CORONARY ARTERY CALCIUM SCORES FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK STRATIFICATION IN SMOKERS: MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

BY

JOHN ADAM LEIGH, MD

A Thesis Submitted to the Graduate Faculty of WAKE FOREST UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

In Partial Fulfillment of the Requirements For the Degree of Master of Science Clinical and Population Translational Sciences

August 2017 Winston-Salem, North Carolina

Approved By

Joseph Yeboah, M.D., M.S., Advisor

Michael E. Miller, Ph.D., Chair

David Herrington, M.D., MHS, Committee Member

Fang-Chi Hsu, Ph.D., Committee Member
# TABLE OF CONTENTS

List of Illustrations and Tables...........................................................................................................III

List of Abbreviations................................................................................................................................IV

Abstract...................................................................................................................................................V

Chapter 1: Introduction...........................................................................................................................1

  Literature Review...................................................................................................................................1

  Specific Aims...........................................................................................................................................13

Chapter 2: Manuscript............................................................................................................................14

  Background...........................................................................................................................................14

  Methods...............................................................................................................................................16

  Statistical Analysis.........................................................................................................................19

  Results...............................................................................................................................................20

  Discussion..........................................................................................................................................24

  Conclusions.......................................................................................................................................27

Chapter 3: Analysis of National Lung Screening Trial cohort and Future Work.................................36

  NLST and Case Cohort Studies........................................................................................................36

  Introduction.......................................................................................................................................36

  Methods..............................................................................................................................................37

  Statistical Analysis.........................................................................................................................39

  Results...............................................................................................................................................40

  Discussion..........................................................................................................................................42

  Future Work.......................................................................................................................................44

References.............................................................................................................................................49

Curriculum Vitae.................................................................................................................................56
LIST OF TABLES AND FIGURES

Chapter 2

Table 1. Demographic and risk factors in all smokers and LDCT-eligible participants

Table 2. Hazard ratios of CAC strata for incident ASCVD

Table 3. Reclassification tables for all smokers and LDCT-eligible samples

Figure 1. Flow Diagram of subject selection from MESA cohort

Figure 2. Percent of subjects with ASCVD events during follow-up by CAC strata

Figure 3. Kaplan-Meier curves by of event-free survival by sample

Figure 4. Receiver operator curve comparisons by sample

Chapter 3

Table 1. Baseline characteristics of NLST sub-sample

Table 2. Weighted logistic regression analysis of CAC presence by mortality category

Figure 1. Distribution of CAC by mortality category

Figure 2. Receiver operator curve comparisons by outcome
LIST OF ABBREVIATIONS

ACC, American College of Cardiology
AHA, American Heart Association
ASCVD, Atherosclerotic cardiovascular disease
AUC, Area under the curve
CAC, Coronary artery calcium
CHD, Coronary heart disease
CMS, Centers for Medicare & Medicaid Services
CT, Computed tomography
CVD, Cardiovascular disease
LDCT, Low-dose computed tomography
LDCT-SE, Low-dose computed tomography screening eligible
MESA, Multi-Ethnic Study of Atherosclerosis
MI, Myocardial infarction
NLST, National Lung Screening Trial
NRI, Net reclassification improvement
PCE, Pooled cohort equation
ROC, Receiver operator curve
USPSTF, United States Preventive Services Task Force
ABSTRACT

Introduction: Screening for lung cancer with low-dose computer tomography (LDCT) is recommended for a specified group of cigarette smokers. Coronary artery calcium (CAC) can be obtained from these LDCT scans. The utility of CAC for atherosclerotic cardiovascular disease (ASCVD) risk stratification remains unclear in this high-risk group. We assess this potential in smokers, especially those eligible for LDCT lung cancer screening.

Methods: A total of 3,356 Multi Ethnic Study of Atherosclerosis participants were smokers (2,476 former and 880 current) and 481 were LDCT screening eligible (LDCT-SE). Kaplan Meier, Cox proportional hazard, area under the curve (AUC) and net reclassification improvement (NRI) analyses were used to assess the association between CAC and ASCVD events.

Results: Smokers had a mean age of 62.1 years, 43.5% were females, and had a mean of 23.0 pack-years of smoking. The LDCT-SE sample had a mean age of 65.3 years, 39.1% female, and had a mean of 56.7 pack-years of smoking. ASCVD events occurred in 13.4% of smokers and 20.8% of LDCT-SE after a mean of 11.1 years of follow-up. 6.7% of all smokers and 14.2% of LDCT-SE smokers with CAC=0 had an ASCVD event during the follow up. CAC was associated with increased ASCVD risk in all-smokers and LDCT-SE in all the Cox models. AUC of the PCE for ASCVD events was higher in all-smokers compared with LDCT-SE (0.693 vs. 0.545). CAC significantly improved the AUC of the PCE in all-smokers but not in LDCT-SE. The event and non-event NRI for all smokers and LDCT-SE were: -0.155 and 0.440 vs. -0.07 and 0.265, respectively.
Conclusion: The PCE and PCE with CAC have modest to poor discriminative ability for future ASCVD events in the LDCT-SE sub-sample. 14.2% of LDCT-eligible smokers with CAC=0 had ASCVD events during follow-up. LDCT-eligibility self-identifies a high-risk cohort in which the PCE ± CAC has significant limitations for ASCVD risk assessment. Replication of our findings in larger cohort is needed.
CHAPTER 1: INTRODUCTION

Introduction

Coronary artery calcium (CAC) scoring is a radiographic assessment of calcifications within the vascular walls. The usefulness of CAC as a marker of clinical and pre-clinical marker of atherosclerosis has been extensively studied since the expansion of computed tomography (CT) scanning technology. Multiple medical societies have recommended CAC scoring for use in intermediate risk patients where the results could be expected to change management by reclassifying the patient to a lower or higher risk group. Wider usage has not been recommended due to a number of reasons including concerns of radiation exposure, cost-effectiveness, and number needed to scan in order to get clinically meaningful data. The use of CAC scoring in smokers is less extensively studied. With the spread of CT scanning for lung cancer screening in certain groups of heavy smokers there is an opportunity for CAC assessment in patients where it would otherwise not be recommended without incurring undue radiation exposure or significantly increased cost. We seek to assess the utility of adding CAC to a widely used clinical risk score to modify cardiovascular risk prediction in current and smokers, as well those who are eligible for lung cancer screening with CT.

Literature Review

Cardiovascular disease (CVD) is a broad term used to address a constellation of diseases which affect the heart and vascular system. It includes such conditions as hypertension, myocardial infarction, stroke, peripheral vascular disease, valvular heart disease, and arrhythmias. While some diagnoses are related only by virtue of anatomy,
the majority of the population-level disease mortality burden, coronary disease and stroke, share the common pathway of atherosclerotic cardiovascular disease (ASCVD). CVD as a whole remains the most common cause of death in the United States as well as worldwide despite a steady decrease in CVD events and age-adjusted mortality for decades\(^1\). More than one third of Americans are estimated to have at least one CVD condition including 80.0 million adults with hypertension and 15.5 million with coronary heart disease (CHD). Hypertension alone was estimated to cost $42.7 billion dollars annually in direct health expenditures. The US Department of Health and Human Services estimates that one in six American healthcare dollars are spent on CVD\(^2\). In 2011, the total cost of these diseases was estimated at $316.6 billion in direct health care costs and lost productivity.

Among the risk factors for CVD are multiple lifestyle behaviors, including physical activity, dietary choices, and smoking or tobacco use\(^3\). Cigarette smoking has been recognized as a risk factor for CVD for decades despite the incomplete definition of the mechanisms by which smoking promotes ASCVD\(^4\). Since the 1964 Surgeon General report linking smoking and ill health, tobacco has been the subject of public health concerns, specific tax laws, and statements by major medical societies advocating for abstinence or cessation\(^5\). The effect of this multi-faceted message can be seen in the decreasing prevalence of smoking amongst youth and adults since that time. However, despite large gains the percent of Americans who are current cigarette smokers remains significant at 15.1\(^6\%\).

While the mechanisms by which cigarette smoking promotes ASCVD are not fully understood, the association between the two has been demonstrated time and time
In the United States, it has been estimated that cigarette smoking and second-hand smoke exposure are responsible for one third of CHD deaths and one in five of all deaths per year or about 480,000 deaths. Cigarette smoking is an independent risk factor for all-cause mortality, myocardial infarction (MI), all ASCVD, peripheral artery disease, and cerebrovascular disease. Not only has smoking repeatedly been associated with ASCVD but the magnitude of the impact has been found to be quite large. In follow-up of the population-based prospective Finnmark study, the incidence of MI was threefold higher in men and six fold higher in women who smoked at least 20 cigarettes (1 pack) per day compared to those were never smokers. Multivariate analysis showed that current smoking conferred a relative risk of 1.9 in men and 3.3 in women for initial MI. Later work with nearly 25,000 Danish subjects showed similar findings: for MI, current smokers had a relative risk of 1.43 for males and 2.24 for females compared to never smokers. In the INTERHEART study, a case-control study with nearly 30,000 participants from 52 countries, it was observed that those who had an acute MI were 2.87 times more likely to smoke and a population attributable risk of 35.7% was seen for current and former smokers compared to never smokers.

