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

Alexander T Sandhu, MD, MS[1,2,3,4], **Fatima Rodriguez, MD, MPH**[1,3,4,5], **Summer Ngo, BS**[1], **Bhavik N Patel, MD, MBA**[6], **Domenico Mastrodicasa, MD**[4,7], **David Eng, MS**[8,9], **Nishith Khandwala, MS**[8,9], **Sujana Balla, MBBS**[10], **Doug Sousa, BS**[11], **David J. Maron, MD**[1,4,5]

[1]Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, CA

[2]Veterans Affairs Palo Alto Healthcare System, Palo Alto, CA

[3]Center for Digital Health, Department of Medicine, Stanford University, Stanford, CA

[4]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA

[5]Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, CA

[6]Department of Radiology, Mayo Clinic Arizona, Phoenix, AZ

[7]Department of Radiology, Stanford University School of Medicine, Stanford, CA, US

[8]Department of Computer Science, Stanford University School of Medicine, Stanford, CA

[9]Bunkerhill Health, Palo Alto, CA, US

[10]Department of Internal Medicine, University of California San Francisco-Fresno, Fresno, CA

[11]Patient Representative, Hollister, CA

Abstract

Background: Coronary artery calcium (CAC) can be identified on non-gated chest CTs, but this finding is not consistently incorporated into care. A deep learning algorithm enables opportunistic CAC screening of non-gated chest CTs. Our objective was to evaluate the impact of notifying clinicians and patients of incidental CAC on statin initiation.

Methods: NOTIFY-1 was a randomized quality improvement project in the Stanford healthcare system. Patients without known atherosclerotic cardiovascular disease (ASCVD) or prior statin prescription were screened for CAC on a prior non-gated chest CT from 2014-2019 using a validated deep learning algorithm with radiologist confirmation. Patients with incidental CAC

Address for Correspondence: Alexander T Sandhu, MD MS, 870 Quarry Road, Stanford, CA 94305, ats114@stanford.edu, @ATSandhu.

Twitter: Notifying clinicians and statin-naïve patients of incidental CAC identified on prior, non-gated chest CT via DL algorithm increased statin rates to 51% #CAC #AI #Opportunistic Screening

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were randomized to notification of the primary care clinician and patient versus usual care. Notification included a patient-specific image of CAC and guideline recommendations regarding statin use. The primary outcome was statin prescription within 6 months.

Results: Among 2,113 patients who met initial clinical inclusion criteria, CAC was identified by the algorithm in 424 patients. After additional exclusions following chart review, a radiologist confirmed CAC among 173 of 194 patients (89.2%) who were randomized to notification or usual care. At 6 months, the statin prescription rate was 51.2% (44/86) in the notification arm versus 6.9% (6/87) with usual care ($p<0.001$). There was also more coronary artery disease testing in the notification arm (15.1% [13/86] vs. 2.3% [2/87], $p=0.008$).

Conclusions: Opportunistic CAC screening of prior non-gated chest CTs followed by clinician and patient notification led to a significant increase in statin prescriptions. Further research is needed to determine whether this approach can reduce ASCVD events.

Over 700,000 Americans have a first acute myocardial infarction or die from coronary artery disease annually.[1] Many events could be avoided with greater application of preventive interventions among individuals at increased risk, including statin therapy. Multiple analyses have demonstrated sub-optimal statin therapy rates compared with guideline recommendations.[2-4] Strategies to promote shared decision-making discussions between patients and clinicians are needed to address patient-level factors that may influence decisions to initiate statin therapy.[5]

Coronary artery calcium (CAC) testing is a promising approach to identify high-risk individuals and motivate adoption of preventive interventions. The presence of CAC is a strong predictor of atherosclerotic cardiovascular disease (ASCVD) events.[6] The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on Management of Blood Cholesterol include a IIa recommendation for initiating statin treatment among patients with CAC≥100, CAC≥75th percentile for age and sex, or CAC>0 with age ≥55.[7] However, traditional CAC testing, which is performed on ECG-gated, non-contrast computed tomography (CT) scans, is rarely performed. However, over 19 million non-gated, non-contrast chest CT scans are performed annually for reasons other than to measure CAC.[8] We previously developed a deep learning algorithm to estimate CAC score (DL-CAC) on non-gated, non-contrast chest CT scans to efficiently implement opportunistic screening for incidental CAC.[9] For detecting CAC, the DL-CAC algorithm demonstrated a sensitivity of 82–94%, a specificity of 79%-100%, and a positive predictive value of 87–100% across 4 external datasets.

With no prior randomized studies using incidental CAC, the impact of notifying clinicians and patients regarding the presence of incidental CAC is unknown. We designed a randomized quality improvement project, NOTIFY-1, to understand whether notifying primary care clinicians and patients of incidental CAC would impact statin prescription rates among statin-naïve patients without known ASCVD.

METHODS

This was a prospective, randomized quality improvement project comparing notification of incidental CAC on prior non-gated chest CT scans with usual care among statin-naïve patients without known ASCVD in the Stanford Healthcare System. This project was motivated by institutional efforts to increase primary prevention statin therapy among high-risk patients. The QI project was deemed exempt from human subjects research requirements by the Stanford Institutional Review Board. The project was registered on clinicaltrials.gov (NCT04789278).[10] To protect confidentiality, de-identified data are available from the corresponding author only on reasonable request.

