, hemoglobin A1c levels, systolic/diastolic blood pressure, body mass index) - Change in 10-year pooled cohort equations risk of atherosclerotic cardiovascular disease (calculated from age, sex, race, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes status, smoking status, blood pressure treatment status) - Number of blood pressure medications - Healthcare resource use (primary care clinical encounters, cardiology referrals, cardiac testing)
Project Design	This is a randomized quality improvement project evaluating the impact of notifying patients and their providers of an incidental finding of coronary artery calcification (CAC) indicating increased cardiovascular risk. Patients will be identified by screening previous non-gated chest CTs and the electronic health record. The presence of CAC will be confirmed by a board-certified radiologist. Eligible patients will be randomized in a 1:1 fashion to CAC notification or usual care.
Number of Patients	All eligible patients; approximately 200 patients at Stanford will be randomized in addition to approximately 200 patients at the Palo Alto VA.
Location	Stanford Health Care system (including Stanford Hospital and affiliated clinics; ValleyCare Hospital and affiliated clinics) and Palo Alto Veteran's Affairs Healthcare System
Inclusion Criteria	• Age ≥18 and <85 • Non-gated chest CT from 2014-2019 with CAC

	• Visit to Stanford affiliated clinician from one of the following clinics since 2018:
	  ○ Stanford Internal Medicine (includes University affiliated clinics)
	  ○ Stanford Family Medicine (includes University affiliated clinics)
	  ○ Palo Alto VA Internal Medicine
	  ○ Palo Alto VA Family Medicine

Exclusion Criteria	• Prior diagnosis of coronary artery disease, peripheral artery disease, or cerebrovascular disease • Dementia • Metastatic cancer or active cancer undergoing chemotherapy • Prior cardiac gated chest CT • Prior coronary angiogram • Current or previous statin therapy • History of medical non-adherence • Non-English speaking
Intervention	For patients randomized to notification, the affiliated primary care provider will receive an EHR message notifying them of the presence of CAC (with images) and the ACC/AHA guideline recommendation to consider starting statin therapy. We will notify the patient after 2 weeks elapse unless the primary care provider responds that the patient has already been diagnosed with atherosclerotic cardiovascular disease, is already taking a statin, or cannot take a statin. Patients will then receive messages (via either EHR portal-based messages or US postal mail) with images showing the presence of CAC on their previous chest CT, and the recommendation to discuss statin therapy with their clinician. For the notification arm, we will check for either statin prescription or a documented discussion in the EHR at 3 months. For those not prescribed a statin and without a documented discussion in Epic at 3 months follow-up, we will send a repeat notification to their home address and to their primary care provider.
Adaptive Design	The project will use two independent cohorts – the first 50 patients and then all remaining patients. At the start of the project, the first cohort of 50 patients will be randomized to notification or usual care. Based on feedback from primary care clinicians and observed statin rates over the subsequent 6 weeks, potential modifications to the protocol will be made prior to randomization of the second cohort.

	If any changes are made to the protocol, each cohort will be evaluated separately with primary analyses based on the second cohort. If no changes are made to the initial protocol, all analyses will pool both cohorts.
Primary Endpoint	6-month statin prescription rate
Secondary Endpoints	Change in the following at 6 months: • Statin prescription rate • Aspirin prescription rate • Lipid panel (Total cholesterol, HDL, LDL, Triglycerides) • Average systolic blood pressure • Hemoglobin A1c • Number of blood pressure medications • Body mass index • 10-year pooled cohort equations risk of atherosclerotic cardiovascular disease (calculated from age, sex, race, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes status, smoking status, blood pressure treatment status) Healthcare resource use at 6 months: • Number of primary care clinical encounters • Number of cardiology referrals • Number of cardiovascular diagnostic tests ordered
Other Outcomes of Interest	• Specific statin prescribed and dose at 6 months
Assessment Schedule	• Eligibility screening using list of prior CT scans and electronic health record • AI algorithm CT screening for presence of coronary artery calcification • Manual electronic health record review to confirm clinical inclusion/exclusion criteria • Manual radiologist review of CT scan to confirm the presence of CAC followed by randomization • 3-month assessment of statin prescription rates using electronic health record evaluation • 6-month assessment of outcomes using electronic health record evaluation
Duration	At each site, we will enroll a maximum of 3 patients per primary care provider notified per week. Expected follow-up will be 6 months for all primary and secondary endpoints.

