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Running Title: Coronary Calcifications Detected on Lung Screening

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ABSTRACT

Individuals eligible for lung cancer screening (LCS) are at risk for atherosclerotic cardiovascular disease (ASCVD) due to smoking history. Coronary artery calcifications (CAC), a common incidental finding on low-dose CT (LDCT) for LCS, is a predictor of cardiovascular events. Despite findings of high ASCVD risk and CAC, a substantial proportion of LCS patients are not prescribed primary preventive statin therapy for ASCVD. We assessed the frequency of statin prescription in LCS patients with moderate levels of CAC. Among 259 individuals with moderate CAC, 95% had ASCVD risk ≥7.5%. Despite this, 27% of patients were statin-free prior to LDCT and 21.2% remained statin-free after LDCT showing moderate CAC. Illustratively, while a substantial proportion of LCS patients are statin-eligible, many lack a statin prescription, even after findings of CAC burden. CAC reporting should be standardized, and interdisciplinary communication should be optimized to ensure that LCS patients are placed on appropriate preventive therapy.

INTRODUCTION

Individuals eligible for lung cancer screening (LCS) are at increased risk for cardiovascular disease due to their smoking history and high frequency of comorbidities such as diabetes and hypertension.[1] In fact, atherosclerotic cardiovascular disease (ASCVD) was the primary cause of mortality in the low-dose CT (LDCT) arm of the National Lung Screening Trial (NLST), and subsequent studies have demonstrated that the radiologic presence of coronary artery calcifications (CAC) is associated with increased cardiovascular and all-cause mortality in LCS-eligible populations. [2-12] CAC

reporting guidelines from the Society of Cardiovascular Computed Tomography (SCCT) and Society of Thoracic Radiology (STR) state that a visual method for CAC scoring is less complex, quicker, and remains comparable to quantitative Agatston scoring for evaluating ASCVD risk on ungated CT scans. [3, 6, 13] Together, these studies demonstrate that detection and grading of CAC on LDCT is feasible and may offer added benefit by identifying ASCVD risk among individuals undergoing LCS.

In the general population, CAC is an independent predictor of cardiovascular events, and coronary calcium scoring may add incremental value when used in addition to ASCVD risk assessment for primary prevention of cardiovascular disease. [4] The 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend statin therapy as first-line primary prevention therapy for individuals with LDL≥190 mg/dL, diabetes mellitus, and for individuals determined by physicians to be at sufficient ASCVD risk. [14] Specifically, high risk individuals, or those with a 10-year risk of ASCVD ≥20%, should be initiated on a high intensity statin. [14] The decision to initiate primary preventive therapy in intermediate risk individuals (≥7.5 – <20% ASCVD risk) requires additional risk discussions, and CAC scoring can be useful to make decisions on initiating preventive therapy. [15] Intermediate risk individuals with CAC score >100 Agatston Units (AU) should be initiated on statin therapy, as this may lead to a greater reduction in major cardiovascular event risk compared to individuals with lower burdens of CAC. [14, 16] Consistent with this, the National Lipid Association has recommended that for patients incidentally found to have moderate or severe CAC, statin therapy should be initiated without any further testing, including dedicated CAC imaging. [15, 17] Even in individuals found to have incidental

mild CAC, it may be reasonable to obtain a dedicated CT scan for CAC scoring to guide preventive treatment decision-making. [15]