Study Population

Patients under 85 years old with any amount of CAC on a non-contrast, non-gated chest CT scan between 2014-2019 were considered for inclusion. Patients required a Stanford primary care clinician or a Stanford endocrinologist with whom they had a prior encounter (in-person or telehealth) in the prior 2 years. Patients with an ASCVD diagnosis, prior statin prescription, or prior invasive coronary angiography or coronary CT angiography were excluded. Patients with dementia, hospice enrollment, metastatic cancer or non-metastatic cancer receiving treatment, or other advanced diseases with limited life expectancy were also excluded. Exclusions were identified in two stages: first via structured electronic health record (EHR) data review, and second via manual chart review (see Figure 1 for Study Flow Diagram). Inclusion and exclusion criteria are listed in Supplement Table S1.

Identification of CAC

Following the initial exclusions using structured EHR data, the DL-CAC algorithm identified potentially eligible patients using the most recent non-gated chest CT scan between 2014-2019. The algorithm calculated the DL-CAC score in Agatston units; patients with a DL-CAC score of 0 were excluded. Following manual chart review of exclusion criteria, a radiologist reviewed each chest CT to confirm the presence of CAC.

Notification

Eligible patients with confirmed CAC were randomized 1:1 to notification or usual care via permuted block randomization using an online randomization module by study personnel. Patients randomized to notification first had an EHR message sent to their primary care clinician or endocrinologist. The clinician message (Supplement Figure S1) notified them regarding the presence of CAC on the prior non-gated chest CT. The letter included an axial image of the patient's chest CT with a circle around the CAC and a reference to the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on Management of Blood Cholesterol, which included a IIa recommendation for statin treatment of patients with CAC.[7] The letter to clinicians stated that their patient would be contacted in 2 weeks with the same information unless they thought patient notification would be clinically inappropriate and recommended against it. Before the start of the project, we held educational sessions regarding CAC with primary care leadership and a subset of primary care clinicians in the Stanford Healthcare System.

Two weeks after clinician notification, messages were sent to patients via the EHR patient portal. These messages (Supplement Figure S2) noted the increased cardiovascular risk associated with the presence of CAC, included the same CT image with CAC encircled as in the clinician notification, and recommended discussion of risk-reducing interventions with their clinician including statin use. The notification did not include the DL-CAC score. If patients did not open their message within 2 weeks, we sent the same letter via postal mail.

The EHR was reviewed for documentation of any discussions regarding incidental CAC or statins. For patients without any discussion with their care team or prescription of a statin within 3 months, we resent messages once to both the clinician and patient.

This project used an adaptive two-stage design. In the first stage, 50 patients were randomized to notification versus usual care. In the second stage, the remainder of the cohort was randomized. This allowed potential modification to the protocol based on feedback from patients and clinicians. There were no modifications to the intervention after the first stage. Therefore, both stages were pooled for the analysis.

If the intervention increased statin rates at 6 months and was deemed acceptable by primary care at the end of this project, we planned to also send notifications to the usual care arm following the 6-month follow-up.

Outcomes

The primary outcome was the statin prescription rate within 6 months of randomization. We evaluated statin prescription rates at 6 weeks, 3 months, and 6 months post-randomization. As secondary outcomes, we captured discussions of statin therapy, aspirin rates, anti-hypertensive therapy rates, individual biological cardiovascular risk factors, and cardiovascular resource use. The biological cardiovascular risk factors extracted from the EHR were last systolic blood pressure, lipid levels (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), hemoglobin A1c, and body mass index during follow-up. Using lipid measurements, systolic blood pressure, and antihypertensive therapy rates during follow-up, we calculated the 10-year risk of atherosclerotic cardiovascular disease events using the ACC/AHA Pooled Cohort Equations. For resource use, we captured the number of primary care encounters (in-person or telehealth), total cardiology encounters, new cardiology encounters, and CAD testing. CAD testing included coronary CT angiograms, CAC scans, stress tests, and invasive coronary angiograms. We evaluated diagnostic testing as a pooled composite outcome and as individual outcomes. All outcomes were assessed via the EHR by a non-blinded investigator (SN).

Statistical Analysis

The power analysis found that 150 patients would provide 87% power for a 20% absolute difference in statin prescription rates. All analyses were conducted with the intention-to-treat principle. The primary analysis compared statin prescription rates at 6 months across arms using Fisher’s exact test. The primary outcome was also compared across pre-specified subgroups: above and below median age, sex, ethnicity/race, low-density lipoprotein cholesterol level >100mg/dL or ≤100mg/dL, time since last primary care/endocrinology visit

stratified at the median, antihypertensive medication use, and the DL-CAC score stratified at the study median. Heterogeneity in the effect across subgroups was tested via the Tarone test.

For secondary outcomes, we compared continuous variables (laboratory values, systolic blood pressure, and 10-year ASCVD risk) using analysis of covariance with adjustment for baseline value and age. For binary outcomes (lab testing, CAD testing, and new cardiology encounters), we used logistic regression with adjustment for age. For the ordinal resource use outcomes (number of primary care encounters, cardiology encounters, and blood pressure medications), we used negative binomial regression with adjustment for age and baseline frequency (e.g., number of cardiology encounters in the prior year). Adjustment variables were identified a priori. We repeated all analyses for secondary outcomes without adjustment.