Smoking cessation is such a powerful risk factor for CVD that the American Heart Association (AHA) has made it part of the “Life’s Simple 7” campaign which promotes healthy lifestyle choices to improve cardiovascular health. While smoking confers increased risk of an ASCVD event, a person’s CVD risk can be decreased if cessation is maintained for a period of years. In those with previous MI and left ventricular dysfunction, smoking cessation decreased morbidity from CHD and heart failure as well as all-cause mortality. Smoking cessation after MI or CHD diagnosis has
also been found to be associated with decreased risk of sudden cardiac death and all-cause mortality\textsuperscript{18,19}. The risk of recurrent coronary events is greater in those who continue to smoke but can drop to equal that of non-smokers by 3 years after cigarette cessation\textsuperscript{20}. Cessation confers such a benefit that only current smoking status is considered in CVD risk algorithms such as the Framingham Risk Score and its modifications as well as the American College of Cardiology (ACC) / AHA guideline-endorsed Pooled Cohort Equation (PCE)\textsuperscript{21–24}.

In addition to the promotion of CVD, smoking is the major behavioral risk factor for the development of lung cancer\textsuperscript{25}. Despite the decrease in smoking, lung cancer remains the second most common cancer diagnosis as well the most deadly cancer in America\textsuperscript{25}. For years, the benefits of screening for lung cancer with CT scanning were recognized but not widely implemented due to concerns over cost effectiveness, high false positive rate, and radiation exposure \textsuperscript{26}. However, official stances changed after the work of the National Lung Screening Trial (NLST). In the early 2000s, the NLST study group conducted a randomized controlled trial to determine the effect of screening with yearly low-dose helical CT (LDCT) scanning compared to yearly posterior-anterior chest X-rays. The study screenings were conducted for three years with the primary outcome being lung cancer mortality. The cohort had 53,456 subjects split between the two screening modalities. At the initial screening visit, the sensitivity of LDCT was 92.5% compared to only 71.6% in the X-ray group for identifying potential lung cancers\textsuperscript{27}. This improved lung cancer detection persisted during the study period and by the end of the planned follow-up period there was a 20% relative reduction in lung cancer mortality in the LDCT screening group compared to those who underwent chest radiography\textsuperscript{28}. Based
on the strength of the results from NLST there were recommendation and guideline changes by the United States Preventive Services Task Force (USPSTF) in 2013, American Association for Thoracic Surgery in 2012, and by the American College of Chest Physicians / American Society of Clinical Oncology / American Cancer Society in 2013. In February 2015 the Centers for Medicare and Medicaid Services (CMS) determined that there was significant evidence to reimburse for annual screening for lung cancer with LDCT as well as counseling about the screening and shared decision making visits. The CMS eligibility criteria for LDCT screening include patients aged 55-77 years, no signs or symptoms of lung cancer, and those who have smoked at least 30 pack-years. Both current smokers and those who have quit within the past 15 years are considered eligible.

It has been projected that there were approximately 8.6 million Americans who qualified for LDCT lung cancer screening in 2010. Based on these numbers, it was then estimated that over 12,000 lung cancer deaths could be prevented annually if the screening regimen from the NLST was fully implemented in the US population. These numbers are likely on the conservative side as the calculations were based on the NLST age range of 55-74 years instead of the ranges endorsed by CMS (55-77 years) and USPSTF (55-80 years). While this analysis highlighted the magnitude of a widespread screening program, little work had been done to address the number one cause of death in the NLST, cardiovascular disease. Looking further into the results from the NLST it was observed that cardiovascular illness was the top cause of death, responsible for 24.8% of all deaths in the trial. Given the high cardiovascular risk associated with smoking, these screenings present an opportunity to also assess for cardiovascular pathology in the form
of vascular calcifications. Additionally, if clinically significant information can be
gleaned from a CAC assessment in these scans there is the potential to change treatment
plans for millions of Americans annually.

While CAC is relatively new as a clinical tool, the anatomical phenomenon has
been recognized for hundreds of years. Long before the invention of radiology,
physicians and anatomists had described the association between vascular calcifications
and disease via post-mortem examination. After the advent of fluoroscopy, coronary
artery calcifications were observed in living patients as early as the 1950s. By the
1980’s, cardiac catheterizations were being performed and clinicians used fluoroscopy
and cineangiography to delineate the lumens of the coronary arteries. Using these
technologies, it was found that there was a high prevalence of calcifications in those with
significant coronary stenosis and that those who did have calcifications ended up with a
lower survival rate compared to those with stenosis but no calcifications. While
computed tomography (CT) scanning had been around since the 1970s, the first (and still
most prevalent) scoring system, the Agatston score, was first published in 1990. This
initial study used ultrafast electron beam CT to detect and quantify coronary artery
calcium (CAC) in subjects with and without clinical CHD. The score is calculated by
assessing the brightness of calcific lesions and measuring the area of lesions >130
Hounsfield units. The total calcium score was determined by adding up each of the
regional scores for all the CT slices (20 in the original study). Agatston’s results showed
that CAC assessed via CT was a more sensitive assessment for coronary disease than
fluoroscopy, exercise testing, and exercise thallium scanning. CT proved to have strong
sensitivity for detecting calcified lesions and a high negative predictive value for calcific CHD.

As technology improved, electron beam CT gave way to multidetector row or multi-slice CT scanners which both allow better assessment of the heart with less motion artifact. While newer studies rely more on multidetector systems, the older electron beam CT scans have been included in the protocols of large studies such as the Multi-Ethnic Study of Atherosclerosis (MESA) and the Coronary Artery Risk Development in Young Adults (CARDIA) study due to their initiation before or during the transition period in technologies\textsuperscript{38}. Despite the differences in the scanners, there is strong agreement in CAC scoring between the two CT scanner types\textsuperscript{39}.

In addition to identifying potential vascular blockages, CAC has also found to have clinical usefulness in the form of future CVD risk prediction. An early prospective study found a significant association between the presence of CAC in low and intermediate risk adults and cardiac events\textsuperscript{43}. Importantly, CAC was able to predict CVD events in even initially asymptomatic subjects\textsuperscript{44,45}. A subsequent meta-analysis demonstrated that those with higher CAC scores had an increased risk of cardiovascular events, including fatal and non-fatal myocardial infarction, coronary reperfusion procedures, and stroke\textsuperscript{46}. While the target populations of our study are inherently higher risk, the incorporation of CAC into traditional risk scores have the potential to identify those patients who may need more aggressive medication and lifestyle interventions in addition to those who, despite their history, could be at a lower than expected risk for an ASCVD event.
CAC score assessment matured as a clinical marker and serial measurements started to be performed in research settings. In scans performed an average of 3.1 years apart, progression of CAC was associated with increased risk of death in those with detectable CAC at the initial scan. In MESA, progression was found to be greater in those with metabolic syndrome and diabetes mellitus, with this change also associated with a higher risk of cardiovascular events. In all MESA participants, similar results were found with incident CAC and progression of CAC being associated with an increased risk of events. The usefulness of serial measurements is an important factor to consider for future work if we are to consider the lung cancer screening population. The protocol for use of LDCT requires annual screening which would allow clinicians to not only assess a baseline CAC score for their patients but also to follow progression over a period of years.

Despite the well-demonstrated association between CAC and ASCVD outcomes, there is debate over the clinical utility of incorporating CAC into routine CVD risk prediction. One of the deterrents from more wide-spread assessments of CAC is the risk from ionizing radiation from the CT scan. A review of the radiation dosages reported in the MESA scans showed that the mean radiation exposure was slightly greater than that recommended by the AHA and Council of Cardiovascular Radiology and Intervention. Additionally, there has been skepticism over the effectiveness of using CAC to improve primary prevention treatment. Among subjects who met criteria for statin treatment by AHA/ACC guidelines, 62% had no identifiable disease or mild disease, defined by CAC of <100. As a result, the number needed to screen to prevent one CVD event is likely very high and the largest benefit from this cohort was proposed to be in up-classifying
low-risk patients. One of the complicating factors to CAC assessment is the potential for incidental findings on CT scanning which may increase follow-up costs, particularly for non-CVD pathologies.

Despite the ongoing debate in proper usage of performing CT for the purpose of CAC scoring, the ACC and AHA have recommended that CAC can be used as a marker to identify patients who would otherwise be considered intermediate risk but who may benefit from statin therapy\(^4\). The use of CAC appears often as a “non-traditional risk factor” with a lower strength of evidence (IIb) supporting usage. Arguments in favor of wide use of CAC for risk assessment have shown that there is significant heterogeneity in patients eligible for statin treatment by ACC/AHA guidelines. In MESA subjects who were initially eligible for statin therapy, the absence of CAC was able to reclassify half of the participants into a lower risk group who would not benefit from statin therapy\(^5\). If CAC testing is limited to patients with an intermediate ASCVD risk (5-20% 10 year risk via Adult Treatment Panel III), it has been estimated that paying for CAC assessments breaks even when scans cost approximately $235 each\(^6\).

