SUPPLEMENTAL MATERIAL

Incidental Coronary Artery Calcium: Opportunistic Screening of Prior Non-gated Chest CTs to Improve Statin Rates (NOTIFY-1 Project)

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Supplement Methods.

Educational Sessions

The study team hosted three separate 1-hour educational sessions to primary care clinicians in the Stanford healthcare system. Each 1-hour session was directed to a different set of clinicians in the healthcare system. Not all primary care clinicians that received a notification attended an educational session, and not all clinicians that attended an educational session received a notification (but may have had one or more patients in the control group). The sessions, hosted by members of the project team, included a discussion of the prognostic significance of CAC and the opportunity for primary care clinicians to ask questions about CAC. There was no additional education provided to primary care outside of the intervention.

Imputation

Outcome data were extracted from the electronic health record. For body mass index, blood pressure, hemoglobin A1c, and lipid levels, we included the last measurement in the 6 months following randomization. We recalculated the 10-year atherosclerotic cardiovascular disease (ASCVD) risk post-randomization using the American College of Cardiology/American Heart Association Pooled Cohort Equations and repeat lipid levels, systolic blood pressure, and number of anti-hypertensives. We characterized the 10-year ASCVD risk as missing if there were missing lipid levels or systolic blood pressure.

We applied two imputation approaches for missing data. First, we used the last observation carried forward imputation and used baseline values to impute missing values. Second, we used multiple imputation with chained equations with 100 imputations. We imputed the following

variables with missingness: baseline and follow-up hemoglobin A1c, baseline and follow-up lipid levels, baseline and follow-up 10-year ASCVD risk, follow-up body mass index, and follow-up systolic blood pressure. We included age, aspirin treatment, baseline body mass index, baseline systolic blood pressure, cancer, chronic kidney disease, diabetes, randomization arm, smoking status, and use of anti-hypertensives in the imputation model. We combined estimates from each imputation via Rubin's rule.

Statistical Analysis

The primary analysis compared statin prescription rates across arms at 6 months using Fisher's exact test. We evaluated heterogeneity in the treatment effect across pre-specified subgroups using the Tarone test. We stratified low-density lipoprotein cholesterol level at >100 mg/dL, ≤100mg/dL, or missing. We stratified other subgroups based on continuous characteristics (age, time since last primary care/endocrinology visit, and DL-CAC score) using median values. For the race and ethnicity subgroup, we used race and ethnicity designations from the electronic health record. We first categorized individuals as Hispanic of any race and then by race. We did not display subgroup results for race categories with fewer than 10 individuals to protect confidentiality. We also evaluated subgroup effects by evaluating the interaction between statin prescription rates and specific characteristics as continuous variables: age, DL-CAC, and time since last primary care/endocrinology visit (Supplement Table S2).

For each secondary outcome, we analyzed each outcome with and without adjustment for age and/or baseline value. For continuous variables (lab values, systolic blood pressure, and 10-year ASCVD risk), we evaluated the change from the pre-randomization level using analysis of

covariance. We modeled the outcome variable at 6 months as the dependent variable while adjusting for the baseline value and age (Table 2). Age was modeled as a restricted cubic spline with a knot at the median, the 5th percentile, and 95th percentile. We repeated the analysis without adjustment for age (Supplement Table S4).

We analyzed binary outcomes (lab testing, aspirin prescription, and new cardiology encounters) via multivariable logistic regression with adjustment for age (Table 2). We repeated the analysis with Fisher's exact test without adjustment for age (Supplement Tables S4 and S5). For cardiovascular testing, we evaluated a composite outcome of coronary artery disease testing (stress testing, ECG-gated coronary CAC scans, coronary CT angiography, and invasive CT angiography) in addition to each individual testing modality. We also evaluated rest echocardiography as a separate outcome. The pre-specified analysis plan included adjustment for age and baseline frequency. We adjusted for baseline age in evaluating the composite outcome of coronary artery disease testing with multivariable logistic regression (Table 3) and repeated the analysis without adjustment (Supplement Table S5). However, given the low frequency of individual testing outcomes, we only performed unadjusted analyses for individual testing modality outcomes (Table 3).

For ordinal outcomes (number of primary care encounters, number of cardiology encounters, or number of anti-hypertensive medications), we used negative binomial regression with adjustment for age and the frequency of each outcome in the baseline period. We repeated the analysis without adjustment (Supplement Tables S4 and S5) with the Mann-Whitney U test.

We used multiple approaches to account for missing data. These included an analysis of non-missing data (complete case), imputed data via last observation carried forward, and imputed data via multiple imputation via chained equations. Results with non-missing data are displayed in Table 2. Results with imputed data are displayed in Supplement Tables S3 and S4. Imputed samples were combined via Rubin's rule.