There were missing values for baseline and follow-up lab values, baseline and follow-up 10-year ASCVD risk, and follow-up body mass index. For missing data, we performed a complete case analysis and two imputation analyses: last observation carried forward and multiple imputation with chained equations. With multiple imputation with chained equations, we imputed 100 datasets using missing variables, randomization allocation, baseline values, and comorbidities. Further statistical analysis details are included in the supplement.

Statistical significance was evaluated at a two-sided p-value threshold of 0.05. All statistical analyses were performed in STATA v16 (StataCorp LLC).

RESULTS

There were 2,113 patients with non-gated, non-contrast chest CTs between 2014-2019 after excluding patients with prior diagnoses of ASCVD or dementia, statin prescription, or coronary angiography (Figure 1). Among this cohort, 424 (20.1%) were identified as having CAC on non-gated chest CT by the DL-CAC algorithm. Of these, an additional 230 patients were excluded based on manual chart review (non-Stanford primary care [n=58], prior statin [n=48], metastatic cancer or non-metastatic cancer receiving treatment [n=38], death [n=25], hospice/advanced disease [n=19], non-English speaking [n=18], ASCVD/prior coronary testing [n=14], and limited Stanford follow-up [n=10]). Of the remaining 194 patients, a radiologist confirmed CAC among 173 (89.2%) patients, and these patients were randomized between March 30, 2021 and June 7, 2021.

Baseline Characteristics

Patient characteristics were balanced across both arms (Table 1). The median patient age was 70.8 (IQR: 64.0-75.8). The median 10-year pooled cohort equation risk for an ASCVD event was 14.6% (IQR: 8.7%-27.7%) among the 149 patients in whom the risk could be calculated. The 10-year risk was ≥7.5% for 94.0% of patients (140/149). The median time from chest CT to notification was 857 days (IQR: 641-1,069 days). The most common indication for the CT was to evaluate a pulmonary nodule (63/173; 36.4%) followed by lung

cancer screening (22/173; 12.7%). Most radiology reports noted CAC in the body of the report (146/173; 84.4%) but only 3 reports (1.7%) noted CAC in the final impression.

Notification was sent to all 86 patients in the notification arm following notification of their clinicians. No clinicians objected to notifying their patients. Two endocrinologists requested the clinician notification be sent to the patient's primary care clinician outside of the Stanford Healthcare System.

Primary Outcome

The notification arm was more likely to receive a statin prescription than the usual care arm (Table 2). Six months post randomization, statins were prescribed to 51.2% (44/86) of the notification arm versus 6.9% (6/87) of the usual care arm ($p<0.001$) (Figure 2). Among patients prescribed statins in the notification arm, 72.7% (32/44) received a moderate-intensity statin prescription and 18.2% (8/44) received high-intensity statin therapy.

Figure 3 displays statin rates stratified by patient characteristics. There was no significant effect modification across the pre-specified subgroups (Supplement Table S2). Statins were prescribed to 59.1% of women in the notification group compared with 42.9% of men ($p=0.108$ for difference in the effect of notification across sex).

The notification arm was more likely to have discussions about statin therapy with clinicians. Among patients in the notification arm, 77.9% (67/86) had a documented statin discussion or new statin prescription compared with 12.0% (10/87) in the usual care arm ($p<0.001$).

Secondary Clinical Outcomes

At 6 months post-randomization, the aspirin treatment rate was similar across notification and usual care arms (18.6% vs. 19.5%, $p=0.848$, respectively) (Table 2). There was also no significant difference in the change in number of antihypertensives at 6 months.

Lipid levels were checked during follow-up among 58.1% (50/86) of the notification arm compared with 33.3% (29/87) of the usual care arm ($p=0.002$). Among those with repeat lipid testing, low-density lipoprotein cholesterol levels were lower in the notification arm vs. usual care (97.2 mg/dL [SD: 30.3] vs. 115.3 mg/dL [SD: 29.4], $p=0.005$, respectively). These results were consistent after imputing missing values (Supplement Table S3). There was no significant difference between groups in the change in hemoglobin A1c levels or systolic blood pressure during follow-up. The results were similar without adjustment for age (Supplement Table S4).

Healthcare Utilization

Over the 6-month follow-up period, there were more primary care encounters per patient in the notification arm compared with the usual care arm (2.2 [SD: 2.2] vs. 1.4 [SD: 1.6]; $p=0.011$). There was no significant difference in the number of cardiology encounters per patient across arms, but there were more patients with new cardiology encounters in the notification arm (16.3% vs. 4.6%, $p=0.015$).

There was an increase in CAD testing in the notification arm (Table 3). Among the notification arm, 15.1% (13/86) underwent testing for coronary artery disease compared with 2.3% (2/87) among the usual care arm (p=0.008). The largest absolute difference was among non-invasive stress testing (11.6% vs. 2.3%, p=0.018). No patients underwent invasive coronary angiography over the 6-month follow-up. The results were similar without adjustment (Supplement Table S5).