Despite existing guidelines for CAC reporting and management, multiple knowledge gaps remain in the systematic identification, characterization, and treatment of CAC among individuals undergoing LCS. Moreover, although most LCS patients are eligible for statin therapy, many lack a prescription both prior to screening and following the detection of significant CAC on LDCT. [18, 19] Most importantly, it is not known how to implement guideline-directed statin use among the LCS population, which is at high risk for cardiovascular mortality. Detection of moderate CAC, which approximately corresponds to an Agatston score 101-400 AU, may serve as a reclassifier for LCS-eligible individuals who are at intermediate ASCVD risk. [3, 5, 11] Our group has previously demonstrated that among patients found to have severe CAC on LDCT for lung cancer screening, 70% had known ASCVD and 88% were already on statin therapy prior to LDCT. [20] In the present study we focused on individuals with LDCT-detected moderate CAC given the likelihood that this cohort would have a lower incidence of known ASCVD, higher rates of statin non-prescription, and therefore greater potential for intervention. Thus, we aimed to characterize LCS-eligible patients with moderate CAC to determine the frequency of moderate and high intensity statin use and identify predictors of statin non-prescription.

METHODS

Study Cohort

Individuals who underwent LDCT through the Jefferson Lung Cancer Screening Program between January 1, 2018 and December 31, 2019 were identified via the LCS Program's prospective Registry. A retrospective chart review using the electronic medical record (EMR) was carried out for individuals with moderate CAC to extract baseline medical history and cardiovascular outcomes following LDCT for events occurring through March 31, 2021. Two individuals with moderate CAC were excluded due to extensive missing data in the EMR. Standardized training was provided for consistent and accurate data collection and reporting. The Thomas Jefferson University IRB granted a waiver of informed consent due to the minimal risk nature of the study (Control# 17D.150).

Lung Cancer Screening Program

The Jefferson LCS Program is a centralized program screening high-risk patients using USPSTF, CMS, and NCCN group II criteria for lung cancer since 2015. [21-23] Once a primary care provider (PCP) electronically refers a patient to the LCS Program, a nurse navigator contacts the patient via telephone to confirm eligibility, schedule a shared decision-making (SDM) visit and LDCT scan, and obtain insurance authorization for screening. During the study period, all SDM visits were performed in-person and immediately followed by a same-day LDCT scan. All patients with a positive LDCT result are reviewed at a Multidisciplinary Nodule Conference on a weekly basis. Screening results and incidental findings are conveyed to patients and PCPs via telephone and EMR, respectively. During the study period, all incidentally reported CAC findings were reviewed with patients with the recommendation to follow up with their

primary care physician. PCPs were notified of incidental CAC in a standardized results notification letter. No standardized recommendations about CAC management were made by the LCS Program or in the LDCT report.

Reporting of Coronary Artery Calcifications

LDCT results were reported using the American College of Radiology (ACR) Lung-RADS reporting system. The presence of an “S” modifier and the CAC severity were extracted from the LCS Program Registry. LDCT scans were reviewed at the time of original reporting by a thoracic radiologist who assigned a CAC severity classification by visual estimation based on STR/SCCT guidelines [13], using 4 categories of none, mild, moderate or severe coronary calcium.

Clinical Outcomes and Definitions

For all patients, an “index LDCT date” was identified, defined as the date of the screening LDCT performed by the LCS Program which first reported moderate CAC. All cardiac data were collected relative to the index LDCT date. Baseline cardiac comorbidities and medications were extracted from the primary care provider’s most recent office note and active problem lists just prior to the index LDCT scan or if this was unavailable, from any outpatient office note within 12 months preceding LCS. ASCVD was defined as coronary heart disease, cerebrovascular accident or transient ischemic attack, or peripheral vascular disease. Statins were grouped into moderate vs. high intensity regimens, with the latter including atorvastatin 40-80mg daily and rosuvastatin 20-40mg daily. [14] Medication changes, procedures, and cardiology

appointments within 12 months following the LDCT, and cardiac events including myocardial infarction or hospitalization for cardiac cause at any point during the study period following the index LDCT were identified from the EMR. The 10-year risk of cardiovascular disease was calculated for each individual using the 2013 AHA/ACC ASCVD risk model. [24, 25] Lipid panels closest in proximity to the LDCT scan were used for calculation of the ASCVD risk.