Supplement Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria
Age ≥18 and <85
Stanford non-gated non-contrast chest CT from 2014-2019
Coronary artery calcium >0 on DL-CAC algorithm confirmed by radiologist
Clinic encounter with Stanford primary care or endocrinology from 2018-2020
Exclusion Criteria[*]
Coronary artery disease, peripheral artery disease, or cerebrovascular disease diagnosis
Coronary or peripheral arterial revascularization
Current or previous statin therapy
Dementia
History of medical non-adherence
Metastatic cancer or active cancer undergoing chemotherapy
Non-English speaking
Prior CT coronary angiogram or invasive coronary angiogram

[*] Exclusion criteria were based on structured data elements in the electronic health record (diagnoses and procedures) in addition to manual chart review. Prior ASCVD was determined by diagnosis of coronary artery disease, peripheral arterial disease, or cerebrovascular disease or prior percutaneous coronary intervention, coronary artery bypass graft surgery, or peripheral revascularization based on either structured elements in the electronic health record or manual chart review.

Supplement Table S2. Interaction Between Subgroup Characteristics and Statin Rates

Categorical Classifications	p-value for Effect Modification*		
Age (<70.8 vs. ≥ 70.8)	0.573		
Sex	0.108		
Ethnicity or Race	0.537		
DL-CAC Score (<18.6 vs. ≥ 18.6)	0.174		
LDL-C (<100, ≥ 100, or missing)	0.457		
Antihypertensive Medication Use	0.125		
Time from Prior Visit, days (<130 vs. ≥130)	0.792		
Continuous Variables	**Coefficient for Effect Modification**	**95% CI**	**p-value for Effect Modification**
Age x Notification	1.01	0.90-1.12	0.914
DL-CAC Score x Notification	1.00	1.00-1.00	0.532
Time Since Last Visit x Notification	1.00	1.00-1.01	0.762

Abbreviations: DL-CAC: Deep Learning-Coronary Artery Calcium; LDL-C: low-density lipoprotein cholesterol.
* Absolute statin prescription rates displayed in Figure 3.

Supplement Table S3. Secondary Clinical Outcomes With Imputation of Missing Data*

	Notification Arm N=86	Usual Care N=87	p-value
Hemoglobin A1c Measured	29 (34%)	23 (26%)	0.211
Hemoglobin A1c, % (Non-missing)	5.7 (0.7)	5.5 (0.5)	0.107
Hemoglobin A1c, % (LOCF)	5.6 (0.6)	5.6 (0.6)	0.187
Hemoglobin A1c, % (MICE)	5.5 (1.2)	5.4 (1.4)	0.419
Lipids Measured	50 (58%)	29 (33%)	0.002
LDL-C, mg/dL (Non-missing)	97.2 (30.3)	115.3 (29.4)	0.005
LDL-C, mg/dL (LOCF)	105.1 (31.7)	114.5 (29.0)	0.003
LDL-C, mg/dL (MICE)	99.8 (47.9)	116.0 (55.5)	0.033
HDL-C, mg/dL (Non-missing)	64.2 (21.6)	61.7 (22.5)	0.872
HDL-C, mg/dL (LOCF)	64.1 (21.0)	62.4 (20.7)	0.789
HDL-C, mg/dL (MICE)	64.9 (25.6)	65.5 (31.2)	0.917
Triglycerides, mg/dL (Non-missing)	87.1 (40.7)	123.4 (70.8)	0.009
Triglycerides, mg/dL (LOCF)	107.2 (79.6)	116.9 (74.8)	0.132
Triglycerides, mg/dL (MICE)	97.4 (77.4)	115.6 (101.7)	0.058
Systolic Blood Pressure Measured	69 (80.2%)	64 (73.6%)	0.287
Systolic Blood Pressure, mmHg (Non-missing)	131.3 (17.4)	128.9 (15.0)	0.374
Systolic Blood Pressure, mmHg (LOCF)	130.8 (16.9)	131.3 (18.2)	0.721
Systolic Blood Pressure, mmHg (MICE)	131.3 (19.4)	129.1 (19.2)	0.282
Body Mass Index Measured	66 (76.7%)	63 (72.4%)	0.486
Body Mass Index, kg/m^2 (Non-Missing)	25.5 (5.1)	26.7 (5.6)	0.630
Body Mass Index, kg/m^2 (LOCF)	26.0 (4.9)	26.2 (6.8)	0.718
Body Mass Index, kg/m^2 (MICE)	26.0 (5.0)	26.1 (5.9)	0.949
10-year ASCVD Risk, Available†	47.7%	31.0%	0.030
10-year ASCVD Risk (Non-Missing)	21.2% (16.5%)	18.1% (12.1%)	0.714
10-year ASCVD Risk (LOCF)	20.5% (15.9%)	18.3% (12.8%)	0.886
10-year ASCVD Risk (MICE)	20.9% (17.1%)	18.1% (14.0%)	0.215