DISCUSSION

In this randomized quality improvement project, notifying clinicians and patients about the presence of incidental CAC on previously performed non-gated chest CT scans led to a significant increase in statin prescription rates. The effect of notification was consistent across patient subgroups. The novel DL-CAC algorithm allowed rapid screening of thousands of previous CT scans for the presence of CAC. This demonstrates the potential of using a deep learning algorithm to perform opportunistic screening for incidental CAC in the millions of non-gated chest CT scans performed annually for other reasons.[8]

A general concern with diagnostic imaging is incidental findings.[11, 12] CAC is a unique incidental finding because it can be leveraged to improve population health. The presence or absence of CAC improves risk assessment for a high-prevalence, preventable condition – ASCVD.[8, 13-17] Currently, most non-gated chest CT reports do not focus on the presence or severity of CAC.[18-20] CAC was mentioned in the initial CT report for 90% of our cohort, but CAC was included in the final impression in only 2% of reports and none of the patients was taking a statin. This suggests identifying CAC in the radiology report may not be as effective at promoting statin therapy as targeted clinician and patient notification tied to actionable recommendations. Extracting and disseminating this valuable, often unused finding with actionable information about its significance could promote implementation of lifestyle and pharmacologic interventions that substantially reduce cardiovascular morbidity.[21]

There is increasing interest in leveraging imaging data that is incidental to the clinical indication of the test to better understand a patient's risk of future events.[22] This has been commonly termed opportunistic screening, which contrasts with systematic screening of a segment of the population with a test such as mammography. Given the imaging has already been performed, the cost of extracting this data is low. However, there is still an impetus to demonstrate the potential value of the extracted data. This project is an example of how opportunistic screening with previously performed imaging can be leveraged to improve quality of care.

Notifying patients regarding CAC may have multiple potential benefits. Not only does CAC improve risk estimation above existing risk equations, but the image of calcification also has unique motivating effects. The power of visualizing one's atherosclerosis has also been demonstrated for carotid disease.[23] We leveraged that power by providing a personalized image of each patient's CAC. Although 94% of our cohort met guideline criteria for taking a statin based on their 10-year ASCVD risk, none of these patients were on statins at baseline. The notification and visual demonstration of patient-specific CAC led to a substantial increase in statin rates as compared with no notification. These results are overall

consistent with the Early Identification of Subclinical Atherosclerosis Using Non-Invasive Imaging Research (EISNER) trial, in which patients with visualized CAC had improvements in risk factor control and statin adherence compared with those without CAC.[24] The Danish Cardiovascular Screening Trial (DANCAVAS) further strengthened the evidence for CAC testing.[25] Among male participants randomized to a cardiovascular screening invitation, the most frequent positive finding was an elevated CAC score. In this trial, screening led to an increase in lipid-lowering drugs and antiplatelets and, among those between 65-69 years old, a reduction in all-cause mortality. Our opportunistic screening approach is distinct from EISNER and DANCAVAS by leveraging imaging data that already exists.

Our project does not separate out the effect of notification alone versus notification with the CAC image. Notifying patients of their elevated risk, based on their 10-year ASCVD risk alone, may have led to an increase in statin rates. However, prior efforts to notify clinicians of elevated cardiovascular risk based on risk equations have traditionally demonstrated smaller effect sizes.[26-30] Therefore, we tested a novel approach of notifying patients regarding incidental CAC with personalized images of their CAC.

While opportunistic CAC screening may have multiple potential clinical benefits, there are important considerations before a health system implements such a program. First, there is a fine balance between motivating action and excessively increasing patient anxiety. To ensure access to treatment and counseling, all patients in our project had an active relationship with a health system clinician and messages were sent to both patients and clinicians. Additional qualitative research with patients and their caregivers regarding appropriate wording of notifications and the appropriateness of direct patient notification will be important. Second, clinicians need to feel responsible for the patient's cardiovascular health and feel capable of acting on the results. Prior surveys estimated over half of referring clinicians are unaware of the significance of CAC.[31] We conducted limited educational sessions prior to launching the project for a subset of clinicians who might be notified. More extensive health system education may have augmented the effectiveness of our intervention. Primary care clinicians raised no concerns about the notifications to their patients, possibly due to the education about the intervention before its launch. Ensuring clinicians are aligned with the intervention efforts is likely an important element to implementation success.

Our intervention integrated automated processes – the DL-CAC algorithm and the automated EHR review – with manual processes – manual chart review and radiologist review for the presence of CAC. Our project used strict screening to evaluate the efficacy of our approach; future studies can increase automation to facilitate large-scale implementation of opportunistic screening programs. Manual chart review could be largely replaced with expansion of the automated EHR review and simplifying the exclusion criteria. There is a critical balance between considerations of patient autonomy to know their data and avoiding unnecessary anxiety by not screening for CAC in patients unlikely to benefit from preventive therapies (e.g., patients in hospice). Additionally, manual radiologist review of images may be less critical at higher thresholds where a small absolute error in the DL-CAC estimate would have minimal impact on the implications of notification.

Our project was restricted to patients with CAC who had no known ASCVD and were statin naïve. We therefore excluded patients with ASCVD who already had a Class I guideline recommendation for statin therapy.[7] We also applied additional exclusion criteria, such as requiring a Stanford primary care clinician or endocrinologist, for this proof-of-concept study. However, this limited the total eligible population for notification substantially. In future studies, the population eligible for opportunistic screening and notification will be expanded. Opportunistic screening could be broadened to include patients with known ASCVD given nearly 50% are not on statin therapy.[32] Even for patients on a statin, identification of CAC may lead to dose intensification, improved medication adherence, or lifestyle changes. Increasing the eligible population may reduce the per-patient effect of notification on statin rates; for example, patients without a primary care clinician in the health care system may be less likely to receive statin therapy after notification. However, even if the per-patient effect is smaller, expanding the intervention would still increase the population-level benefit at a low incremental cost.