Statistical Considerations	A sample size of 150 randomized patients has 87% power to detect a 20% higher absolute statin prescription rate (to a rate of 30%) among the notification arm compared with an estimated rate of 10% in the usual care arm. Additional power estimates conditional on sample size are listed below.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

ACC	American College of Cardiology
ASCVD	atherosclerotic cardiovascular disease
AHA	American Heart Association
CAC	coronary artery calcification
CAD	coronary artery disease
CPT	Current Procedural Terminology
CT	Computed Tomography
ECG	electrocardiogram
EHR	electronic health record
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
MI	myocardial infarction
PCE	ACC/AHA Pooled Cohort Equations
PHI	protected health information

2. BACKGROUND AND RATIONALE

Coronary artery disease (CAD) is the #1 cause of death in the US and globally.[1] It develops silently over decades until it strikes as a myocardial infarction (MI) or sudden death. For half of people who die suddenly, death is the first symptom.[1] Risk factors such as smoking, hypertension, and high cholesterol increase the probability of developing plaques inside coronary arteries that cause MI. An electrocardiogram (ECG)-gated computed tomography (CT) scan can identify silent disease by detecting calcification of plaque inside coronary arteries. ECG-gating is used to image the patient during periods of heart muscle relaxation to minimize motion from an otherwise moving organ. A calcium scoring system has been developed—the higher the score, the higher the risk of having an MI or dying.[2-5] Studies have shown that once people learn that they have coronary artery calcification (CAC), they are more likely to make healthy lifestyle choices and take medications that reduce their risk of MI.[6,7] The 2018 ACC/AHA cholesterol treatment guidelines recommend testing for CAC when patients are at borderline to intermediate risk for MI, and there is uncertainty about whether or not to prescribe a statin medication for cholesterol lowering.[8] When the CAC score is $\geq$0 Agatston units among those $\geq$55 years old or $\geq$100 Agatston units (or 75th percentile of age and sex reference values) among those younger, these guidelines recommend consideration of statin therapy to reduce risk. However, CAC testing and preventive therapies remain vastly underutilized, in part because insurers do not pay for these tests. As a result, millions of asymptomatic people remain unaware of their high risk for a heart attack and remain undetected and undertreated.

Statin medications have been shown to reduce the risk of MI and increase survival among patients at moderate to high risk of cardiovascular disease.[9] However, use of statin medications in at-risk populations remains suboptimal.[10] In 2013-2014, statin use among eligible adults in the US was estimated at 55%, and was unchanged from 2011–2012. This leaves an estimated 39 million adults at risk for cardiovascular disease off statin medications. Mechanisms to increase statin prescription rates are needed to reduce the impact of cardiovascular disease.

A large number of non-gated chest CT scans are performed in the Stanford and Palo Alto VA healthcare systems annually. Although these scans include images of the coronary arteries, there is often underreporting of the presence of CAC. Even when CAC is reported in the radiology report, the implications of CAC may be poorly understood and statin uptake may remain suboptimal. This is especially true because the significance of CAC and the benefit of starting statins among these patients was unrecognized until recently. Identifying Stanford and Palo Alto VA patients with prior CT scans with coronary calcium and notifying patients and their primary care providers may help inform discussions between patients and their physicians regarding their cardiovascular risk and the appropriateness of statin therapy. Better understanding one's risk may improve other cardiovascular risk factors such as diet, exercise, and blood pressure. This could provide an additional avenue for identifying our patients at risk for cardiovascular disease in order to start statins and make other changes to reduce the risk of having an MI.

3. HYPOTHESIS

In our health system, notification of statin-naïve patients without a history of atherosclerotic cardiovascular disease and their providers about coronary artery calcification on a prior non-gated chest CT will lead to an increase in statin prescription rates compared with rates among patients who are not notified. Furthermore, as secondary hypotheses, notification will also lead to additional cardiovascular risk reduction at 6 months following notification: lower LDL-cholesterol levels, lower systolic blood pressure, lower body mass index, lower tobacco use rates, and a lower 10-year ACC/AHA pooled cohort equations risk.