Statistical Analysis

Descriptive and inferential statistical methods were used to present the findings of this study. We obtained descriptives, frequencies and cross-tabulations to summarize data in tables. Bivariate analyses including independent t-tests and chi-square tests were performed to examine baseline characteristics of those diagnosed with moderate CAC on LDCT and the entire LCS Program cohort using a $p<0.05$ significance threshold. Bivariate and multivariate logistic regression were used to assess if common risk factors for cardiovascular disease were significant predictors of statin non-prescription at baseline. SPSS version 26 was used. [26]

RESULTS

Patient Characteristics

During the study period, 1,036 individuals underwent LDCT through the LCS Program. This overall screening cohort included 604 women (58.3%), as well as 53.6% White individuals and 40.8% Black/African-American individuals (Table I). More than half of LCS participants were currently smoking tobacco, and the mean smoking

intensity was 52.7 pack-years across the entire screening cohort. Any degree of CAC, including mild, moderate, or severe CAC, was detected in 75.9% of patients (786 of 1,036).

Two hundred fifty-nine individuals, or 25% of the entire screening cohort, were reported to have moderate CAC on LDCT and formed the study cohort. This group included 139 female individuals (53.7%) and was comprised of 61.8% White patients and 35.1% Black/African-American patients. Forty-six percent (46.7%) of individuals were current tobacco smokers. Compared to the entire screening cohort, individuals with moderate CAC had statistically significantly greater age (mean 66.7 vs. 64.4 years, $p<0.001$), and there was a significantly lower proportion of Black/African-American patients (35.1% vs. 40.8%, $p=0.03$). There was also a significantly higher rate of individuals with Medicare insurance (49.8% vs. 40.1%, $p=0.02$) and a greater proportion of patients with former smoking status (53.3% vs. 45.5%, $p=0.02$). There were no differences in gender, educational attainment, smoking intensity, or COPD diagnosis.

Coronary Artery Calcification Reporting on LDCT

Among the 259 individuals with moderate CAC reported on LDCT, 20 individuals (7.7%), had an “S” modifier identified on their LDCT scan report. Variation in CAC reporting among individuals with multiple LDCT scans was also examined. Of 142 individuals with subsequent LDCT scans following the index LDCT with moderate CAC, 58.5% had a subsequent LDCT report which identified moderate CAC. Five individuals (3.5%) had subsequent reports describing no CAC, 35 individuals (24.6%) were

reported to have mild CAC, and 19 individuals (13.4%) were subsequently reported to have severe CAC.

Baseline Cardiac Characteristics of Patients with Moderate CAC

Of the 259 moderate CAC patients, 66 patients (25.5%), had known ASCVD-qualifying diagnoses present in their medical problem list or documented in office notes in the EMR (Table II). The moderate CAC patients had a mean calculated ASCVD risk of 23.0% ± 11.6, and 95% (245 of 259) were at intermediate (≥7.5 – <20% 10-year ASCVD risk) or high (≥20% 10-year ASCVD risk) risk for ASCVD. Even after exclusion of the 66 patients with known ASCVD, 186 of the remaining 195 individuals (95.4%) had at least an intermediate level of ASCVD risk.

Overall, statin medications were found on the active medication list for 189 of 259 moderate CAC patients, or 73%. Individuals were reviewed for the presence of a statin indication including pre-existing ASCVD, diagnosis of diabetes, ASCVD risk ≥7.5 – <20%, or ASCVD risk ≥ 20% (Table III). Approximately 90% of patients with pre-existing ASCVD or diabetes were prescribed a statin at baseline. High-intensity statins were prescribed for 68.2% of individuals with pre-existing ASCVD (45 of 66) and 54.5% of individuals with diabetes (42 of 77). Among individuals with ASCVD risk ≥7.5 – <20% or ≥ 20%, however, 26.4% and 28.1% did not have a statin on the active medication list, respectively. The frequency of high-intensity statin prescription was lower among these groups, with 39.6% (42 of 106) of intermediate risk and 34.5% (48 of 139) of high risk individuals having a high-intensity statin prescription. After excluding 10 individuals

noted to have statin intolerance in their clinical chart, 36 of the 139 high ASCVD risk patients (25.9%) still were not prescribed a statin.