Our approach used the DL-CAC algorithm retrospectively and had a radiologist confirm the binary presence of CAC. The algorithm could also be applied prospectively to assist radiologists in consistently identifying and quantifying CAC. Quantification of CAC severity may further improve the impact of notification, especially among those at highest risk. Future work will include expanding the DL-CAC algorithm to apply to low-dose chest CTs used for lung cancer screening and contrast chest CTs. Applying this approach to broader populations and more CT scans can potentiate the potential impact of opportunistic CAC screening but will require further evaluation.

On average, the DL-CAC scores in our cohort were low. However, the presence of any CAC increases risk compared with patients without CAC; for this reason, the ACC/AHA 2018 Guidelines on Blood Cholesterol have a IIa recommendation for considering statin therapy among patients ≥55 years old and for patients with a CAC score ≥75th percentile for their age, sex, and race. For a 54-year-old woman, a CAC score of 1 would be ≥75th percentile.[33] We did not observe differences in the effect of notification on statin rates between those with higher vs. lower CAC scores, but our CAC range was relatively narrow. Notifying patients with higher CAC scores and more pronounced calcification images may lead to larger increases in statin prescription rates.

Notifications also increased clinical encounters and testing. While the increase in primary care encounters and lipid testing are expected and potentially desirable, the benefit of increased cardiology encounters and CAD testing is unclear. There may also be a distinction between dedicated CAC scans, which could be used to validate the results of the DL-CAC algorithm, with non-invasive stress testing and coronary CT angiograms used to detect obstructive coronary disease but not recommended by guidelines in an asymptomatic cohort. Our results contrast with the EISNER trial, which found no significant increase in testing among the cohort randomized to a CAC scan.[24] These differences may be explained by the differences between unexpected opportunistic screening and patients being actively enrolled and educated in advance of their gated CAC scan as part of a systematic screening program. Additional education for clinicians and patients may mitigate the observed increase in testing rates. We did not collect data regarding the patient experience and any

potential anxiety of those notified. Further research regarding the impact on both healthcare resource utilization and the patient experience will be important steps prior to scaling this intervention.

Limitations

There are important limitations to our intervention. First, while we demonstrated a significant increase in statin rates from notifying patients about their subclinical atherosclerosis, the impact on clinical outcomes among this select cohort is unknown. Future studies to demonstrate whether notification reduces ASCVD events would be valuable. Second, this was performed at a single center; the generalizability to other health systems or to patients who did not meet our inclusion criteria is uncertain. Third, data on persistence of statin therapy beyond 6 months is critical to better understanding the impact of the intervention. We are continuing to follow patients and will plan to subsequently report outcomes at 12 months including statin treatment and downstream testing rates. Fourth, our intervention notified both clinicians and patients to facilitate shared decision-making; we did not investigate the impact of notifying only the clinician or only the patient. Finally, the investigators were not blinded to allocation when evaluating outcomes.

Conclusion

Notifying clinicians and their patients about the presence of incidental CAC detected on previously acquired non-gated chest CT scans led to a significant increase in statin prescription rates as compared with no notification. These findings illustrate the opportunity to use an automated method to screen non-gated chest CTs to identify patients with subclinical coronary atherosclerosis and the power of notification to motivate them and their clinicians to initiate preventive interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ASCVD	atherosclerotic cardiovascular disease
CAC	coronary artery calcium

CAD	coronary artery disease
CT	computed tomography
DL-CAC	deep learning based coronary artery calcium
EHR	electronic health record

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Clinical Perspective

What is New?

- In this randomized quality improvement project, statin-naïve patients with CAC on prior non-gated CT scans were identified via a deep learning algorithm.
- Notification of patients and their clinicians regarding incidental CAC with a personalized image of the CAC increased statin prescription rates.

What are the clinical implications?

- Opportunistic CAC screening on prior chest CT scans is a potential approach to identify patients at high risk of atherosclerotic cardiovascular disease events who would benefit from preventive interventions.
- The impact of such a screening strategy on clinical events is unknown and should be tested in a prospective randomized clinical trial.