4. PROJECT OBJECTIVES

PRIMARY AIM

The primary aim of this project is to estimate the increase in 6-month statin prescription among statin-naïve patients without a history of atherosclerotic cardiovascular disease with incidental CAC on a non-gated chest CT who are randomized to receive notification of their findings vs. usual care in our health system (Stanford and the Palo Alto VA).

SECONDARY AIMS

The secondary aims of this project are to compare the following outcomes in patients randomized to notification or usual care:

- 3-month statin prescription rates
- Change in 6-month aspirin prescription rates
- Change in total cholesterol level
- Change in high-density lipoprotein level
- Change in low-density lipoprotein level
- Change in triglyceride level
- Change in average systolic blood pressure
- Change in number of blood pressure medications
- Change in body mass index
- Change in hemoglobin A1c level
- Change in 10-year Pooled Cohort Equations 10-year risk
- Number of primary care clinical encounters
- Number of cardiology referrals
- Number of cardiovascular diagnostic tests ordered
- Describe specific statin prescribed and dose

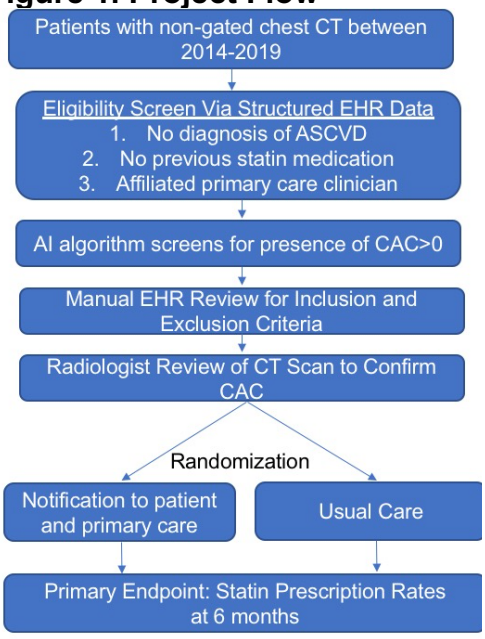
5. PROJECT DESIGN

This is a multi-center, randomized quality improvement project. At least 200 statin-naïve patients without a history of atherosclerotic cardiovascular disease with incidental CAC on a prior non-gated chest CT will be enrolled across the Stanford Healthcare System and the Palo Alto Veteran's Affairs Healthcare System. Patients will be randomized in a 1:1 fashion to notification or usual care arms.

5.1 PROJECT Flow

See Figure 1 for details. All non-gated chest CTs will be screened for the presence of CAC using an artificial intelligence deep learning algorithm that predicts the presence of CAC on a concurrent gated chest CT. Identified patients will be screened for inclusion/exclusion criteria using electronic health record data. Patients who meet eligibility criteria will be sequentially randomized by the project coordinator using the REDCap randomization module. A maximum of 3 patients per week will be randomized to the notification arm for any single primary care provider. After 3 patients are enrolled and randomized to the notification arm for a given primary care provider in a single week, enrollment of eligible patients of that clinician will be delayed until the following week.

Figure 1. Project Flow



After randomization to the notification arm, the coordinator will send a standardized notification message using the EHR to the patient's affiliated provider. The affiliated clinician will be the listed primary care provider within the health system. For patients without an active primary care provider, the affiliated provider can include a clinician from endocrinology clinic. This message will include the option for the provider to exclude their patient from receiving a standardized message if they note their patient has already been diagnosed with atherosclerotic cardiovascular disease, is already taking a statin, or cannot take a statin.

In the absence of the patient being excluded from notification, the coordinator will send a message to the patient after two weeks. For patients with active EHR patient portal accounts, this message will be transmitted via the EHR patient portal. For patients without active patient portal accounts, the message will be sent via postal mail. The message will include an image of the CAC from the chest CT. For patients who do not read the message on the EHR patient portal within 2 weeks, the message will also be sent via postal mail.

The project will be divided into two stages using two independent cohorts. The first cohort will include the first 50 randomized patients. The second cohort will include all other patients randomized for the study. There will be a delay of at least 10 weeks between enrollment of the first and second cohort in order to adapt the notification as necessary based on observations with the first cohort. Adaptations of the notification process will be based on feedback from primary care clinicians based on the initial cohort and observed changes in statin rates in this early period. Changes to the protocol will be agreed upon by study investigators and documented in detail. Following finalization of the protocol for the second stage, the second cohort will be enrolled.

At 3 months after patient notification, the coordinator will check for statin prescription or EHR documentation of a discussion regarding statin therapy. In the absence of statin prescription or a documented conversation, the coordinator will again send standardized messages to patients enrolled in the notification arm and their providers. Final outcome ascertainment will occur at 6 months after patient notification.

The coordinator will have no additional communication with patients or primary care providers over the 6-month follow-up period. Patients will be directed to their affiliated clinicians (their primary care provider or endocrinologist) to discuss statin therapy or information regarding the notification. Clinicians will be able to contact Dr. David Maron, director of Stanford preventive cardiology and co-PI of the project, via electronic health record message or secure email, with any additional questions.

All CT scans being used in this project have been interpreted previously by an attending radiologist and reported to the ordering provider with a standardized report according to clinical standards. Additionally, all clinicians have had access to the standardized report for at least 6 months prior to the project start date. Individuals randomized to the UC arm will not receive additional notification or have any communication with project staff.

A member of the project team will determine primary and secondary outcomes using electronic health record evaluation at 6 months.

5.2 Project Population

Statin-naïve patients without a history of ASCVD who underwent a prior non-gated chest CT found to have CAC.

5.3 Inclusion/Exclusion Criteria

Screening for inclusion/exclusion criteria will be conducted using a non-gated CT screening algorithm and electronic health record evaluation. Patients will be screened for the following inclusion and exclusion criteria:

5.3.1 Inclusion

1. Chest CT Eligibility
    a. Non-gated chest CT between 2014-2019
    b. Algorithm identifies CAC
    c. Presence of CAC confirmed by manual review by a board-certified radiologist
2. Clinical Eligibility
    a. Age ≥18 and <85
    b. Stanford affiliated primary care provider or endocrinologist for Stanford healthcare system patients and VA primary care provider for VA patients
    c. Visit (in-person or via tele-health) to listed clinician since 2018

5.3.2 Exclusion

1. Current or prior statin or PCSK9 inhibitor therapy
2. Prior diagnosis of ASCVD
    a. Coronary artery disease
    b. Peripheral artery disease
    c. Cerebrovascular disease
    d. Coronary revascularization
    e. Peripheral vascular revascularization
3. Prior coronary imaging
    a. Cardiac CT
    b. Invasive coronary angiography
4. Dementia diagnosis
5. Metastatic cancer or active cancer undergoing chemotherapy
6. History of medical nonadherence

7. PROJECT PROCEDURES

6.1 Notification of Participation

This quality improvement project involves a minimal-risk intervention. If notification improves statin rates and is acceptable among stakeholders, we will also apply this intervention routinely in the healthcare system including to the usual care arm.

6.2 Randomization

The sequence generation process will be performed using a secure password-protected computerized block randomization algorithm on REDCap with a 1:1 allocation and randomly selected block sizes of 2, 4, and 6. There will be no stratification for the randomization procedure.

6.3 Notification Messages

For patients randomized to the notification arm, a letter will be sent to the affiliated clinician using the electronic health record messaging system. The letter will include an image of the CAC from their CT scan. The clinician will have the opportunity to exclude a patient from being notified based on additional clinical considerations. We will otherwise send a scripted message via the EHR patient portal or postal mail after two weeks. That message will inform them that we identified coronary artery calcium on a previously performed CT scan.

A member of the project team will evaluate statin rates 3 months after patient notification among all randomized patients. They will also evaluate for documentation of statin discussions among those in the notification arm not prescribed a statin. The coordinator will then again send notifications to patients randomized to the notification arm who were neither started on statin therapy nor had a documented discussion. The coordinator will send messages to both the patient and their primary care provider that are similar to the initial notification.