Abbreviations: LOCF: Last observation carried forward; MICE: multiple imputation by chained equations; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

* For secondary outcomes of lab values, vitals, and aspirin treatment, statistical testing is adjusted for baseline value and age. For lab testing, statistical testing is adjusted for age. MICE performed with 100 imputations with results pooled using Rubin's rule.

† Defined as blood pressure and lipids during the 6-month follow-up period.

Supplement Table S4. Secondary Clinical Outcomes without Adjustment for Age[*,†]

	Notification Arm N=86	Usual Care N=87	p-value
Aspirin Treatment, 6 months	16 (18.6%)	17 (19.5%)	0.824
Number of anti-hypertensives, 6 months	0 (0-1)	0 (0-2)	0.885
Hemoglobin A1c Measured	29 (34%)	23 (26%)	0.323
Hemoglobin A1c, % (Non-missing)	5.7 (0.7)	5.5 (0.5)	0.082
Hemoglobin A1c, % (LOCF)	5.6 (0.6)	5.6 (0.6)	0.150
Hemoglobin A1c, % (MICE)	5.5 (1.2)	5.4 (1.4)	0.409
Lipids Measured	50 (58%)	29 (33%)	0.001
LDL-C, mg/dL (Non-missing)	97.2 (30.3)	115.3 (29.4)	0.003
LDL-C, mg/dL (LOCF)	105.1 (31.7)	114.5 (29.0)	0.002
LDL-C, mg/dL (MICE)	99.8 (47.9)	116.0 (55.5)	0.030
HDL-C, mg/dL (Non-missing)	64.2 (21.6)	61.7 (22.5)	0.904
HDL-C, mg/dL (LOCF)	64.1 (21.0)	62.4 (20.7)	0.767
HDL-C, mg/dL (MICE)	64.9 (25.6)	65.5 (31.2)	0.897
Triglycerides, mg/dL (Non-missing)	87.1 (40.7)	123.4 (70.8)	0.014
Triglycerides, mg/dL (LOCF)	107.2 (79.6)	116.9 (74.8)	0.112
Triglycerides, mg/dL (MICE)	97.4 (77.4)	115.6 (101.7)	0.062
Systolic Blood Pressure Measured	69 (80.2%)	64 (73.6%)	0.368
Systolic Blood Pressure, mmHg (Non-missing)	131.3 (17.4)	128.9 (15.0)	0.379
Systolic Blood Pressure, mmHg (LOCF)	130.8 (16.9)	131.3 (18.2)	0.760
Systolic Blood Pressure, mmHg (MICE)	131.3 (19.4)	129.1 (19.2)	0.305
Body Mass Index Measured	66 (76.7%)	63 (72.4%)	0.601
Body Mass Index, kg/m^2 (Non-Missing)	25.5 (5.1)	26.7 (5.6)	0.590
Body Mass Index, kg/m^2 (LOCF)	26.0 (4.9)	26.2 (6.8)	0.697
Body Mass Index, kg/m^2 (MICE)	26.0 (5.0)	26.1 (5.9)	0.939
10-year ASCVD Risk, Available[‡]	47.7%	31.0%	0.030
10-year ASCVD Risk (Non-Missing)	21.2% (16.5%)	18.1% (12.1%)	0.972
10-year ASCVD Risk (LOCF)	20.5% (15.9%)	18.3% (12.8%)	0.863
10-year ASCVD Risk (MICE)	20.9% (17.1%)	18.1% (14.0%)	0.269

Abbreviations: ASCD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

[*] For all listed secondary outcomes, the statistical testing is without adjustment for age. For lab values, vitals, and aspirin treatment, statistical testing is adjusted for baseline value. MICE performed with 100 imputations with results pooled using Rubin's rule.

[†] Aspirin and number of antihypertensives based on assessment at 6 months post-notification. All other outcomes based on last assessment during the 6-month follow-up period.

[‡] Defined as blood pressure and lipids during the 6-month follow-up period.