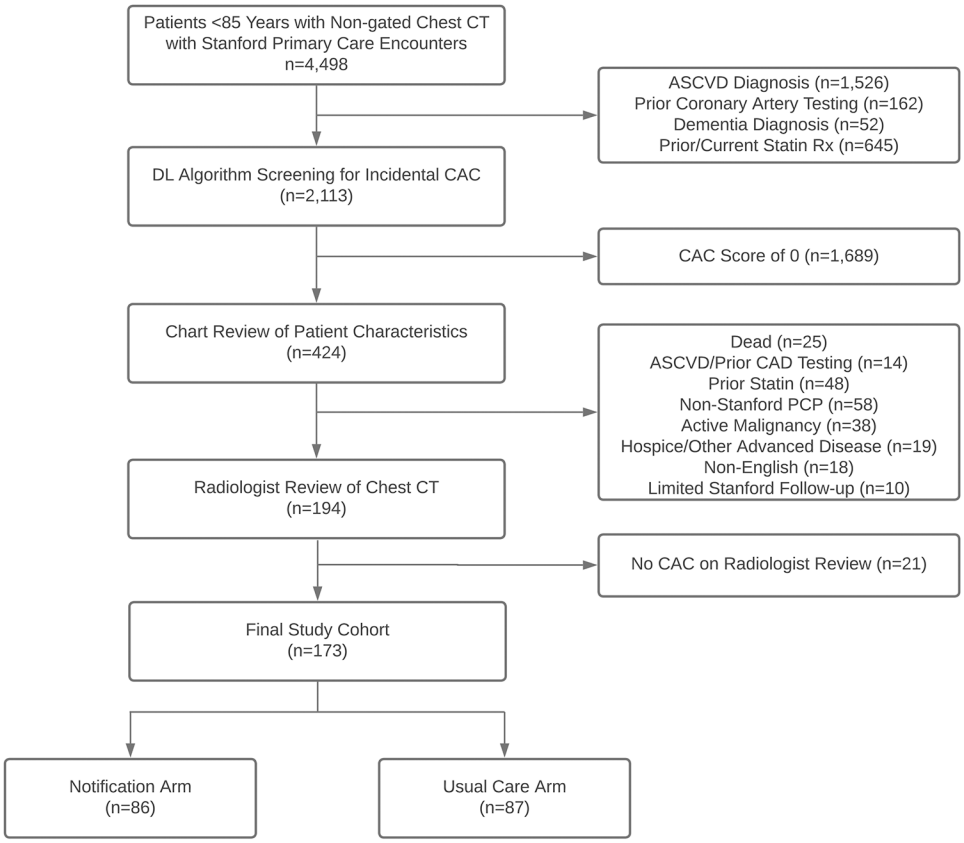

Figure 1. Study Flow Diagram

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CAC: Coronary artery calcium; CT: computed tomography.

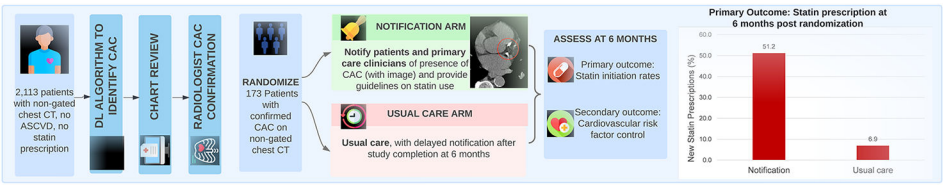

Figure 2. The NOTIFY-1 Quality Improvement Project.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CAC: coronary artery calcium; CT: computed tomography; DL: deep learning.

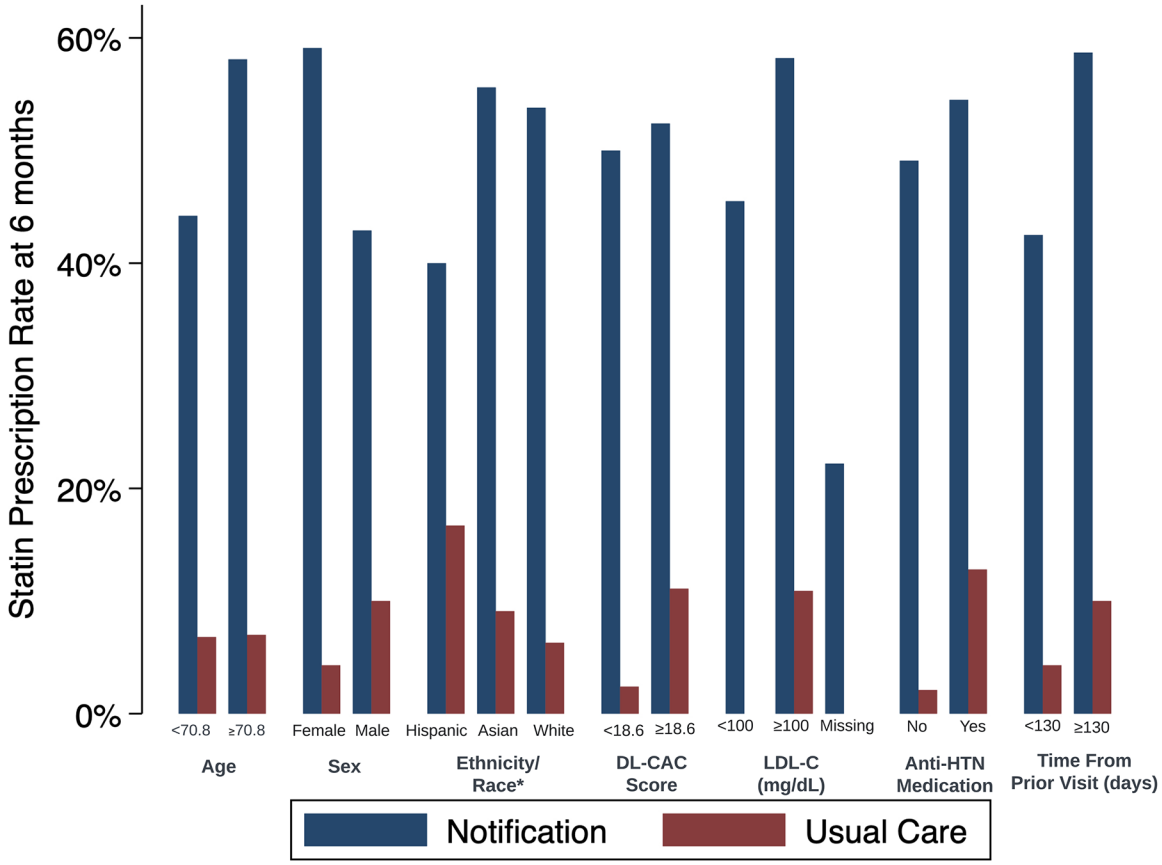

Figure 3. Sub-group Analyses of Statin Prescription Rates at 6 Months

Abbreviations: anti-HTN: antihypertensive; CAC: coronary artery calcium; LDL: low density lipoprotein; Rx: prescription.

This figure demonstrates results of the primary analysis, statin prescription rates at 6 months, stratified by key patient characteristics. For the ethnicity/race subgroup analysis, we first classified patients with Hispanic ethnicity. Among non-Hispanic patients, we made subgroups based on race. We excluded subgroups with fewer than 10 individuals across arms for confidentiality. There was no significant heterogeneity in the treatment effect across patient subgroups (Supplement Table S2). The statin prescription rate was 0% for patients in the usual care arm with LDL-C <100 mg/dL or with missing LDL-C. Testing for heterogeneity of treatment effect using continuous variables (for age, DL-CAC score, and time since last visit) are listed in Supplement Table S2.

Table 1.

Patient Characteristics

	Notification Arm n=86	Usual Care Arm n=87
Age	70.9 (64.0-75.8)	70.8 (64.0-76.0)
Female Sex	44 (51%)	47 (54%)
Race		
Asian	9 (10%)	11 (13%)
Black	4 (5%)	3 (3%)
White	65 (76%)	67 (77%)
Other	7 (8%)	5 (6%)
Unknown	1 (1%)	1 (1%)
Ethnicity		
Hispanic	5 (6%)	6 (7%)
Non-Hispanic	80 (93%)	78 (90%)
Unknown	1 (1%)	3 (3%)
Clinician		
Stanford Primary Care	84 (98%)	84 (97%)
Endocrinology	2 (2%)	3 (3%)
Time from Primary Care/Endocrinology Visit, days	115 (44-304)	170 (43-506)
Prior Cardiology Encounter, %	6 (7%)	7 (8%)
Chest CT Scan Indication		
Pulmonary Nodule Evaluation	23 (27%)	40 (46%)
Lung Cancer Screening	12 (14%)	10 (11%)
Parenchymal Lung Disease Evaluation	4 (5%)	2 (2%)
Malignant Disease Evaluation	7 (8%)	4 (5%)
Pleural Effusion Evaluation	0 (0%)	2 (2%)
Non-specific Symptom Evaluation	8 (9%)	9 (10%)
Other Indications	32 (37%)	20 (23%)
Time from Chest CT, days	848 (623-1056)	882 (646-1105)
DL-CAC Score	18 (7-112)	20 (3-70)
DL-CAC >0 to <100	63 (73%)	69 (79%)
DL-CAC ≥100	23 (27%)	18 (21%)
CAC Description in Radiology Report		
No CAC Noted	6 (7%)	11 (13%)
Mild	53 (62%)	52 (60%)
Moderate	16 (19%)	15 (17%)
Severe	6 (7%)	4 (5%)
Noted, No Qualitative Description	5 (6%)	5 (6%)
CAC Mentioned in Report Impression	1 (1%)	2 (2%)
Vital Signs		
Body Mass Index, kg/m2	25.3 (22.5-29.4)	25.9 (22.8-29.2)
Systolic Blood Pressure, mmHg	128 (120-142)	129 (119-146)

	Notification Arm n=86	Usual Care Arm n=87
Diastolic Blood Pressure, mmHg	78 (72-84)	76 (72-84)
ASCVD Risk, 10-year	16.1% (8.1%-29.7%)	13.6% (9.0%-26.5%)
Medications		
Antihypertensive, %	33 (38%)	39 (45%)
Aspirin, %	12 (14%)	12 (14%)
Comorbid Conditions		
Atrial Fibrillation, %	9 (10%)	6 (7%)
Cancer, %	35 (41%)	34 (39%)
Chronic Kidney Disease, %	14 (16%)	7 (8%)
Chronic Obstructive Pulmonary Disease, %	16 (19%)	20 (23%)
Connective Tissue Disease, %	12 (14%)	5 (6%)
Depression, %	28 (33%)	19 (22%)
Diabetes Mellitus, %	14 (16%)	6 (7%)
Hypertension, %	43 (50%)	44 (51%)
Hypothyroidism, %	28 (33%)	17 (20%)
Liver Disease, %	14 (16%)	13 (15%)
Other Lung Disease, %	17 (20%)	16 (18%)
Smoking, Current %	9 (11%)	9 (10%)
Laboratory Values		
Creatinine, mg/dL	0.9 (0.8-1.0)	0.8 (0.7-0.9)
Missing Creatinine	0 (0%)	1 (1%)
Hemoglobin A1c, %	5.6 (5.4-5.8)	5.6 (5.4-5.8)
Missing Hemoglobin A1c	32 (37%)	32 (37%)
High-Density Lipoprotein, mg/dL	60 (49-77)	60 (44-79)
Missing High-Density Lipoprotein	9 (10%)	15 (17%)
Low-density Lipoprotein (LDL), mg/dL	115 (98-133)	116 (100-128)
LDL <70mg/dL	5 (6%)	4 (5%)
LDL 70-99 mg/dL	17 (20%)	13 (15%)
LDL 100-129 mg/dL	30 (35%)	38 (44%)
LDL ≥130 mg/dL	25 (29%)	17 (20%)
Missing LDL	9 (10%)	15 (17%)
Triglyceride, mg/dL	94 (69-133)	94 (63-145)
Missing Triglyceride	9 (10%)	13 (15%)

Abbreviations: anti-HTN: anti-hypertensive; ASCVD: atherosclerotic cardiovascular disease; CAC: Coronary artery calcium; CT: computed tomography; LDL: low-density lipoprotein. Continuous variables displayed as median (interquartile range) and categorical variables displayed as frequency (percentage).