8. TREATMENT ARMS

7.1 Notification

Patients randomized to notification will receive a message sent by either the EHR patient portal or postal mail that will inform them of the CAC identified on their previous chest CT. It will provide an overview of CAC, an image of their chest CT, and a recommendation that they discuss this finding with their clinician. These clinicians will be notified of these findings via an earlier EHR message. All communications will be signed by David Maron, MD, Director of Stanford Preventive Cardiology. Any treatment decisions will be made by the patient and their clinician.

Patients randomized to notification who are not prescribed a statin medication and do not have a documented discussion regarding statin therapy within three months will be sent a second message at that time. Their primary care providers will receive a second EHR message concurrently.

7.2 Usual Care

Both arms have previously had their CT scans reported according to standard clinical practice. This may include notification of the CAC in the imaging report. The usual care arm will not receive any additional notification beyond this standard of care.

We plan to notify patients in the usual care arm at the end of 6-months unless we determine that notification is ineffective at increasing statin rates and is not acceptable to either patients or their clinicians.

8. PROJECT ASSESSMENTS AND SCHEDULE

8.1 Baseline Clinical Eligibility

Baseline clinical eligibility will be determined for patients who have undergone a non-gated chest CT between 2014-2019. Clinical eligibility screening will be performed using EHR data via the STARR clinical registry.

8.1.1 Affiliated Clinician

Eligible patients must receive active clinical care from an affiliated primary care provider or endocrinology. Patients will be required to have had a visit with one of the following clinics since 2018:

- Stanford Internal Medicine (including university affiliated clinics)
- Stanford Family Medicine (including university affiliated clinics)
- Stanford Endocrinology
- Palo Alto VA Internal Medicine
- Palo Alto VA Family Medicine

8.1.2 Patient Age

Eligible patients must be ≥18 and <85 years old at the time of screening for enrollment.

8.1.3 Exclusion Criteria

Eligible patients will be initially screened for exclusion using EHR structured data elements of medications, diagnostic coding, and procedure coding. A list of diagnostic and procedural codes are attached in Appendix A.

8.2 Non-gated CT Scan Evaluation: AI Algorithm

Among patients who meet the baseline clinical eligibility, Stanford non-gated chest CT scans performed between 2014-2019 will be screened using an automated algorithm that will identify patients with a very high probability of a CAC score >0 Agatston units. This was developed at Stanford using a deep learning model based on patients who had a non-gated chest CT scan within 1 year of a gated coronary CT scan.

8.3 Confirm Clinical Eligibility Based on Manual EHR Review

Patients with CAC >0 based on the AI algorithm will then undergo a manual EHR chart review to confirm they meet the inclusion/exclusion criteria. This will evaluate the same criteria evaluated based on the baseline clinical eligibility screen above in 8.1 to ensure

non-structured data elements are captured. Additionally, the manual review evaluates the following exclusion criteria.

- Active malignancy with one of the following two characteristics
    - Active chemotherapy
    - Metastatic disease
- Medical nonadherence

8.4 Non-Gated CT Scan Evaluation: Manual Review

All patients who meet the clinical eligibility criteria with CAC on non-gated CT scan based on the AI algorithm will then undergo a manual review of the chest CT by a board-certified radiologist. The manual review will confirm the accuracy of the algorithm and the presence of CAC.

8.5 Baseline Clinical Data

Baseline clinical values of the following will be extracted from the EHR:

- Demographic characteristics (age, sex, race)
- Aspirin prescription
- Number of blood pressure medications prescribed
- Most recent blood cholesterol levels (Total cholesterol, HDL, LDL, Triglycerides)
- Most recent hemoglobin A1c level
- Average systolic blood pressure over previous 3 months
- Most recent BMI
- Comorbidities using diagnosis coding
    - Diabetes mellitus
    - Hypertension
    - Hyperlipidemia
    - Smoking status
    - Cancer (non-metastatic, not on active chemotherapy)
- Date of Chest CT
- Chest CT indication
- Prior Clinic Experience (specific to the affiliated clinician's clinic)
    - Date of last clinic visit
    - Number of clinic visits since 2018
    - Number of clinic encounters since 2018
- Other Healthcare utilization
    - Number of total clinic visits since 2018 (tele-health and in-person)
    - Prior cardiology outpatient encounters
    - Prior cardiovascular diagnostic tests ordered (diagnostic tests ordered (CAC scan, electrocardiogram, echocardiogram, exercise electrocardiogram, stress echocardiogram, stress nuclear, CT coronary angiography, invasive coronary angiography)