The idea of using LDCT to assess CAC had been around before its widespread use for lung cancer screening. Despite the differences in modality, it has been demonstrated that CAC can be assessed on a non-cardiac gated, LDCT study\(^7\). This is advantageous for our research question as two of the major concerns for routine CAC assessment are cost and radiation dosage. If LDCT performed for lung cancer screening is used for CAC assessment, the time investment by the radiologist to report CAC is minimal and there is no additional radiation exposure for the patient. However, one potential issue are differences in scoring between gated and non-gated studies and there is
some loss of accuracy with the non-gated scans despite still being feasible for CAC scoring. When comparing the two modalities performed on the same patient, the accuracy of the low-dose protocol increased as the CAC burden increased. The work is ongoing, however, it appears that the scores obtained from low-dose scans correlate well with the gated scores and still provide prognostic information.

Studies specifically examining the role of CAC in smokers are somewhat limited despite the overall number of studies as well as the current prevalence of smoking. In a prospective registry-based study, younger smokers (<55 years old) were found to be more likely to have significant CAC when compared to non-smokers in the same age group, as well as have statistically lower 5-year survival rates. A graded relationship was also found between the degree of CAC and all-cause mortality in both smokers and non-smokers. In this cohort; increasing CAC burden had a larger impact on survival in smokers than non-smokers. While this study benefitted from a large sample size, there were relatively few events and there was not data on specific cause of death. Using the MESA cohort, McEvoy et al. studied cigarette smoking and the role of CAC and high sensitivity C-reactive protein, a marker of inflammation. Predictably, they observed the highest all-cause CVD incidence rate in current smokers with CAC >100. It was also observed that current smokers with no CAC had a lower incidence rate than never smokers with CAC >100. This result shows that there may be potential in utilizing CAC assessment in smokers particularly to down-classify a patient’s risk estimate. However, adjusted hazard ratios for all-cause CVD, all-cause CHD, and hard CHD based on CAC were higher for never smokers than both former and current smokers. CAC >100 was associated with an increased risk for events across all categories but the specificity seems
to be decreased in current and former smokers, perhaps due to the increased baseline risk across these populations.

One finding in the NLST which stands out is that the most common cause of death in the study was CVD. This finding piqued the interest of a research group which included radiologists who had the capability to retroactively score CAC from scans of subjects in the LDCT arm. In an analysis of these data, a retrospective case-cohort study was performed to examine the association between the degree of CAC by subjective and objective measures and cardiovascular mortality\textsuperscript{58}. Models showed that even when controlling for common covariates and using multiple assessment methods, CAC was predictive of cardiovascular events. While there are shortcomings in the available covariates and follow-up data, these results provided an important step towards showing the potential usefulness of incorporating CAC into LDCT for lung cancer screening.

CAC scoring is a well-described marker for both current obstructive CHD as well as future ASCVD risk in the general population. The role of CAC scoring to augment common clinical tools in high-risk smokers is less well defined. With the expansion of LDCT for lung cancer screening the number of patients with potential CAC scoring will increase. We will examine the utility of adding CAC assessment to the PCE in subjects who meet USPSTF guidelines for lung cancer screening for ASCVD risk and mortality prediction. The PCE was our chosen risk predictor because of the wide usage of the ACC/AHA ASCVD Risk Calculator. Additionally, the PCE has been demonstrated to have the best discrimination and net benefit for primary ASCVD risk assessment when compared to other popular risk tools\textsuperscript{59}. To answer our research questions we will use the MESA and NLST cohorts. The MESA cohort was chosen to address the questions related
to ASCVD events for a number of reasons. MESA is a well-defined, multi-ethnic cohort with over 10 years of follow-up data on CVD outcomes. Additionally, there is robust covariate data available from the initial study visit, including all of the information needed to use the PCE to calculate 10-year ASCVD risk. With the MESA focus on pre-clinical atherosclerosis, CAC assessments were done on all subjects at the initial study visit. All scans done in the study used cardiac-gated protocols however, as has previously been demonstrated, there is strong correlation of the scoring between these protocols and LDCT. The NLST will be used in the third chapter to examine the addition of CAC scoring to common CVD covariates to improve discrimination for future mortality. This cohort was selected because all subjects included in the sample had LDCT performed for the purpose of screening for lung cancer. Not all covariates to use the PCE were collected in this study however there is robust follow-up of mortality events. We will use the MESA and NLST cohorts to address the following specific aims:
SPECIFIC AIMS

Primary Aim: To assess the utility of CAC scoring for cardiovascular event prediction in smokers with indications for lung cancer screening according to guidelines published by the USPSTF. In order to achieve this aim, we will address the following sub-aims:

Sub-aim #1: To define the predictive value for cardiovascular events and discriminative ability of CAC scoring among all current and former smokers in the MESA cohort.

Sub-aim #2: To assess the predictive value of CAC among participants in MESA with an indication for LDCT lung cancer screening.

Sub-aim #3: To assess the predictive value and discrimination of the Pooled Cohort Equation in MESA participants with indications for LDCT screening and the change afforded by the addition of CAC.

Sub-aim #4: To assess the change in discrimination afforded by adding CAC to traditional risk factors in subjects from the National Lung Screening Trial.
CHAPTER 2: MANUSCRIPT

Coronary Artery Calcium Scores for Atherosclerotic Cardiovascular Disease Risk Stratification in Smokers: MESA


Introduction

In 2015, Medicare began to pay for annual LDCT of the chest in order to screen for lung cancer\(^3\). To be eligible for these scans a patient must be between the ages of 55-75, have no signs or symptoms of lung cancer, be a current smoker or former smoker who has quit within the last 15 years, and have a tobacco smoking history of at least 30 pack-years. The USPSTF recommends screening for those who meet the Medicare criteria but aged 55-80 (Grade B)\(^6\). These recommendations rely largely on results from the NLST, a randomized double blind study which compared survival of smokers who were screened for lung cancer with either annual chest radiography or LDCT\(^27,28\). The primary result of the NLST study showed a 20% reduction in mortality in the LDCT arm compared with those who underwent chest radiography. However, it was observed that for the entire study, CVD was the most common cause of death (24.8%). While this may have been an unexpected finding in a lung-cancer focused trial, ASCVD remains the most common cause of death in the US and is strongly associated with cigarette smoking\(^1,4\). CAC refers to detectable calcification within the coronary arteries and is associated with vascular disease and ASCVD events\(^37\). Presently most radiologists provide CAC either qualitatively or quantitatively on the report of this lung cancer...
screening test. This data often presents a dilemma to clinicians in terms of ASCVD risk assessment since the value to CAC in this unique population is understudied. The gold standard for assessment of CAC is via cardiac gated CT scanning however assessments can also be made from non-gated scans with a high degree of agreement\textsuperscript{52,53,55}.

In 2013, the ACC/AHA guidelines on the treatment of blood cholesterol recommended statins for ASCVD risk reduction in 4 main groups: those with prior ASCVD, low-density lipoprotein (LDL) cholesterol \( \geq 190\text{mg/dl} \), diabetes mellitus and those with a 10yr. risk calculated using the PCE \( \geq 7.5\% \)\textsuperscript{49}. The ACC/AHA cholesterol guidelines also emphasized a patient-clinician dialogue to guide the initiation of statins. The ACC/AHA cholesterol guidelines also recommend the use of additional markers to improve ASCVD risk assessment and medical decision making, especially in individuals in whom the decision to initiate statins is unclear. The additional markers mentioned included LDL, other genetic hyperlipidemias, family history of premature ASCVD, high-sensitivity C-reactive protein levels, CAC score, lifetime ASCVD risk, and ankle–brachial index.

The discriminative ability of the PCE in smokers remains unclear especially in those eligible for the LDCT for lung cancer screening; a subgroup of smokers who have been shown in the NSLT trial to have a significantly high cardiovascular risk. It also remains unclear if CAC (qualitative or quantitative) is as informative in ASCVD risk assessment for LDCT eligible persons as what has been demonstrated in the general population for primary prevention.

In this report we assess the discriminative ability of the PCE and the improvement in discrimination afforded by the addition of CAC to the PCE, for ASCVD events in
smokers but also in the LDCT-eligible subgroup of participants who are part of the ongoing Multi Ethnic Study of Atherosclerosis

Methods

Study population and data collection

A detailed description of the study design for MESA has been published\textsuperscript{61}. In brief, MESA is a cohort study that began in July 2000 to investigate the prevalence, correlates, and progression of subclinical ASCVD. At baseline, the cohort included 6,814 women and men age 45 to 84 years recruited from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). MESA participants were recruited from four specific race and ethnic groups. In the final sample, 38\% were white, 28\% were African-American, 22\% were Hispanic, and 12\% were Chinese. Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack (TIA) or who had undergone an invasive procedure for ASCVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) were excluded.

Demographics, medical history, and anthropometric and laboratory data for these analyses were obtained at the first MESA examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the past 30 days. Diabetes mellitus was defined as fasting glucose $\geq$126 mg/100 dl or use of hypoglycemic medications. Use of antihypertensive and other medications was based on the review of prescribed medication containers. Resting blood pressure was measured 3 times in a seated position, and the average of the second and third readings was used. Hypertension
was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height$^2$ (m$^2$). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was estimated by the Friedewald equation. The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

**Measurement of CAC score**

Details of the MESA computed tomography (CT) scanning and interpretation methods have been reported previously. Scanning centers assessed CAC by non-contrast cardiac CT with either an electron-beam CT scanner (Chicago, Illinois; Los Angeles, California; and New York, New York field centers) or a multidetector CT system (Baltimore, Maryland; Forsyth County, North Carolina; and St. Paul, Minnesota field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles, Torrance, California). We used the mean Agatston score for the 2 scans in all analyses. Intraobserver and interobserver agreements using kappa statistics were 0.93 and 0.90, respectively.

For the purpose of this analysis, participants were excluded if they lacked baseline data on smoking status or the necessary information to use the PCE [Figure 1]. To
determine eligibility for lung cancer screening by LDCT we used the age range of 55-80 years as recommended by the USPSTF.

Participant characteristics were collected during the initial MESA study visit. Age, gender, race/ethnicity, antihypertensive medication use, and smoking status were self-reported. Participants were considered current smokers if they had smoked within the past six months. Blood samples were obtained after fasting and total cholesterol, LDL, and HDL were used. Blood pressure was measured for each participant after five minutes in the seated position and systolic measurements were recorded three separate times and the mean of the last two values was used. Specifics of CAC assessment have been reported previously and for this analysis we only used the assessment from the initial study visit. CAC was used as a continuous variable after log-transformation, ln(CAC+1). Categorical CAC variables used included the presence or absence of calcium and a three-level variable (CAC of 0, 1-300, and >300). The three-level variable was based on the ACC/AHA recommendations for using CAC >300 as a non-traditional risk factor for upward revision of risk assessment.

**Ascertainment of outcomes in MESA**

The primary outcome was incident ASCVD which was composed of fatal and non-fatal myocardial infarction, other fatal and non-fatal coronary disease, fatal and non-fatal cerebrovascular disease, and other fatal or non-fatal atherosclerotic disease. Only the initial ASCVD event was considered for this analysis. Participants were followed from baseline through December 31, 2012. Follow-up time was defined as the time between the baseline risk score assessment until a diagnosis of ASCVD, loss to follow-up, or end
of follow-up. Every 9-12 months, participants were contacted via telephone to inquire about interim hospital admissions, cardiovascular diagnoses, procedures, and deaths. Additionally, MESA identified medical encounters through cohort clinic visits, participant call-ins, medical record abstractions, and obituaries.

**Statistical Analysis**

Demographic characteristics were reported for the sample MESA participants who had reported on the initial survey if they were a current or former smoker as well as a sub-sample who were deemed to have met eligibility criteria for LDCT lung cancer screening. Due to the LDCT-eligible participants being a sub-sample, the characteristics of the two samples were not compared statistically. Mean and standard deviation or percent were reported for continuous and categorical variables, respectively. We calculated the 10-year risk of incident ASCVD for each participant based on baseline characteristics (age, gender, race/ethnicity, systolic blood pressure, treatment of hypertension, total, high-density lipoprotein cholesterol levels, current smoking) using the PCE. The PCE for estimating ASCVD was developed from sex- and race-specific proportional-hazards models that included the covariates of age, treated or untreated systolic blood pressure level, total cholesterol and high-density lipoprotein cholesterol levels, current smoking status (yes/no), and history of diabetes (yes/no)\textsuperscript{24}.

Kaplan-Meier analysis was used to assess the association between CAC strata and ASCVD event-free survival. Cox proportional hazards regression analysis was used to assess the association between CAC and incident ASCVD in multivariable models adjusting for the confounders of age, gender, race/ethnicity, hypertension, diabetes,
statin use, and smoking status. These potential confounders or mediators were chosen based on prior association with ASCVD events and CAC levels. Receiver operator curve (ROC) analysis was done using the PCE alone and PCE with CAC to determine the improvement of the area under the curve (AUC) conferred by the addition of CAC to the PCE for the diagnosis of incident ASCVD\textsuperscript{62}.

Further, we examined the potential for CAC to the PCE to reclassify subjects into low, intermediate, and high risk categories compared to the PCE alone using net reclassification improvement analysis\textsuperscript{63}. The PCE is known to overestimate ASCVD risk in MESA\textsuperscript{64}. In order to not overestimate the improvement in discrimination afforded by the addition of CAC to the PCE, we used a logistic regression model to generate predicted probabilities of ASCVD event using the PCE estimate at the initial visit. The cut-offs (<5%, 5-7.5%, and >7.5%) were selected because of the ACC/AHA recommendations which promote more aggressive treatment of those with ≥7.5% 10-year risk and ≤5% being previous used as low-risk. The absolute event rates generated for those with a predicted event rates of <5%, 5-7.5%, and >7.5% were <3.56%, 3.56-7.96%, and >7.96%, respectively. A p value of < 0.05 was considered significant for all calculations. All statistical analyses were performed using SAS version 9.4 or JMP Pro version 12.0 (SAS Institute, Cary, NC).

**Results**

A total of 3,356 participants (2,476 former smokers, 880 current smokers) with complete outcome data, CAC score from the initial visit, and the elements needed to calculate the PCE risk score were included in this analysis. From these participants, a
sub-sample was created from 481 participants who met eligibility criteria for lung cancer screening with LDCT. Over a mean follow up period of 11.1±2.9 years, 445 ASCVD events were adjudicated with 100 occurring in the LDCT-eligible sub-sample. Among the current and former smokers 13.3% of participants suffered an ASCVD event while 20.8% suffered an event in the LDCT-eligible sample during the follow-up period. 363 subjects died from non-cardiovascular causes prior to an ASCVD event with 85 of these deaths occurring in the LDCT-eligible sub-sample.

**Current and Former Smokers**

The current and former smoker sample had a mean age of 62.1 years, was mostly male (56.5%), and was made up of a plurality of white participants (43.2%) [Table 1]. The participants had a mean BMI of 28.5 with 11.5% reported a diagnosis of diabetes mellitus, 15.2% reporting statin usage, 36.7% reporting anti-hypertensive usage, and 26.2% reporting currently smoking. The mean 10-year risk of an ASCVD event per PCE was 14.4% with 62.1% of participants having an estimate risk ≥7.5%. Detectable CAC was found in 55.7% of participants with a median score of 177.1 Agatston units.

In the sample containing all current and former smokers, there was a statistically significant (Cochran-Armitage Trend Test, p < 0.0001) increase in number of events in strata with increasing CAC [Figure 2].

Kaplan-Meier analysis using presence or absence of CAC and CAC strata (0, 1-300, and >300) showed significantly decreased event-free survival in all smokers with any CAC as well as increasing CAC by strata (log-rank p <0.001 and p<0.001 respectively) [Figure 3].
In multivariable Cox proportional hazards models, the presence of CAC was associated with an increased risk for ASCVD events in the all-smokers sample (HR 2.07 CI 1.63, 2.65) [Table 2]. When compared to those with no CAC, there was an increase in ASCVD events as CAC burden increased from 0 to 1-300, and > 300 (HR 1.80 CI 1.40, 2.32 Chi-squared p<0.0001, and HR 3.17 CI 2.37, 4.24 Chi-squared p <0.0001 respectively).

In ROC analysis, the PCE alone model had an AUC of 0.6928 for ASCVD events [Figure 4]. The addition of the presence or absence of CAC to the model resulted in an increase in AUC to 0.7042 but this was not a statistically significant increase (p=0.13). The addition of CAC strata to the PCE improved the AUC to 0.7148 (p=0.015). Adding \( \ln(\text{CAC}+1) \) to the PCE yielded an AUC of 0.7173 (p = 0.0089)

Net reclassification was also used to assess the addition of the presence or absence of CAC to the PCE [Table 3]. Examination of the reclassification properties of CAC indicates that a risk model that adds CAC > 0 to the PCE net correctly reclassifies 31.7% of those without an event but incorrectly net reclassifies 12.3% of those who did have an event. The overall net correct reclassification is 19.4% (p < 0.0001). Using the PCE with CAC strata resulted in the loss of two participants being correctly reclassified to a lower risk group and overall net correct reclassification of 19.3% (p < 0.0001). Adding \( \ln(\text{CAC}+1) \) to the PCE resulted in an increase in participants reclassified to a lower risk category, both correctly and incorrectly. The result was an overall net reclassification improvement of 28.5% (p <0.0001).
LDCT-Eligible Sub-sample

The LDCT sub-sample had a mean age of 65.3 years, was mostly male (60.9%), and was made up of a plurality of white participants (49.3%) [Table 1]. The participants had a mean BMI of 28.4 with 15.0% reporting a diagnosis of diabetes mellitus, 19.3% reporting statin usage, 40.3% reporting anti-hypertensive usage, and 45.7% reporting currently smoking. The mean 10-year risk of an ASCVD event per PCE was 17.6% with 81.5% of participants having an estimate risk ≥7.5%. Detectable CAC was found in 72.1% of participants with a median score of 282.6 Agatston units.

In the LDCT-eligible sample, there was an increase in ASCVD event rate across CAC strata (Cochran-Armitage Trend Test, p = 0.0112) [Figure 2]. Kaplan-Meier analysis using presence or absence of CAC showed significantly decreased event-free survival in subjects with any CAC [Figure 3]. With CAC stratification (0, 1-300, and >300), the difference between survival remained significant (log-rank p=0.01 and p=0.006 respectively).