Supplement Table S5. Healthcare Utilization Over 6 Months Stratified Across Arms without Adjustment*

	Notification Arm N=86	Usual Care N=87	p-value
Primary Care/Endocrinology Encounters, count per patient†	2.2 (2.2)	1.4 (1.6)	0.002
Cardiology Encounters, count per patient	0.4 (0.8)	0.2 (1.0)	0.030
New Cardiology Encounters, patients (%)	14 (16%)	4 (5%)	0.022
Coronary Artery Disease Testing, patients (%)‡	13 (15%)	2 (2%)	0.003

* All analyses without adjustment.

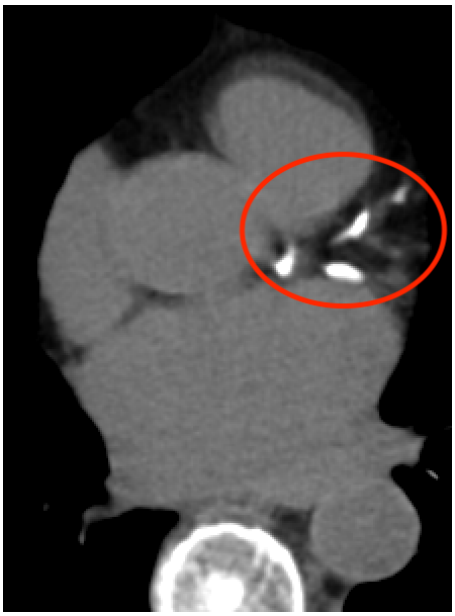
† Primary care encounters for patients with Stanford primary care clinician; primary care and endocrinology encounters for patients without Stanford primary care clinician.

‡ Coronary artery disease testing includes ECG-gated CAC scans, coronary CT angiography, invasive coronary angiography, and stress tests (e.g., echo, nuclear, or treadmill stress tests).

Supplement Figure S1. Clinician Notification Letter Example

Dear Dr. ***:

As part of a quality improvement project at Stanford, we screened non-gated chest CT scans for the presence of coronary calcium with a new, Stanford-developed artificial intelligence (AI) algorithm. The AI program detected coronary artery calcification (CAC) on the chest CT that this patient had on **/**/****. A radiologist verified this finding, about which you may already be aware. An image from the scan is below. The red circle shows the area of calcium.



Based on the presence of CAC, your patient meets the 2019 American College of Cardiology (ACC) and American Heart Association (AHA) Primary Prevention Guidelines for consideration of statin therapy.[1]

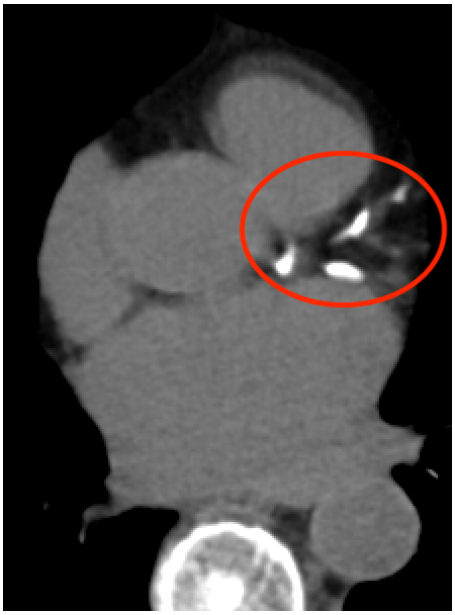
To facilitate shared decision-making, in 2 weeks we will send your patient a similar notification about the presence of CAC and the guideline recommendation to have a discussion with you about starting a statin to reduce their risk for an event. If this patient has already been diagnosed with atherosclerotic cardiovascular disease, is already taking a statin, or cannot take a statin, please let me know and we will not send a notice to your patient.

[1] Link to the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000678

Supplement Figure S2. Patient Notification Letter

Dear ***:

You had a chest CT scan on **/**/****. Using a new, Stanford-developed artificial intelligence software to read CT scans, it was found that you have coronary artery calcification (calcified plaques in the arteries that supply blood to your heart). This was verified by a radiologist. Below is a picture of the calcium in your coronary arteries. The circle shows the area of calcium.



People with calcium in their coronary arteries are at increased risk of having a heart attack compared with people who don't have calcium. Recent guidelines from the American Heart Association recommend that patients should talk with their doctors about a healthy lifestyle, control of their risk factors for heart disease, and treatment with a statin (medication that decreases the risk of heart attacks). **The presence of coronary calcium should be considered when making the decision to start a statin.**

A similar letter was sent to your primary care provider. Please contact your primary care provider to discuss your risk for heart disease and potential treatment to reduce your risk of a heart attack. If you have any questions, please email me at XXX@stanford.edu.