A logistic regression model demonstrated that age was marginally associated with statin non-prescription. Gender, race, smoking status, and educational attainment were not significantly associated with statin prescription. On multivariate analysis, former smoking status was statistically significantly associated with greater likelihood of statin non-prescription after adjustment for covariates (aOR 1.820, 95% CI 1.001-3.308) (Table IV).

Interventions and Events Following CAC Identification

Following LDCT for lung cancer screening, 33 patients with moderate CAC were newly prescribed a statin or had a change in dose or statin type (Supplemental Table I). Thirty-seven patients who had not seen a cardiologist in the year preceding the LDCT were evaluated by a cardiologist in the year following LDCT. Patients who saw both a cardiologist and primary care provider (PCP) prior to their LDCT had a significantly higher rate of statin prescription at baseline, and patients who attended a cardiology appointment after their LDCT had a higher rate of statin addition or modification ($p<0.001$ and $p<0.001$, respectively) compared to patients who only attended a PCP appointment after their LDCT. In addition, individuals seen by a cardiologist either before or after LDCT had a greater frequency of high intensity statin prescription compared to those who did not attend a cardiology appointment ($p=0.049$ and $p=0.007$, respectively).

Fifty-six individuals, or 21.6% of those with moderate CAC, underwent a cardiac stress test in the 12 months following their LDCT, 34% had an echocardiogram, and 6.2% had a cardiac catheterization (Supplemental Table I). Fifteen patients with moderate CAC (5.7%) were hospitalized for a cardiac cause after their LDCT and during the study period. Of these, 10 patients had an ACS event including unstable angina, NSTEMI, or STEMI. Five patients underwent percutaneous coronary intervention and 1 patient underwent a CABG. Of the 16 patients with a cardiac event during the study period, 12 individuals (75%) were on a high intensity statin, 2 individuals (12.5%) were on a low intensity statin, and 2 individuals (12.5%) were not on a statin at all.

DISCUSSION

We conducted a retrospective review of patients found to have moderate CAC on LDCT for LCS to identify trends in statin prescription before and after LDCT scan. Our results demonstrate that over 90% of our cohort had at least intermediate ASCVD risk, with more than half of individuals in the highest category of cardiovascular risk. Despite this, 27% of moderate CAC individuals were not on a statin prior to LDCT, and even after the LDCT 21.2% of patients remained statin-free. Moreover, we found that a relatively low percentage of individuals were on a high intensity statin despite significant risk factors for cardiovascular disease.

Similar to our findings, Ruparel and colleagues showed that in the UK, 98% of LCS patients were statin-eligible but fewer than half were on a statin. [18] There are several potential reasons for why statin prescription may be low in such a high-risk population including non-standardization in CAC identification and reporting, poor

communication between centralized LCS programs and PCPs, and lack of provider awareness of the clinical significance of CAC and ASCVD risk. [27] Attention to non-nodule incidental findings on LDCT and communication among health care providers is critical for comprehensive care of the LCS patient,and centralized screening programs should develop standardized protocols for managing incidental findings such as CAC. [28, 29] Future efforts should be guided toward optimizing the use of the EMR to ensure statin prescription in LCS-eligible patients, particularly those with high ASCVD risk.