In multivariable Cox proportional hazards models, the presence of CAC was associated with an increased risk for ASCVD events in the LDCT-eligible sample (HR 1.94 CI 1.17, 3.37 Chi-squared p=0.009) [Table 2]. When compared to those with no CAC, there was an increase in ASCVD events as CAC burden increased from 0 to 1-300 and >300 (HR 1.75 CI 1.03, 3.09 Chi-squared 0.038 and HR 2.57 CI 1.40, 4.86 Chi-squared <0.003 respectively).

In ROC analysis, the PCE alone model had an AUC of 0.5452 for ASCVD events [Figure 4]. The addition of the presence or absence of CAC to the model resulted in an
increase in AUC to 0.5660 which was not statistically significant (p=0.30). The addition of CAC strata to the PCE yielded an AUC of 0.5840 but again this was not significantly improved (p=0.13). Adding ln(CAC+1) to the PCE resulted in an AUC of 0.5962 but was not significantly improved from the PCE alone (p = 0.07).

Net reclassification was also used to assess the addition of the presence or absence of CAC to the PCE [Table 3]. Examination of the reclassification properties of CAC indicates that a risk model that adds CAC > 0 to the PCE net correctly reclassifies 17.1% (p <0.0001) of those without an event but incorrectly net reclassifies 5.0% (p=0.34) of those who did have an event. The overall net correct reclassification is 12.1% (p = 0.0232). The addition of CAC strata to the PCE results in the loss of one participant correctly reclassified to a lower risk and an overall net correct reclassification of 11.8% (p = 0.0259). Using ln(CAC+1) in addition to the PCE resulted in an improvement to the non-event NRI with worsening of the event NRI and a resultant overall net correct reclassification of 19.5% (p = 0.0004).

Discussion

The goal of this study was to examine the discriminative ability of the PCE for ASCVD events and the improvement afforded by the addition of CAC in smokers, particularly those eligible for LDCT screening. Our study showed that the PCE has a modest discriminative ability in all smokers and relatively poor discrimination in the sub-sample of participants who were LDCT-eligible. CAC categorized in multiple ways improved the discriminative ability of the PCE in all smokers as well as those eligible for LDCT when using net reclassification. The improved discrimination in the LDCT-
eligible came from correctly reclassifying participants with no events to a lower-risk tier. However, the improvement in net reclassification should be viewed cautiously due to the poor performance of the PCE for ASCVD events in the LDCT-eligible.

So far there is no consensus as to whether to include CAC on LDCT performed for lung cancer screening. However, the utility of CAC in these scans has been investigated as they have become more prevalent. Jacobs et al used the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) to show that Agatston scores from LDCT performed for lung cancer screening were predictive of all-cause mortality and ASCVD events. Subsequent analysis of the same cohort produced a 3-year ASCVD event risk prediction model using automated quantification of coronary and aortic calcium combined with demographic and history elements. This analysis and prediction model was limited by using only males in the cohort used to derive the model. While both of these analyses showed the prognostic ability of CAC, the designs failed to directly address how the incorporation of CAC would make a clinically significant impact.

Using 1,575 scans from the original NLST, a group of cardiothoracic radiologists retrospectively interpreted CAC scores from the original LDCT scans. They performed a case-control study to examine the relationship between multiple different CAC scoring methods and both all-cause and coronary heart disease (CHD) mortality. They were able to demonstrate that an overall subjective assessment of CAC, coronary artery segment totals, and Agatson score based strata were all associated with CHD deaths. However, this study was limited by the CHD endpoint which only captures a portion of ASCVD deaths. Additionally, despite controlling for available co-variates, the NLST had not collected data such as blood pressures and lipid levels which are necessary to use the
PCE or other clinical risk factor calculators. While this study shows that CAC from LDCT has some potential usefulness for the lung-cancer screening population, it was not possible to evaluate for improvement over common risk tools in discrimination.

The ACC/AHA recommends utilizing the PCE to estimate ASCVD risk in the general population, which includes current and former smokers. While the PCE has been shown to overestimate risk in the general population, there is a lack of data on performance specifically in smokers. This analysis adds somewhat to this lack of evidence by examining events in samples of wholly current or former smokers. In the current and former smoker sample, the PCE alone overestimated risk with mean predicted risk of 14.4% and 10.8% (362/2994) of subjects with ASCVD events within 10 years of follow up. In the LDCT-eligible sample, the mean 10-year predicted risk was 17.6% with 18.9% (91/481) of subjects having an ASCVD event within 10 years of follow up. In a population similar to these samples, the utility of the PCE may be limited due to the high baseline 10-year risk as well as high proportion of participants with 10-year risk scores of ≥7.5% which is used as a cut-off for consideration of high-dose statin prescription. In the larger sample, this proportion was 62.1% and 81.5% in the LDCT-eligible sample. While the PCE alone seems to have modest and poor discrimination in these samples, the addition of CAC may still be useful in risk assessment. Interestingly, with respect to reclassification, the absence of CAC appears more useful to identify people at low risk than the presence of CAC is to identify people at high risk – a pattern that has also been described in the larger MESA cohort as well as the Framingham Heart Study.
This analysis has some limitations in answering our proposed question. First, in the MESA study, all CT scans used in this analysis were performed using ECG-gating. While this is the preferred method for a detailed assessment of CAC, non-gated protocols are used in the LDCTs performed for lung cancer screening. While the difference in protocol is significant, there is a wealth of evidence that shows concordance between gated and non-gated scans\textsuperscript{69–71}. This analysis did not control for Type I error despite using some multiple comparisons. Competing risk of death from other causes was not taken into account with this analysis and as a result we may have overestimated by using the Kaplan-Meier incidence estimate in lieu of a cumulative incidence function which would take into account the competing mortality risks. Finally, by excluding those with missing smoking status we may have introduced selection bias.

Another weakness of this analysis is the relatively small number of subjects who are eligible for lung cancer screening. This cohort was not designed to focus on smokers and the age range extended below the guideline-recommended age for lung cancer screening. As such there was limited power to assess different effect sizes conferred by CAC burdens in the LDCT-eligible sub-sample, particularly when examining outcomes in participants with very high CAC (>1000). Our multivariable models controlled for common ASCVD risk factors but there is the possibility of residual confounding. Additionally, the poor performance of the PCE alone in the LDCT-eligible sample limits the assumptions that can be made from the NRI results.

Conclusion
The presence of CAC predicts ASCVD events in smokers as well as a sub-group who would be eligible for LDCT lung cancer screening. The PCE alone has a modest discriminative ability in all smokers and poor ability in those who are LDCT-eligible. The addition of CAC assessment to the PCE can improve the discriminative ability of the PCE in smokers as well as those who are LDCT-eligible. The potential clinical impact of the improvement in discrimination for the LDCT-eligible sample should be approached cautiously given the poor AUC of the PCE and CAC model. Given the high event rate we observed, it is possible that the USPFTF recommendation for lung cancer screening identify a subgroup of smokers with such high baseline risk to warrant statin eligibility and aggressive primary prevention strategies without any further testing. Further studies in larger cohorts are needed to better define possible clinical benefits above more commonly used tools. In addition to CAC, LDCT has the potential to identify calcification of the aortic valve and aorta which may provide additional prognostic information for multiple ASCVD outcomes.
Figure 1. Flow Diagram of subject selection from MESA cohort

Total MESA participants: N = 6,814

NOT ASSESSED FOR ELIGIBILITY
- Never smokers = 3,418
- Missing smoking status = 22

Assessed for Eligibility: N = 3,374

EXCLUDED
- Missing outcome data = 3
- Missing variables to calculate PCE = 15

Former Smokers = 2,476
Current Smokers = 880
All Smokers = 3,356

LDCT-Eligible participants: N = 481

Aged 55-80 years
Total pack years ≥ 30
Quit < 15 years ago

NON-EVENTS CENSORED FOR MORTALITY
- N= 363
- Non-cardiovascular disease death = 351
- Death type unknown = 3
- Adjudication pending = 9

NON-EVENTS CENSORED FOR MORTALITY
- Non-cardiovascular disease death = 85
Table 1 – Demographic and risk factors in smokers and LDCT-eligible participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Current and Former Smokers*</th>
<th></th>
<th>LDCT-eligible</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 3356</td>
<td></td>
<td>n = 481</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.1</td>
<td>9.9</td>
<td>65.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>43.5</td>
<td>39.1</td>
<td>49.3</td>
<td>39.1</td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>43.2</td>
<td>49.3</td>
<td>5.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>5.9</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>30.4</td>
<td>32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>20.5</td>
<td>13.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.54</td>
<td>5.4</td>
<td>28.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>192.5</td>
<td>36.1</td>
<td>193.1</td>
<td>38.7</td>
</tr>
<tr>
<td>LDL</td>
<td>116.3</td>
<td>31.5</td>
<td>117.7</td>
<td>34.8</td>
</tr>
<tr>
<td>HDL</td>
<td>50.2</td>
<td>14.9</td>
<td>48.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>132.4</td>
<td>92.3</td>
<td>134.8</td>
<td>74.0</td>
</tr>
<tr>
<td>Statin Use (%)</td>
<td>15.2</td>
<td>19.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126.2</td>
<td>21.1</td>
<td>128.1</td>
<td>20.6</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.3</td>
<td>10.4</td>
<td>72.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Antihypertensive use (%)</td>
<td>36.7</td>
<td>40.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>11.5</td>
<td>15.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>26.2</td>
<td>45.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers (%)</td>
<td>73.8</td>
<td>54.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD 10-year risk (%)</td>
<td>14.4</td>
<td>12.8</td>
<td>17.6</td>
<td>11.9</td>
</tr>
<tr>
<td>≥7.5% 10-year risk (%)</td>
<td>62.1</td>
<td>81.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agatston score</td>
<td>177.1</td>
<td>459.8</td>
<td>282.6</td>
<td>576.0</td>
</tr>
<tr>
<td>CAC absent, n (%)</td>
<td>1488 (44.3)</td>
<td></td>
<td>134 (27.9)</td>
<td></td>
</tr>
<tr>
<td>CAC present, n (%)</td>
<td>1361 (55.7)</td>
<td></td>
<td>229 (72.1)</td>
<td></td>
</tr>
<tr>
<td>CAC 1-300</td>
<td>1361 (40.6)</td>
<td></td>
<td>229 (47.6)</td>
<td></td>
</tr>
<tr>
<td>CAC &gt;300</td>
<td>507 (15.1)</td>
<td></td>
<td>118 (24.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Contains the 481 LDCT-eligible participants
Table 2 – Hazard ratios for CAC for incident ASCVD by strata

<table>
<thead>
<tr>
<th></th>
<th>All Smokers = 3,356</th>
<th>LDCT-Eligible = 481</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASCVD Events = 445</td>
<td>ASCVD Events = 100</td>
</tr>
<tr>
<td></td>
<td>Non-event censored for mortality = 363</td>
<td>Non-event censored for mortality = 85</td>
</tr>
<tr>
<td></td>
<td>*p to CAC = 0</td>
<td>*p to CAC = 0</td>
</tr>
<tr>
<td>HR</td>
<td>CI</td>
<td>HR</td>
</tr>
<tr>
<td>CAC = 0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CAC &gt; 0</td>
<td>2.07</td>
<td>1.63-2.65</td>
</tr>
<tr>
<td>CAC 1-300</td>
<td>1.80</td>
<td>1.40-2.33</td>
</tr>
<tr>
<td>CAC &gt;300</td>
<td>3.17</td>
<td>2.37-4.24</td>
</tr>
</tbody>
</table>

Model – age, race / ethnicity, sex, hypertension, diabetes, statin use, smoking status

*Chi-Squared
Table 3 – Reclassification tables by sample

### Current and Former Smokers

<table>
<thead>
<tr>
<th>Predicted Risk</th>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Non-Event NRI</th>
<th>Event NRI</th>
<th>Total NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Event NRI</td>
<td>Event NRI</td>
<td>Total NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.56</td>
<td>15 1231 2125</td>
<td>3371</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.56-7.96</td>
<td>413 1395 0.3169</td>
<td>-0.1233 -0.1233</td>
<td>0.1936</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7.96 Total</td>
<td>270 1626 0.44</td>
<td>-0.1547 &gt;0.0001</td>
<td>0.2853</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **PCE**: 15 1231 2125
- **PCE + CAC > 0**: 833 577 1961
- **PCE + CAC Strata**: 833 575 1963
- **PCE + ln(CAC+1)**: 976 665 1730

Non-Event NRI – Net reclassification improvement for subjects who did not have an ASCVD event during follow-up

Event NRI – Net reclassification improvement for subjects who did have an ASCVD event during follow-up

Total NRI – sum of event and non-event NRI

### LDCT-Eligible

<table>
<thead>
<tr>
<th>Predicted Risk</th>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Non-Event NRI</th>
<th>Event NRI</th>
<th>Total NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Event NRI</td>
<td>Event NRI</td>
<td>Total NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.56</td>
<td>0 85 396</td>
<td>481</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.56-7.96</td>
<td>51 121 0.1706</td>
<td>-0.05 0.34</td>
<td>0.1206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7.96 Total</td>
<td>40 148 0.2651</td>
<td>-0.07 0.19</td>
<td>0.1951</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **PCE**: 0 85 396
- **PCE + CAC > 0**: 34 87 360
- **PCE + CAC Strata**: 34 86 361
- **PCE + ln(CAC+1)**: 45 103 333

Non-Event NRI – Net reclassification improvement for subjects who did not have an ASCVD event during follow-up

Event NRI – Net reclassification improvement for subjects who did have an ASCVD event during follow-up

Total NRI – sum of event and non-event NRI
Figure 2 – Percent of subjects with ASCVD events during follow-up by CAC strata

Cochran-Armitage Trend Test – p < 0.0001 for all smokers, 0.0112 for LDCT-eligible
Figure 3 – Kaplan-Meier curves of ASCVD event-free survival by sample

All smokers

Log-rank p <0.001 and p<0.001

LDCT-eligible Participants

Log-rank p=0.01 and p=0.006
Figure 3 – ROC curve comparisons by sample

All Smokers

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>p  (to PCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCE</td>
<td>0.6928</td>
<td>-</td>
</tr>
<tr>
<td>PCE + CAC &gt; 0</td>
<td>0.7042</td>
<td>0.1298</td>
</tr>
<tr>
<td>PCE + CAC Strata</td>
<td>0.7148</td>
<td>0.0148</td>
</tr>
<tr>
<td>PCE + ln(CAC+1)</td>
<td>0.7173</td>
<td>0.0089</td>
</tr>
</tbody>
</table>

LDCT-Eligible Sub-sample

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>p  (to PCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCE</td>
<td>0.5452</td>
<td>-</td>
</tr>
<tr>
<td>PCE + CAC &gt; 0</td>
<td>0.5660</td>
<td>0.30</td>
</tr>
<tr>
<td>PCE + CAC Strata</td>
<td>0.5840</td>
<td>0.13</td>
</tr>
<tr>
<td>PCE + ln(CAC+1)</td>
<td>0.5962</td>
<td>0.07</td>
</tr>
</tbody>
</table>
CHAPTER 3: ANALYSIS OF NATIONAL LUNG SCREENING
TRIAL COHORT AND FUTURE WORK

NLST and Case-Cohort Designs

One of the weaknesses of the analysis presented in Chapter 2 is the relatively small number of subjects who met the USPSTF inclusion criteria for annual lung cancer screening with LDCT. This occurred because while the chosen cohort (MESA) had robust risk factor, CAC, and outcomes data, it was not designed to focus on heavy smokers. Other cohorts will need to be examined if we are to more completely assess the utility of CAC scoring for risk prediction in heavy smokers. In this subsequent analysis, we will examine a sample of the data from the previously described National Lung Screening Trial (NLST)\textsuperscript{27,28}.

Introduction

Cigarette smoking is the major risk factor for the development of lung cancer as well as CVD. In the NLST, which showed there was a benefit in lung cancer mortality with LDCT, the most common cause of death was CVD. As such, there has been interest in assessing the utility of measuring and reporting of CAC on LDCT performed for lung cancer screening as a strategy to identify those smokers at the highest risk of ASCVD events. While literature from American cohorts has been more limited, European lung cancer screening trials have demonstrated that CAC assessed LDCT has been shown to be an independent predictor of all-cause mortality and ASCVD events\textsuperscript{72–74}. 
As was previously shown using data from the MESA cohort, the addition of CAC to the PCE, a widely used ASCVD risk estimator, showed improved discrimination for ASCVD events in current and former smokers. This was demonstrated by a modest, statistically significant improvement in the C-statistic after the addition of either a stratified CAC variable or Ln (CAC+1) to the PCE. However, when applied to a sample of participants eligible for lung cancer screening with LDCT, the modest improvement in the C-statistic failed to demonstrate statistical significance.

The objective of this analysis is to use a sample from the NLST to assess the potential for the addition of CAC to traditional ASCVD risk factors to improve discrimination for ASCVD and all-cause mortality. If the addition of CAC to a risk model is informative in heavy smokers and the LDCT-eligible population there would be evidence to routinely assess and report CAC on LDCT performed for lung cancer screening.

Methods

In this chapter, we will use data from an analysis of the NLST cohort which was assembled using a case-cohort design. The case-cohort design was introduced by Ross Prentice in 1986 as a technique to use sub-sampling in survival data for estimating the risk of disease in a cohort study without collecting data from the entire cohort. Case-cohort studies are used because of their potential for improved efficiency compared to similar nested case-control design. In a true case-cohort study, complete covariate data are collected only for cases and controls which are randomly selected from the larger study. In this case, most covariate data were already available with the exception of CAC.
assessment which was performed on all subjects with CHD death, a random sample of non-CHD deaths, and a random sample of the surviving subjects who were used as controls. In his original design, Prentice estimated hazard ratios using weighted Cox proportional hazards models. Later work has shown that risk prediction models can be derived from case-cohort studies and allows the usage of commonly used techniques such as Harrell’s C-statistic (or ROC)\textsuperscript{77}.

The sample used in this analysis is a part of the larger NLST cohort. The NLST was launched 2002 and was designed to compare two methodologies for detecting lung cancers, annual screenings with either LDCT or chest x-ray. The study enrolled a total of 53,454 subjects aged 55 to 74 years old who were randomized to undergo screening for lung cancer with either LDCT (n=26,722) or chest x-ray (n=26,732). All subjects had to have at least 30 pack-years of smoking history and were either current or former smokers. Former smokers were included if they had quit less than 15 years prior to the start of the study. Additionally, subjects were excluded if they had any signs, symptoms, or history of lung cancer diagnosis.

For this analysis, only participants enrolled at sites which are part of the American College of Radiology Imaging Network (ACRIN) were used. The sample is the same which was used by Chiles et al. to perform a retrospective, randomly selected, case cohort study to analyze the relationship between baseline CAC, CHD death, and all-cause mortality\textsuperscript{58}. CHD deaths were defined using the ICD 10 codes for ischemic heart disease (I20-I25), cardiac arrest (I46), and congestive heart failure (I50). All cause-deaths were defined as any deaths not included in the CHD death category and controls were those who survived the follow-up period. In total, 1,442 subjects who were found to have scans
suitable for CAC analysis were included in the study. 171 had CHD death, 295 had non-CHD death, and 976 were control cases. After being blinded to outcome, five cardiothoracic radiologists assessed CAC both qualitatively and quantitatively from the initial LDCT scans from each subject. For this analysis, we will be using the same 1,442 subjects; however, the CHD-deaths and non-CHD death subjects were collapsed to create an all-cause mortality group with 466 subjects. The aim of this analysis is to use receiver operator curve (ROC) analysis to determine if the addition of CAC to available co-variates and ASCVD risk factors improves discrimination for CHD death and all-cause mortality.

**Statistical Analysis**

Demographic characteristics were reported for a sub-sample of the NLST cohort with CAC assessment available. Mean and standard deviation or count and percent were reported for continuous and categorical variables, respectively. Controls were compared to the CHD-death group and all-cause death groups separately. Continuous CAC score was used to create categorical variables which consisted of the presence or absence of CAC and a three-tiered variable for CAC = 0, 1-300, and >300. Ln (CAC+1) was also used as a continuous variable. Continuous variables were compared using weighted t-tests and categorical variables were compared using X² statistics (Pearson and Fisher’s exact test).

Separate weighted logistic regression models were used to calculate the odds ratios of CAC presence or strata in those with CHD death or all-cause death compared to controls. The weights of each sampling group corresponded to the inverse of the
sampling probabilities. The model included age, gender, race, ethnicity, presence of hypertension, presence of diabetes mellitus, and cigarette smoking status. ROC analysis was done to determine if the addition of CAC to the above model helped to improve the area under the curve (AUC) for CHD deaths and all-cause deaths. CAC > 0 and the stratified CAC variable were both used. A p value of < 0.05 was considered significant for all calculations. All statistical analyses were performed using SAS version 9.4 or JMP Pro version 12.0 (SAS Institute, Cary, NC).

Results

There were 1,442 subjects used in this analysis with a maximum of 7.4 years of follow-up. Median follow-up time for the groups was 6.3 years for control subjects, 3.4 years for CHD deaths, and 3.8 years for all-cause death subjects. Compared to the control group, both the CHD death and all-cause death groups had significantly older subjects [Table 1]. There were a lower proportion of women in both of the death groups compared to control. Both of the death groups had higher proportions of hypertension, diabetes, and current smoking status. The all-cause death group had a higher proportion of COPD diagnosis than control but the CHD-death group failed to reach statistical significance (p=0.054). Compared to the control group, there was not a difference in racial make-up when compared to the CHD-death group; however, there was a significant difference to the all-cause death group which had a small proportion of whites and larger proportion of African-Americans. There were only 12 subjects who identified as Hispanic / Latino (0.8%) in the entire cohort. Compared to controls, both death groups had significantly higher mean Agatston scores and proportion of subjects with detectable CAC.
The proportion of those with any detectable CAC was higher in both the CHD death and all-cause death groups (88.3% and 84.3% respectively) compared to the control group (66.5%) [Figure 1]. In the control group, 45.7% had CAC 1-300 and 20.8% had CAC >300. In the all-cause death group, 38.8% had CAC 1-300 with 45.5% having CAC > 300. In the CHD-death group, 33.9% had CAC 1-300 with 54.4% having CAC > 300.

Based on the sampling weights, it can be estimated that 3.5% of subjects with no CAC died by any cause during the follow-up period compared to 8.8% of those with any detectable CAC (p<0.0001). Assuming the distribution of CAC was consistent with what was observed in the ACRIN sub-sample, it can be estimated that 36,242 (67.8%) of all NLST subjects had detectable CAC and that 3253 of the 3875 observed deaths in the NLST occurred in participants with detectable CAC.

In weighted multiple logistic regression models, the odds of CAC > 0 were higher in those who suffered either CHD death (OR 2.57 CI 1.63, 4.27, Chi-squared p=0.0001) or all-cause death (OR 1.75 CI 1.34, 2.32, Chi-squared p<0.0001) [Table 2]. When CAC was stratified, the odds of having CAC 1-300 vs. 0 were higher in CHD deaths (OR 1.69 HR 1.03, 2.90 Chi-squared p=0.044) and all-cause death (OR 1.44 CI 1.08, 1.93 Chi-squared p=0.002). The odds of CAC > 300 vs. 0 were highest in CHD deaths (OR 4.97 CI 3.02, 8.52 Chi-squared p <0.0001) and all-cause deaths (OR 2.61, CI 1.92, 3.58 Chi-squared p<0.0001).

In ROC analysis, the model which contained age, gender, race, ethnicity, hypertension, diabetes, and smoking status had an AUC of 0.7055 for CHD-deaths, and 0.6801 for all-cause deaths [Figure 2]. The addition of CAC > 0 to the model
significantly improved the AUC for CHD-deaths to 0.7257 (p=0.0184). However, for all-cause deaths the improvement in AUC to 0.6874 was not statistically significant (p=0.1128). The addition of the CAC strata to the model improved the AUC for CHD-deaths to 0.7550 (p=0.0004) and to 0.6950 (p=0.0216) for all-cause deaths. Adding Ln (CAC+1) to the model improves the AUC to 0.7581 (p=0.0003) for CHD-death and 0.6986 (p=0.0116) for all-cause death. While the addition of Ln (CAC+1) to the model showed improvement in the AUC, there was no statistical difference between that model and the one which contained CAC strata instead (p = 0.61 and 0.30 for CHD-death and all-death, respectively).

Discussion

In this analysis of a case-cohort study where all subjects underwent LDCT screening for lung cancer we demonstrated that the odds of having any detectable CAC were over 2.5 times as high in those who suffered a CHD-death compared to those in the control group. The odds of having CAC > 300 were nearly five times higher in those who had a CHD-death compared and over 2.5 times higher in those who had an all-cause death when compared to controls. With different study designs, these results are not directly comparable however in the LDCT-eligible subsample of the MESA cohort we observed a hazard ratio of 2.57 for ASCVD events in those with CAC >300 compared to those with no CAC.

The addition of CAC > 0 to a model of common risk factors and covariates improved the AUC for both CHD-death and all-cause death. In both CHD-death and all-cause death, the largest improvement in AUC was accomplished by the addition of Ln
(CAC+1). This addition had statistically significant improvement over models with CAC > 0 in both CHD-deaths and all-deaths. However, the model with Ln (CAC+1) offered no statistically significant improvement in either group over the models with the CAC strata.

Ideally, by adding CAC interpretation to LDCT scans which would be performed for lung cancer screening we would be able to gain some information about a patient’s risk of future ASCVD events. While we have demonstrated that the AUC for death can be improved with the addition of CAC, the clinical utility may be limited by the high baseline risk of LDCT-eligible patients. In the original NLST, after a median follow-up of 6.5 years, 7% (1,865/26,722) of subjects in the LDCT arm had died from any cause with 1.3% dying from cardiovascular illnesses. As previously mentioned, the NLST did not capture other common non-fatal ASCVD end points such as myocardial infarction, heart failure diagnosis, or stroke. Unfortunately, this limits our ability to address many of the important sources of morbidity in ASCVD disease. In the work previously presented in the LDCT-eligible participants of the MESA cohort we showed that the addition of CAC to the PCE allows for successful reclassification of those with no CAC to a lower risk category. However, even in those MESA subjects with CAC=0, over 21% of participants had an ASCVD event during follow-up. With such a high rate of events in those who are free of CAC, it seems the absence of CAC in this population may not identify a sub-set of patients who are truly low-risk enough to consider an alternative treatment strategy such as statin de-prescription.

A weakness of this analysis is the race and ethnic make-up of the sample. 92.3% of this sample was white with 98.8% reported as non-Hispanic or Latino. The homogeneity should be considered as it limits the generalizability of the results.
Additionally, due to the data collected at the initial study visit, it is not possible to utilize commonly used clinical risk estimators such as the PCE or Framingham Risk Calculator.

**Future Work**

One of the limitations of the previously published work in the NLST is the narrowly defined outcomes. In the paper by Chiles et al. only assessed the association between CAC and CHD mortality or all-cause mortality\(^5^8\). While CHD, heart failure, and cardiac arrest are important causes of ASCVD death, the available outcome variables failed to capture deaths by stroke, aortic or peripheral arterial disease, and valvular disease. In order to improve on the clinical relevance of this sort of analysis we plan to review the data and create outcome variables for all-ASCVD deaths based on ICD-10 codes. If there are an adequate number of cases, this would allow us to describe the relationship between CAC and these additional ASCVD outcomes using the more traditional Cox models and survival analysis with consideration of competing risks.
Table 1 – Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n=1442</th>
<th>Control Cases n=976</th>
<th>CHD Deaths n=171</th>
<th>All-Cause Deaths n=466</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>61.9 (5.2)</td>
<td>61.3 (5.0)</td>
<td>63.5 (5.4)</td>
<td>63.3 (5.4)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>596 (41.3%)</td>
<td>444 (45.5%)</td>
<td>56 (32.7%)</td>
<td>152 (32.6%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>508 (35.2%)</td>
<td>315 (32.2%)</td>
<td>89 (52.0%)</td>
<td>193 (41.4%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>138 (9.6%)</td>
<td>67 (6.9%)</td>
<td>32 (18.7%)</td>
<td>71 (15.2%)</td>
</tr>
<tr>
<td><strong>Current Smoking</strong></td>
<td>773 (53.6%)</td>
<td>474 (48.6%)</td>
<td>109 (63.7%)</td>
<td>299 (64.2%)</td>
</tr>
<tr>
<td><strong>COPD Diagnosis</strong></td>
<td>109 (7.6%)</td>
<td>51 (5.2%)</td>
<td>17 (9.9%)</td>
<td>58 (12.4%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1331 (92.3%)</td>
<td>911 (93.3%)</td>
<td>157 (91.8%)</td>
<td>420 (90.1%)</td>
</tr>
<tr>
<td>Black or AA</td>
<td>90 (6.2%)</td>
<td>52 (5.3%)</td>
<td>10 (5.8%)</td>
<td>38 (8.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (0.6%)</td>
<td>7 (0.7%)</td>
<td>1 (0.6%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Native American</td>
<td>6 (0.4%)</td>
<td>4 (0.4%)</td>
<td>3 (1.8%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>1425 (98.8%)</td>
<td>965 (98.9%)</td>
<td>167 (97.7%)</td>
<td>460 (98.7%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>12 (0.8%)</td>
<td>9 (0.9%)</td>
<td>3 (1.8%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td><strong>Detectable CAC</strong></td>
<td>1042 (72.3%)</td>
<td>649 (66.5%)</td>
<td>151 (88.3%)</td>
<td>393 (84.3%)</td>
</tr>
<tr>
<td><strong>Agatston Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>364 (708)</td>
<td>248 (544)</td>
<td>720 (971)</td>
<td>606 (919)</td>
</tr>
<tr>
<td>Median</td>
<td>73</td>
<td>37</td>
<td>365</td>
<td>231</td>
</tr>
</tbody>
</table>

Categorical variables presented as n (%), continuous variables presented with (standard deviation). Not all categories presented for race and ethnicity and will not total 100%.

† t-test, *Pearson, **Fischer Exact Test
Table 2 – Weighted logistic regression analysis of CAC presence by mortality category

<table>
<thead>
<tr>
<th></th>
<th>CHD Death</th>
<th>All Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
</tr>
<tr>
<td>CAC = 0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CAC &gt; 0</td>
<td>2.57</td>
<td>1.63, 4.27</td>
</tr>
<tr>
<td>CAC 1-300</td>
<td>1.69</td>
<td>1.03, 2.90</td>
</tr>
<tr>
<td>CAC &gt; 300</td>
<td>4.97</td>
<td>3.02, 8.52</td>
</tr>
</tbody>
</table>

Model – age, gender, race, ethnicity, smoking status, diabetes status, hypertension status

*Chi-squared
Figure 1 – Distribution of CAC by mortality category
Figure 2 – Receiver operator curve comparisons by outcome

CHD Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>p (to model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>0.7055</td>
<td>-</td>
</tr>
<tr>
<td>Model + CAC &gt; 0</td>
<td>0.7257</td>
<td>0.0184</td>
</tr>
<tr>
<td>Model + CAC Strata</td>
<td>0.7550</td>
<td>0.0004</td>
</tr>
<tr>
<td>Model + Ln(CAC+1)</td>
<td>0.7581</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

All-Cause Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>p (to model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>0.6801</td>
<td>-</td>
</tr>
<tr>
<td>Model + CAC &gt; 0</td>
<td>0.6874</td>
<td>0.1128</td>
</tr>
<tr>
<td>Model + CAC Strata</td>
<td>0.6950</td>
<td>0.0216</td>
</tr>
<tr>
<td>Model + Ln(CAC+1)</td>
<td>0.6986</td>
<td>0.0116</td>
</tr>
</tbody>
</table>
REFERENCES


CURRICULUM VITAE

John Adam Leigh, M.D.
Medical Center Boulevard
Department of Cardiology
Winston-Salem, NC 27157
Office - (336) 716-4305
Mobile - (612) 325-9962
aleigh@wakehealth.edu

Current Position
Fellow, Cardiovascular Research Training Program 2015-Present
Wake Forest School of Medicine
Winston-Salem, NC

Education and Training
Residency, Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 2013-2015
Internship, Internal Medicine, Medical University of South Carolina, Charleston, SC 2012-2013
M.S. in Clinical and Population Translational Science 2015-Present
M.D., Wake Forest School of Medicine, Winston-Salem, NC 2008-2012
M.S. in Physiology, Georgetown University, Washington, DC 2007-2008
B.S. in Biology, Minors in Neuroscience and Psychology, Wake Forest University, Winston-
Salem, NC 2003-2007

Employment
Hospitalist 2015-Present
Novant Inpatient Care Specialists
Forsyth Hospital
Winston-Salem, NC

Certification and Licensure
American Board of Internal Medicine 2015-Present
DEA Registration – Practitioner 2015-Present
Kentucky Board of Medical Licensure 2017-Present
North Carolina Medical Board 2015-Present
North Carolina Medical Board - Resident Training License (inactive) 2014-2016
South Carolina Board of Medical Examiners - Limited License (inactive) 2012-2013

Professional Memberships and Activities
American Heart Association 2015-Present
American College of Cardiology 2015-Present
American College of Physicians 2012-Present
American Society of Echocardiography 2014

Honors and Awards
Silver Award - Wake Forest School of Medicine Dept. of Internal Medicine Research Day 2014
Wake Forest University Dean’s List, 6 semesters 2003-2007
Alpha Epsilon Delta – Pre-medical Honor Society 2006
Beta Beta Beta – National Biological Honor Society 2006
Peer Reviewed Publications


Review Articles


Manuscripts


National/International Meetings


Coronary Artery Calcium Scores for Atherosclerotic Cardiovascular Disease Risk Stratification in Smokers: MESA 2017

American College of Cardiology Annual Scientific Sessions, Washington, DC
Association of the Intensity and Duration of Cigarette Smoking Exposure with Cardiac Structure and Function in Current Daily Smokers: The Echocardiographic Study of Hispanic/Latinos (ECHO-SOL)
American College of Cardiology Annual Scientific Sessions, Chicago, IL 2016

Leigh JA, O’Neal WT, Soliman EZ. Electrographic Versus Echocardiographic Left Ventricular Hypertrophy as a Predictor of Cardiovascular Disease Events in the General Population
American Heart Association, Epidemiology and Prevention/Lifestyle Sessions, Phoenix, AZ 2016

Leigh JA, et al, Comparison of Reference Values for Cardiac Structure in Hispanics with the American Society of Echocardiography Reference Ranges: The Echocardiographic Study of Latinos (ECHO-SOL)
American Society of Echocardiography Scientific Sessions, Portland, OR 2014

Local/Regional Meetings

Wake Forest School of Medicine Department of Internal Medicine Research Day, Winston-Salem, NC 2017

Leigh JA, et al, Comparison of Reference Values for Cardiac Structure in Hispanics with the American Society of Echocardiography Reference Ranges: The Echocardiographic Study of Latinos (ECHO-SOL)
Wake Forest School of Medicine Department of Internal Medicine Research Day, Winston-Salem, NC 2014

Leigh JA, Callahan K, The Devil is in the Details: Using an accurate history in the diagnosis of a rare cause of psychosis
American College of Physicians, North Carolina Chapter Meeting, Greensboro, NC 2014

Clinical Research Experience

Co-Investigator
NCT01492361: Evaluation of the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients With Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events With EPA - Intervention Trial)
2015-2017

Co-Investigator
NCT02104817: A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia (STRENGTH)
2015-2017
Co-Investigator
B1481022: Phase 3 Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Evaluation Of The Efficacy, Safety, And Tolerability Of Pf-04950615, In Reducing The Occurrence Of Major Cardiovascular Events In High Risk Subjects, Pfizer 2015-2017

Co-Investigator

Grants
T35 Ruth L. Kirschstein NRSA Short-Term Institutional Research Training Grant PI – Christos Constantinidis, PhD. Medical Student Summer Research Program 2009