Table 2.

Outcomes Across Arms

	Notification Arm N=86	Usual Care N=87	p-value
Statin Discussion/Prescription, 3 months	53 (64.6%)	7 (8.4%)	<0.001
Statin Discussion/Prescription, 6 months	67 (77.9%)	10 (12.0%)	<0.001
Statin Prescription, 6 weeks	7 (35.0%)	0 (0.0%)	0.008
Statin Prescription, 3 months	32 (39.0%)	4 (4.8%)	<0.001
Statin Prescription, 6 months	44 (51.2%)	6 (6.9%)	<0.001
Statin Intensity			<0.001
High-Intensity	8 (9.3%)	3 (3.4%)	
Moderate-Intensity	32 (37.2%)	3 (3.4%)	
Low-Intensity	4 (4.7%)	0 (0.0%)	
No Statin	42 (48.8%)	81 (93.1%)	
Secondary Outcomes[*,†]			
Aspirin Treatment, 6 months	16 (18.6%)	17 (19.5%)	0.848
New Aspirin Treatment, 6 months[‡]	7/74 (9.5%)	7/75 (9.3%)	0.879
Number of anti-hypertensives, 6 months	0 (0-1)	0 (0-2)	0.985
Hemoglobin A1c Measured, follow-up	29 (33.7%)	23 (26.4%)	0.211
Hemoglobin A1c, % (Non-missing), follow-up	5.7 (0.7)	5.5 (0.5)	0.107
Lipids Measured, follow-up[§]	50 (58.1%)	29 (33.3%)	0.002
Low-Density Lipoprotein (LDL), mg/dL (Non-missing), follow-up	97.2 (30.3)	115.3 (29.4)	0.005
LDL <70mg/dL	9 (10.5%)	2 (2.3%)	
LDL 70-99 mg/dL	20 (23.3%)	6 (6.9%)	
LDL 100-129 mg/dL	12 (14.0%)	12 (13.8%)	
LDL ≥130 mg/dL	9 (10.5%)	9 (10.3%)	
Missing LDL	36 (41.9%)	58 (66.7%)	
High-Density Lipoprotein, mg/dL (Non-missing), follow-up	64.2 (21.6)	61.7 (22.5)	0.872
Triglycerides, mg/dL (Non-missing), follow-up	87.1 (40.7)	123.4 (70.8)	0.009
Systolic Blood Pressure Measured, follow-up[§]	69 (80.2%)	64 (73.6%)	0.287
Systolic Blood Pressure, mmHg (Non-missing), follow-up	131.3 (17.4)	128.9 (15.0)	0.374
Body Mass Index Measured, follow-up[§]	66 (76.7%)	63 (72.4%)	0.486
Body Mass Index, kg/m^2 (Non-Missing), follow-up	25.5 (5.1)	26.7 (5.6)	0.630

Abbreviations: ASCD: atherosclerotic cardiovascular disease.

[*]For secondary outcomes of lab values, vitals, anti-hypertensives, and aspirin treatment, statistical testing is adjusted for baseline value and age. For lab testing, statistical testing is adjusted for age. Results with imputation via last observation carried forward and multiple imputation available in Supplement Table 2.

[†]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.

[‡]New aspirin treatment among those not on treatment at baseline.

[§]Defined as a measurement during the 6-month follow-up period.

Table 3.

Healthcare Utilization Over 6 Months Stratified Across Arms *

	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)	0.011
Cardiology Encounters, count per patient	0.4 (0.8)	0.2 (1.0)	0.143
New Cardiology Encounters, patients (%)	14 (16.3%)	4 (4.6%)	0.015
Coronary Artery Disease Testing, patients (%) ‡	13 (15.1%)	2 (2.3%)	0.008
ECG-gated CAC Scans, patients (%)	3 (3.5%)	0 (0.0%)	0.121
Coronary CT Angiography, patients (%)	1 (1.2%)	0 (0.0%)	0.497
Invasive Coronary Angiography, patients (%)	0 (0.0%)	0 (0.0%)	---
Stress Tests, patients (%)	10 (11.6%)	2 (2.3%)	0.018
Resting Echocardiograms, patients (%)	5 (5.8%)	7 (8.0%)	0.766

Abbreviations: CAC: coronary artery calcium; CT: computed tomography; ECG: electrocardiogram.

* The number of primary care/endocrinology visits and number of cardiology encounters was adjusted for baseline frequency and age. The new cardiology encounter and coronary artery disease testing outcomes were adjusted for baseline age. Unadjusted analyses available in Supplement Table 4.

† 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).