    - Number of health system ED visits since 2018
    - Number of health system hospitalizations since 2018

For all eligible patients without missing data, 10-year Pooled Cohort Equations risk (calculated from age, sex, race, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes status, smoking status, blood pressure treatment status) will be calculated.

8.4 Endpoint Assessments

Primary and secondary endpoints will be assessed using EHR structured data elements. Endpoints will be assessed by a member of the project team who will be blinded to allocation. The following will be assessed at 3-months after patient notification:

- Statin prescription rates

The following will be assessed at 6-months after patient notification:

- Specific statin prescribed, dose, and type of statin (high-, moderate-, or low-intensity)
- Aspirin prescription
- Number of blood pressure medications prescribed
- Most recent total cholesterol level
- Most recent high-density lipoprotein level
- Most recent low-density lipoprotein level
- Most recent triglyceride level
- Most recent hemoglobin A1c level
- Average systolic blood pressure over previous month
- Most recent body mass index
- 10-year Pooled Cohort Equations risk (calculated from age, diabetes status, sex, race, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure treatment status)
- Number of primary care clinical encounters
- Cardiology outpatient encounters
- Number of cardiovascular diagnostic tests ordered (CAC scan, electrocardiogram, echocardiogram, exercise electrocardiogram, stress echocardiogram, stress nuclear, CT coronary angiography, invasive coronary angiography)

Patients in the first cohort will also have statin prescription rates assessed at 8 weeks following notification. This information will guide potential changes to the protocol prior to randomization of the second cohort.

9. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

9.1 Sample Size Assumptions

We plan to have at least 150 patients in the second cohort. With 150 patients, we will have 87% power for a 20% higher absolute statin prescription rate (to a rate of 30%) among the notification arm compared with an estimated 10% statin prescription rate in the usual care arm. Because prior studies have demonstrated the difficulty in improving preventive therapy interventions, we estimated a relatively modest increase in statin initiation rates.[11] The following table lists additional sample size calculations:

alpha	Sample Size	Control Arm Statin Rate	Notification Arm Statin Rate	Difference in Statin Rates	Power
0.05	100	0.05	0.2	0.15	0.624
0.05	150	0.05	0.2	0.15	0.799
0.05	200	0.05	0.2	0.15	0.900
0.05	250	0.05	0.2	0.15	0.953
0.05	300	0.05	0.2	0.15	0.978
0.05	100	0.05	0.25	0.2	0.809
0.05	150	0.05	0.25	0.2	0.937
0.05	200	0.05	0.25	0.2	0.981
0.05	250	0.05	0.25	0.2	0.995
0.05	300	0.05	0.25	0.2	0.999
0.05	100	0.05	0.3	0.25	0.921
0.05	150	0.05	0.3	0.25	0.986
0.05	200	0.05	0.3	0.25	0.998
0.05	250	0.05	0.3	0.25	1.000
0.05	300	0.05	0.3	0.25	1.000
0.05	100	0.05	0.35	0.3	0.973
0.05	150	0.05	0.35	0.3	0.998
0.05	200	0.05	0.35	0.3	1.000
0.05	250	0.05	0.35	0.3	1.000
0.05	300	0.05	0.35	0.3	1.000
0.05	100	0.05	0.4	0.35	0.993
0.05	150	0.05	0.4	0.35	1.000
0.05	200	0.05	0.4	0.35	1.000
0.05	250	0.05	0.4	0.35	1.000
0.05	300	0.05	0.4	0.35	1.000
0.05	100	0.1	0.2	0.1	0.286
0.05	150	0.1	0.2	0.1	0.402
0.05	200	0.1	0.2	0.1	0.508
0.05	250	0.1	0.2	0.1	0.601
0.05	300	0.1	0.2	0.1	0.681

0.05	100	0.1	0.25	0.15	0.506
0.05	150	0.1	0.25	0.15	0.680
0.05	200	0.1	0.25	0.15	0.802
0.05	250	0.1	0.25	0.15	0.882
0.05	300	0.1	0.25	0.15	0.932
0.05	100	0.1	0.3	0.2	0.712
0.05	150	0.1	0.3	0.2	0.872
0.05	200	0.1	0.3	0.2	0.948
0.05	250	0.1	0.3	0.2	0.980
0.05	300	0.1	0.3	0.2	0.993
0.05	100	0.1	0.35	0.25	0.861
0.05	150	0.1	0.35	0.25	0.963
0.05	200	0.1	0.35	0.25	0.991
0.05	250	0.1	0.35	0.25	0.998
0.05	300	0.1	0.35	0.25	1.000
0.05	100	0.1	0.4	0.3	0.946
0.05	150	0.1	0.4	0.3	0.993
0.05	200	0.1	0.4	0.3	0.999
0.05	250	0.1	0.4	0.3	1.000
0.05	300	0.1	0.4	0.3	1.000

9.2 Statistical Analysis Plan

This project uses an adaptive design with a potential change to the protocol following randomization of the first 50 patients (the first cohort). If there are any changes to the protocol following the first cohort, the primary analysis will only include the second cohort (patients randomized after the protocol change). In this case, the combined cohort will only be used for post-hoc analyses. The project is adequately powered based on the second cohort as described above in Section 9.1. If there are no changes to the protocol following the first cohort, the cohorts will be pooled for all analyses.

The primary endpoint is the statin prescription rate at 6 months. We will compare the difference in proportion of patients prescribed statins between arms using either the Chi-squared test or Fisher's exact test depending on the number of statin initiations observed in either arm. Specifically, we will use the Fisher's exact test if there are under 10 statin initiations in either the usual care or notification arm. Multiple pre-specified subgroups will be tested with formal testing for effect modification:

- Age – stratified into above and below median and as a continuous variable
- Sex
- Prior LDL value – stratified into above or below 100mg/dL or missing
- Time since last clinician visit - stratified into above and below median and as a continuous variable
- Taking anti-hypertensive medication
- Clinical site (Stanford, University Affiliated, Palo Alto VA)
- Specialty of clinician notified
- Estimated CAC score on AI derived score – stratified into above and below median and as a continuous variable

For secondary endpoints, we will compare the change in continuous variables from baseline to 6-months across arms using analysis of covariance. The outcome variable at 6 months will be the dependent variable while adjusting for baseline values of the outcome variable. The difference in healthcare resource use (number of primary care encounters, and cardiovascular tests ordered) will be evaluated using negative binomial regression models while adjusting for two baseline characteristics thought to be likely prognostic. These include age modeled as a cubic spline with a knot at the median, the 5^{th} percentile, and 95^{th} percentile and prior resource utilization (specific to the outcome being tested). The difference in cardiology encounters post-randomization will be assessed using multivariable logistic regression with adjustment for age (as specified above) and history of prior cardiology encounters. The binary endpoint, aspirin prescription, will be compared using Chi-squared or Fisher's exact test depending on cell sizes as described above.

Baseline characteristics will be compared using standardized mean differences to assess balance across arms. The analysis will use a two-sided α of 0.05 as a threshold for significance.

10. DATA HANDLING AND RECORD KEEPING

10.1 Electronic Data Capture (EDC) System

EHR data will be extracted via the STARR registry and kept on the REDCap system. After data extraction, patients will be de-identified and labeled with a project ID number. Linkage between the medical record number and project ID will be kept separately as a locked file and only be available to the data analyst.

10.2 Data Confidentiality and Security

Computerized data will be accessible only by password. The Stanford University computer network is protected by a firewall. Patients will be identified by project number only, to ensure participant anonymity. No participant identifiers will be used in the presentation of data. Records that might identify patients will be kept confidential as required by law. Except when required by law, patients will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in project records.

10.3 Training

All investigational site staff authorized to enter the project data will receive training on the EDC system.

10.4 Records Retention

Project records will be maintained by the site investigators for a period of six (6) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

11. REFERENCES

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