However, several quality improvement studies analyzing physician communication through the EMR have shown that while the EMR may be effective for increasing statin prescribing, these likely need to be combined with other interventions to increase their effect, including enhanced physican-patient communication. [30] This communication should make clear the association between CT-detected CAC and ASCVD events. Moreover, when patients are scheduled for LDCT, it may be beneficial to advise them about potentially identifying CAC, among other common incidental findings as an integral part of the share decision-making process.[31-34]

We found that after adjusting for covariates, individuals with former smoking status had significantly higher odds of statin non-prescription compared to individuals who currently smoke. Although cardiac risk diminishes somewhat within 5 years of smoking cessation, it can take 15 years or longer for cardiovascular event incidence rates among heavy former smokers to approach those of never-smokers. [35] Several commonly used ASCVD risk calculators do not distinguish between former and current smoking status, and we hypothesize that this may contribute to under-recognition of ASCVD risk among individuals who previously smoked and may be categorized as

“nonsmokers.” Even among LCS participants predicted to have intermediate ASCVD risk, the presence of a ≥30 pack-year smoking history likely favors statin benefits over harms, particularly if radiologic CAC is present. Furthermore, intermediate risk individuals in this populations with a CAC score of 0 likely should not be down-classified as their significant smoking history is still a clinically important risk factor. [36]

Statin therapy is indicated for all individuals with diabetes or high (≥20%) ASCVD risk [14]. Furthermore, high-intensity statin therapy lowered LDL to a greater extent and also achieved greater reduction in ASCVD outcomes compared to placebo treatment. [37] The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease suggests that in cases where maximal ASCVD risk reduction is desired (as in individuals with high ASCVD risk or diabetes), it is reasonable to use a high-intensity statin. [14] We noted a lower frequency of high intensity statin prescription among individuals managed by primary care physicians (PCPs), compared with those who were evaluated by a cardiologist. This demonstrates an opportunity for education-based interventions geared towards PCPs and cardiology specialists that emphasize risk discussions to balance the potential benefits and harms of using high-intensity statins in the LCS population.

Our findings also demonstrate variability in CAC identification and reporting by radiologists interpreting LDCT for LCS due in part to expected inter- and intra-observer variability. [5] Our study reports CAC classified into four categories of none, mild, moderate, or severe, according to the STR/SCCT guidelines. [13] It is well-documented that there is significant variation between CAC evaluation on LDCT compared with standard CT electrocardiographic gated quantitative calcium scoring. [33] Following

ACC/AHA guidelines, there is a moderate level of evidence to suggest that patients found to have moderate and severe CAC on a non-calcium-scoring CT scan can be reasonably initiated on statins without further evaluation. [15, 17] Additionally, longitudinal assessment of coronary calcium on subsequent CTs at different time points may vary due to other factors including technique, type of scanner, patient heart rate, respiratory/patient motion, and radiation dose. We also found low utilization of the S modifier on LDCT reports. Although the ACR recommends that the category S should be used to report clinically significant or potentially clinically significant findings, there is often uncertainty among radiologists about what constitutes a clinically significant result. [38] Standardized application of the S modifier for moderate or severe CAC, as well as adherence with CAC scoring and reporting guidelines such as those developed by the STR/SCCT, may improve identification of high-risk patients who would benefit from lipid-lowering therapy. [13]

Our study has several limitations including its single-institution approach, which limits generalizability to other LCS programs. Additionally, due to the nature of retrospective studies, we cannot be certain that the presence of a statin on the active medication list correlated with patient adherence. We also cannot verify that medication changes and cardiac testing in the 12 months after LDCT were direct responses to the moderate CAC findings on LDCT. Furthermore, our data may be limited by the COVID-19 pandemic as many patients were unable to attend in-person appointments during the latter part of the study period. Finally, although we chose to focus on individuals with moderate CAC, we found variability in CAC reporting. While this may be expected due

to issues noted above, we cannot be certain this cohort comprises all LCS patients with true moderate CAC.

In summary, the vast majority of LCS patients are statin-eligible but a substantial proportion of these patients lack a statin prescription prior to and after LDCT despite findings of CAC. Future work should be oriented towards improving statin prescription by leveraging LDCT findings in this high-risk population, assessing how statins may decrease cardiovascular events and mortality among individuals undergoing LCS, and standardizing reporting of CAC using a visual assessment.

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TABLES: