Impact of Slice Thickness on the Predictive Value of Lung Cancer Screening Computed Tomography in the Evaluation of Coronary Artery Calcification

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Background**—**Image reconstruction thickness may impact quantitative coronary artery calcium scoring (CACS) from lung cancer screening computed tomography (LCSCT), limiting its application in practice.

Methods and Results**—**We evaluated Agatston-based quantitative CACS from 1.25-mm LCSCT and cardiac computed tomography for agreement in 87 patients. We then evaluated Agatston-based quantitative CACS from 1.25-, 2.5-, and 5.0-mm slice thickness LCSCT for agreement in 258 patients. Secondary analysis included the impact of slice thickness on predictive value of 4-year outcomes. Median age of patients who underwent 1.25-mm LCSCT and cardiac computed tomography was 63 years (interquartile interval, 57, 68). CACS from 1.25-mm LCSCT and cardiac computed tomography demonstrated a strong Pearson correlation, R=0.9770 (0.965, 0.985), with good agreement. The receiver operating characteristic curve areas under the curve for cardiac computed tomography and LCSCT were comparable at 0.8364 (0.6628, 1.01) and 0.8208 (0.6431, 0.9985), respectively (*P*=0.733). Median age of patients who underwent LCSCT with 3 slice thicknesses was 66 years (interquartile interval, 63, 73). Compared with CACS from 1.25-mm scans, CACS from 2.5- and 5.0-mm scans demonstrated strong Pearson correlations, R=0.9949 (0.9935, 0.996) and R=0.9478 (0.9338, 0.959), respectively, though bias was largely negative for 5.0-mm scans. Receiver operating characteristic curve areas under the curve for 1.25-, 2.5-, and 5.0-mm scans were comparable at 0.7040 (0.6307, 0.7772), 0.7063 (0.6327, 0.7799), and 0.7194 (0.6407, 0.7887), respectively (*P*=0.6487). When using individualized high-risk thresholds derived from respective receiver operating characteristic curves, all slice thicknesses demonstrated similar prognostic value.

Conclusions**—**Slice thickness is an important consideration when interpreting Agatston CACS from LCSCTs. Despite the absence of ECG gating, it appears reasonable to report CACS from either 1.25- or 2.5-mm slice thickness LCSCT to help stratify cardiovascular risk. Conversely, 5.0-mm scans largely underidentify calcium, limiting practical use within the established CACS values used to categorize cardiovascular risk. **(*J Am Heart Assoc.* 2019;8:e010110. DOI: 10.1161/JAHA.118.010110)**

Key Words: computed tomography • coronary artery calcification • coronary computed tomography • lung cancer screening computed tomography

Ischemic heart disease caused by atherosclerosis remains the single leading cause of morbidity and mortality in the United States and throughout the world.[1] Calcification of atherosclerotic plaque has tremendous predictive value in terms of total atherosclerotic burden and risk of cardiovascular mortality and all-cause mortality.[2–4] In addition, organization of calcific deposits within individual atherosclerotic plaque has predictive value for the plaque's vulnerability.[5–7] ECG-gated cardiac computed tomography (CCT) defines coronary calcium by a threshold attenuation coefficient measurement of 130 Hounsfield units with an area of 1 mm^2, and coronary artery calcium scores (CACS) are then determined by the product of calcified plaque area and relative density as determined by attenuation.[8] Other large epidemiological studies have used a threshold of 130 Hounsfield units with an area of 1.48 mm^2 to identify coronary calcium.[9,10]

Lung cancer is the second-most common cancer and the leading cause of cancer-related death in the United States, accounting for 1 in 4 cancer deaths.[11] The most important risk factor for lung cancer is smoking, which results in ≈85% of all US

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Received June 27, 2018; accepted October 29, 2018.

Clinical Perspective

What Is New?

- Quantitative coronary artery calcium scoring from 1.25- and 2.5-mm slice thickness lung cancer screening computed tomography is largely comparable with current cardiac computed tomography standards and may help to stratify patients for cardiovascular risk.
- Quantitative coronary artery calcium scoring from 5.0-mm slice thickness lung cancer screening computed tomography tends to underidentify calcium, limiting practical use within the established coronary artery calcium scoring values used to categorize cardiovascular risk.

What Are the Clinical Implications?

- Image reconstruction thickness is an important consideration when interpreting quantitative coronary artery calcium scoring from lung cancer screening computed tomography regarding outcomes.

lung cancer cases.[12] Surgical resection is potentially curative in the earliest stages of disease, and low-dose, non-ECG-gated, noncontrast lung cancer screening chest computed tomography (LCSCT) scans have provided a significant benefit in identifying early disease.[12,13] Thus, the US Preventative Services Task Force has recommended annual screening for lung cancer with low-dose computed tomography (CT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.[13]

Because smoking is also a major risk factor for ischemic heart disease and there is significant overlap between eligibility for LCSCT and elevated cardiovascular risk, there is broad interest in using information regarding coronary calcification from LCSCT to aid in personalized cardiovascular event risk assessment.[14–16] Addition of Agatston-based CACS to prediction models based on traditional risk factors significantly improves the classification of risk and can place more individuals in the most extreme risk categories, having the potential to influence decision making with regard to preventive medical therapy for patients with a history of smoking.[17,18]

Although qualitative CACS reporting has become more prevalent because of its inclusion in Centers for Medicare and Medicaid Services lung cancer screening registries, it was not until very recently that formal guidelines regarding reporting of either visual-based qualitative or Agatston-based quantitative CACS from LCSCT scans were established.[19–23] Visual estimation was derived, in part because of concerns over quantitative accuracy of nongated relative to ECG-gated CT, and a number of studies have also demonstrated that simple visual estimation, using ordinal scoring to qualify degree of calcification, can be accurate and have significant prognostic value.[24,25] Although there are studies that have demonstrated reasonable agreement between CACS from various types of non-ECG-gated, noncontrast chest CT, and ECG-gated CCT, clinical outcomes have rarely been evaluated.[20,26–29] Furthermore, acquisition and reconstruction parameters of LCSCT scans can vary by institution, though the American College of Radiology recently recommended a slice thickness of ≤2.5-mm.[21] Narrow slice thickness has demonstrated increased identification of coronary calcium,[30–32] but it is unclear what effect this has on predictive value of cardiovascular events. Conversely, recent studies that demonstrated predictive value of CACS from LCSCT for outcomes did not directly compare Agatston-derived CACS values from LCSCT with the gold standard, ECG-gated CCT, for agreement.[27]

Recently, our group demonstrated that 2.0-mm LCSCT scans have reasonable agreement and comparable risk assessment to CCT despite the absence of ECG gating.[14] We sought to determine whether varying slice thickness would impact agreement and predictive value of Agatston-based CACS when controlling for all other acquisition and reconstruction parameters. Here, we first identified a patient population who had undergone both LCSCT at 1.25-mm slice thickness and CCT to validate their agreement for CACS. We then identified a separate patient population who underwent LCSCT with reconstruction at 3 slice thicknesses (1.25, 2.5, and 5 mm) at time of scan acquisition, where all other acquisition and reconstruction parameters were constant. We subsequently evaluated agreement and predictive value of Agatston-based CACS at each slice thickness. To our knowledge, this is the largest direct evaluation of LCSCT slice thickness for prediction of outcomes in an elevated risk population.

Materials and Methods

This study was approved by the Providence Veterans Affairs (VA) Medical Center Institutional Review Board and complies with the Declaration of Helsinki, and all patient data were handled in compliance with Health Insurance Portability and Accountability Act regulations. All patient records were deidentified and analyzed anonymously. Through the Providence VA Medical Center and the office of the Associate Chief of Staff for Research at Providence VA Medical Center, all data, analytical methods, and study materials are available upon request to other researchers, who meet the Institutional Review Board criteria for access to VA confidential research data, for purposes of reproducing the results or replicating the study.

Study Design and Patient Population

We undertook a retrospective study design. This study was performed at a single site, the Providence VA Medical Center in Providence, Rhode Island. This study included all US

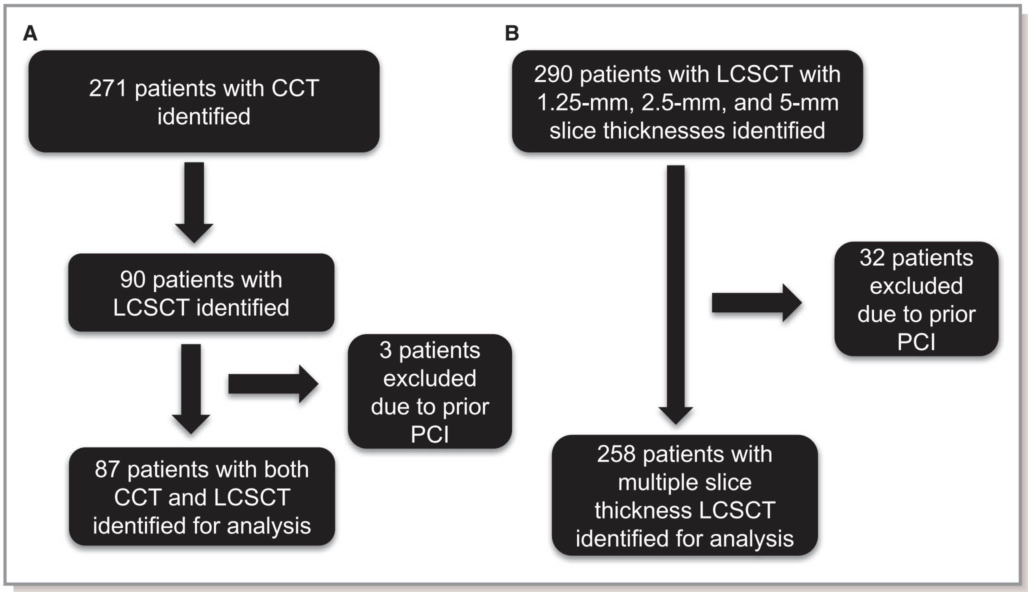

Figure 1. Flow charts of study design. **A**, Flow chart for study validating 1.25-mm LCSCT against CCT. **B**, Flow chart for study comparing impact of varying slice thicknesses (1.25-, 2.5-, and 5.0-mm) from LCSCT. CCT indicates cardiac computed tomography; LCSCT, lung cancer screening computed tomography; PCI, percutaneous coronary intervention.

veterans who had undergone both a CCT and 1.25-mm slice thickness LCSCT between August 1, 2009 and August 31, 2018. In order to validate use of 1.25-mm slice thickness LCSCT scans, we identified 90 veterans who met these criteria, and 3 patients were excluded because of previous percutaneous intervention with a stent (Figure 1). We then included all US veterans who had undergone LCSCT between October 1, 2013 and January 31, 2014, where LCSCT scans were reconstructed at 3 slice thicknesses (1.25, 2.5, and 5.0 mm) at time of acquisition. We identified 290 patients who met these criteria, and 32 patients were excluded because of previous percutaneous intervention with a stent (Figure 1).

CT Acquisition and Reconstruction Parameters

Table 1 summarizes all CT acquisition and image reconstruction parameters.

Cardiac computed tomography

Studies at the Providence VA Medical Center were performed using a 128-slice CT scanner (Siemens SOMATOM Definition AS; Siemens Healthineers, Erlangen, Germany) with a 128×0.6 mm collimation, using an axial acquisition protocol. Rotation time was 0.3 seconds. All scans were ECG gated and electrocardiographically triggered at 70% of the R-R interval. Scanning field of view was set to 380 mm. Matrix size was 512×512. Based on these parameters, the minimum area required to identify calcium was 0.55 mm^2. A 120-kV tube voltage was applied for all subjects. Tube current was 80 mA. Image reconstruction slice thickness was 3.0-mm.

Lung cancer screening computed tomography

Studies at the Providence VA Medical Center were performed using a 128-slice CT scanner (Siemens SOMATOM Definition AS; Siemens Healthineers) with a 128×0.6 mm collimation, using a helical acquisition protocol. Rotation time was 0.5 seconds, and pitch was 0.84. Studies were not ECG gated. Scanning field of view was set to 380 mm. Matrix size was 512×512. Based on these parameters, the minimum area required to identify calcium was 0.55 mm^2. Average tube

Table 1. CT Acquisition and Image Reconstruction Parameters

	CCT	LCSCT
Collimation	128×0.6 mm	128×0.6 mm
Acquisition protocol	Axial	Helical
Rotation time	0.3 sec	0.5 sec
Pitch	N/A	0.84
Field of view	380 mm	380 mm
Matrix size	512×512	512×512
Area required to identify calcium	≥0.55 mm^2	≥0.55 mm^2
Tube voltage	120 kVp	120 kVp
Tube current	80 mA	40 mA
Image reconstruction slice thickness	3.0-mm	1.25-, 2.5-, and 5-mm

CCT indicates cardiac computed tomography; CT, computed tomography; LCSCT, lung cancer screening computed tomography; N/A, not applicable.

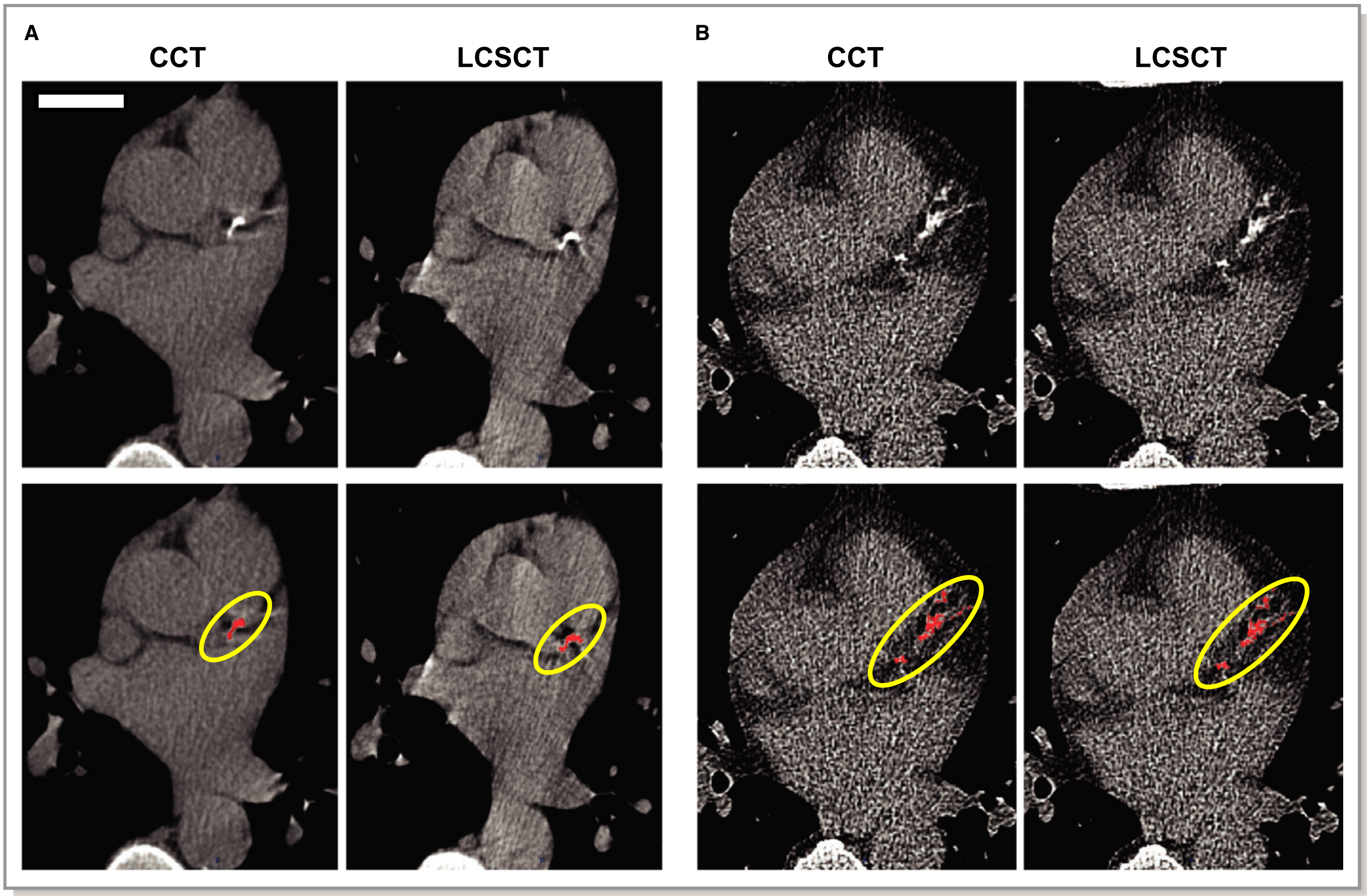

Figure 2. Examples of similar detection of coronary calcium using 1.25-mm LCSCT relative to CCT in a single-slice plane of the left anterior descending (LAD) coronary artery from 2 individual patients. Upper panels: computed tomography (CT) images at the level of proximal LAD coronary artery. Lower panels: CT images as displayed at the imaging work station with pixels of Agatston threshold of 130 Hounsfield units (HU) highlighted in red and region of interest circled in yellow. **A**, CCT and 1.25-mm LCSCT of LAD coronary artery from the same patient with total Agatston CACS of 302 and 341, respectively. **B**, CCT and 1.25-mm LCSCT of LAD coronary artery from the same patient with total Agatston CACS of 826 and 982, respectively. Bar, 3 cm. LCSCT and CCT scans were acquired within 1 month of each other. CACS indicates coronary artery calcium scoring; CCT, cardiac computed tomography; LCSCT, lung cancer screening computed tomography.

voltage was 120 kV, and tube current was 40 mA. Image reconstruction slice thickness was 1.25-, 2.5-, and 5.0-mm.

CACS for CCT and LCSCT were calculated using the Agatston method.[8] Coronary artery calcium scoring was performed using previously described methods for other epidemiological studies, and images were viewed and scored using a CarestreamVue PACS (Carestream Health, Rochester, NY) imaging workstation (Figure 2).[9,10,14] The calcium scoring application in the CarestreamVue PACS displays axial image slices for the reader for both scan types, CCT and LCSCT. The reader scrolls through axial slices and identifies coronary arteries with potential calcium to be scored. The reader indicates the appropriate coronary vessel to the program by circling a region of interest. Pixels of attenuation coefficient measurements above 130 Hounsfield units and an area $\geq$0.55 mm^2 within the region of interest are identified by the program as calcified are incorporated into the calcium score. All scans were scored by a resident (E.S.) and preventive cardiology fellow (J.L.C.) after being trained on 50 scans by the CCT board-certified cardiologist (A.R.M.). Readers were blinded to patient clinical data, calcium scores from the different CT modalities (CCT and LCSCT), as well as various slice thicknesses. Interobserver agreement was quantified for total CACS values, and the overall kappa was found to be very good at 0.907 (0.859–0.956).

Covariates

The VA electronic medical record was searched for patient demographics and cardiovascular covariates, including age, sex, race, and body mass index. Medical history included smoking status, hypertension, hypertensive medication, cholesterol medication, diabetes mellitus, and fasting lipid profile. From the acquired data, 10-year Framingham risk and atherosclerotic cardiovascular disease risk scores were calculated.

Outcomes

The full VA electronic medical record for each patient was searched in order to identify major adverse cardiovascular events (MACE) as defined by all-cause mortality, nonfatal myocardial infarction, acute coronary syndrome, and revascularization by either percutaneous coronary intervention or coronary artery bypass graft surgery. Those investigators searching the medical records were blinded to CACS.

Statistical Analysis

All statistical data were analyzed with the use of Prism (version 7; GraphPad Software Inc, La Jolla, CA) or R software (version 3.3.1; R Core Team; R Foundation for Statistical Computing, Vienna, Austria). Baseline demographics and clinical characteristics were compared between the cohort that underwent LCSCT and the subgroup who also underwent CCT. Results are presented as mean (standard error) for continuous variables with normal distribution, median (interquartile range) for continuous variables without normal distribution, and number (percentage) for categorical data. The *t* test was used to compare normally distributed continuous variables between 2 independent groups. The Wilcoxon rank-sum test was used for continuous variables not normally distributed, and the chi-square test was used for categorical variables. Differences between multiple groups were assessed by ANOVA followed by Tukey's post-hoc multiple comparisons test. For analysis of CACS, the Pearson product-moment correlation coefficient with standard error of estimate was determined followed by a Bland–Altman plot for bias and agreement. Categorical agreement was assessed using Cohen's kappa value. For receiver operating characteristic (ROC) curves, comparison of the areas under the curve (AUCs) were carried out by the method established by Hanley and McNeil.[33] Using a 2-sided alpha of 0.05, our study had an 80% power to detect a 15% difference in AUC for ROC curves between CCT and 1.25-mm LCSCT. Using a 2-sided alpha of 0.05, our study had an 80% power to detect a 12% difference in AUC for ROC curves between differing slice thicknesses of the LCSCT.

Time-to-event curves using the Kaplan–Meier method were calculated. Results were compared using the log-rank statistic. A 2-sided $P<0.05$ was considered statistically significant.

Results

Correlation and Agreement Between CCT and 1.25-mm LCSCT

We evaluated a total of 87 patients who had undergone 1.25-mm slice thickness LCSCT as well as CCT within a period of 9 years between August 1, 2009 and August 31, 2018 (Table 2) with a median time between LCSCT and CCT of 10 (interquartile interval [IQI], 1.5, 22.5) months. The 87 patients in this study had a median age of 63 years (IQI, 57, 68). All patients were US veterans. A majority of the patients were white men and smokers with elevated cardiovascular risk. Median cholesterol was 168 mg/dL, and median body mass index was 29.0 kg/m^2. Approximately 26% of patients carried a history of diabetes mellitus, and 8% of patients had a family history of early coronary artery disease. Fourteen percent of patients had known coronary artery disease, but did not have a previous history of myocardial infarction or coronary artery bypass graft surgery. Sixteen (18%) patients had a calcium score of 0 by CCT. Median CACSs, as determined by CCT and LCSCT, were comparable by the Wilcoxon rank-sum test at 79.7 (IQI, 11, 345.6) and 133.0 (IQI, 19.5, 370.5), respectively (P=0.3468). The Pearson correlation between CACS from 1.25-mm LCSCT (comparator) to CCT (referent) was strong, with an R=0.9770 (0.9650, 0.9850) and a standard error of estimate of 7.33 (Figure 3). A Bland–Altman plot for agreement demonstrated good agreement between the 2 modalities, with a mean bias of 99.9 with 95% limits of agreement between −498.8 and 698.6.

Recent guidelines recommend that CACS values be assigned to the following categorical risk ranges to help inform treatment strategy decisions: 0, very low risk; 1 to 99, mildly increased risk; 100 to 299, moderately increased risk; and >300, moderate to severely and severely increased risk.[22] We evaluated the agreement between CCT and 1.25-mm LCSCT for these categorical risk ranges (Table 3). A high degree of association was observed between CCT and 1.25-mm LCSCT, with 84% of 1.25-mm LCSCT scores being in the same category as CCT scores. There were no scores that varied by more than 1 category. Overall Cohen's kappa value was very good at 0.883.

Cardiovascular Risk Assessment in CCT Versus 1.25-mm LCSCT

In our patient population comparing CCT and 1.25-mm LCSCT, median follow-up time for MACE was 11.5 (IQI, 2.5, 26.75) months, and there was a total of 10 MACE events; 2 deaths, 2 non-ST-segment elevation myocardial infarctions, 0 ST-segment elevation myocardial infarctions, 2 coronary artery bypass graft surgeries, and 4 percutaneous coronary interventions. Figure 4 demonstrates the receiver operating characteristic (ROC) curves for the 2 imaging modalities of CCT and LCSCT. AUCs for ROC curves were 0.8364 (0.6628, 1.01) and 0.8208 (0.6431, 0.9985) for CCT and LCSCT, respectively. Comparison of AUCs revealed no significant differences between CCT and LCSCT (P=0.7330). At CACS of ≥343, CCT scans had 80% sensitivity and 80% specificity with a likelihood ratio of 4.1 for MACE in this patient population. At

Table 2. Baseline Demographics and Clinical Characteristics of Patients for CCT Versus 1.25-mm LCSCT Study and for Slice Thickness LCSCT Study

	CCT vs 1.25-mm LCSCT (n=87)	Slice Thickness LCSCT (n=258)	*P* Value
Age, y, median (IQI)	63 (57, 68)	66 (63, 73)	<0.0001
BMI, median (IQI)	29.0 (25.9, 32.7)	27.7 (24.4, 31.8)	0.0609
Male, n (%)	74 (85.0)	249 (96.5)	0.0002
White, n (%)	80 (91.9)	239 (92.6)	0.8350
Black, n (%)	3 (3.4)	13 (5.0)	0.5418
Diabetes mellitus, n (%)	23 (26.4)	73 (28.2)	0.7381
Hypertension, n (%)	42 (48.2)	157 (60.8)	0.0400
Hyperlipidemia, n (%)	64 (73.5)	174 (67.4)	0.2858
Total cholesterol, median (IQI)	168 (149, 213)	169 (144, 200)	0.3581
HDL cholesterol, median (IQI)	43 (36, 51)	42 (36, 50)	0.9210
Statin use, n (%)	51 (58.6)	162 (62.7)	0.4889
Current smoker, n (%)	40 (45.9)	118 (45.7)	0.9686
Family history of early CAD, n (%)	7 (8.0)	12 (4.6)	0.2300
CAD, n (%)	13 (14.9)	53 (20.5)	0.2508
Previous MI, n (%)	0 (0)	10 (3.8)	0.0624
Previous CABG, n (%)	0 (0)	13 (5.0)	0.0328
Framingham Risk Score, median (IQI)	12.9 (7.1, 18.9)	16.0 (12.0, 22.1)	<0.0001
ASCVD Risk Score, median (IQI)	15.7 (7.7, 22.5)	22.8 (13.9, 34.8)	<0.0001
All-cause mortality, n (%)	2 (2.3)	51 (19.7)	<0.0001
MACE, n (%)	10 (11.4)	71 (27.5)	0.0025

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CCT, cardiac computed tomography; HDL, high-density lipoprotein; IQI, interquartile interval; LCSCT, lung cancer screening computed tomography; MACE, major adverse cardiac event; MI, myocardial infarction.

CACS of ≥329, LCSCT scans had 80% sensitivity and 75% specificity with a likelihood ratio of 3.1 for MACE in this patient population.

LCSCT Patient Population

Table 2 describes baseline demographic and clinical characteristics of the 258 patients with LCSCT scans identified for analysis. Overall, the patient population was older, with a median age of 66 years (IQI, 63, 73). The population was predominantly male (96.5%) and white (92.6%). The population had comparable rates of diabetes mellitus (28.2%) and hyperlipidemia (67.4%), but a higher rate of hypertension (60.8%). Median cholesterol was 169 mg/dL, and median body mass index was 27.7 kg/m^2. Median Framingham Risk Score was 16.0%, whereas median atherosclerotic cardiovascular disease risk score was 22.8%. Despite this, only 62.7% of the population was on a statin. Twenty percent of patients had known coronary artery disease, and 5% of patients had a previous history of coronary artery bypass grafting. Sixteen (6%) patients had a calcium score of 0 by 1.25-mm LCSCT.

Correlation and Agreement Between Differing Slice Thicknesses With LCSCT

Agreements for CACS between 1.25- (referent) and 2.5-mm (comparator) as well as 1.25- (referent) and 5.0-mm (comparator) slice thickness LCSCTs were evaluated (Figure 5). The Pearson correlation between CACS from the 1.25- and the 2.5-mm LCSCTs was strong with R=0.9949 (standard error of estimate=1.17; P<0.0001). Bland–Altman analysis showed a mean bias of −132.0 (−503.5, 239.4). The Pearson correlation between 1.25- and the 5.0-mm LCSCTs was R=0.9478 (0.9935, 0.996; standard error of estimate=46.0; P<0.0001). The Bland–Altman analysis showed a much lower mean bias of −605.2 with 95% limits of agreement between (−1869, 658.4).

We then evaluated the agreement between 1.25- and 2.5-mm LCSCT for categorical risk ranges. A high degree of association was observed between 1.25- and 2.5-mm LCSCT, with 93% of 2.5-mm LCSCT scores being in the same category as 1.25-mm LCSCT scores (Table 4). There were no scores that varied by more than 1 category. Overall Cohen's kappa

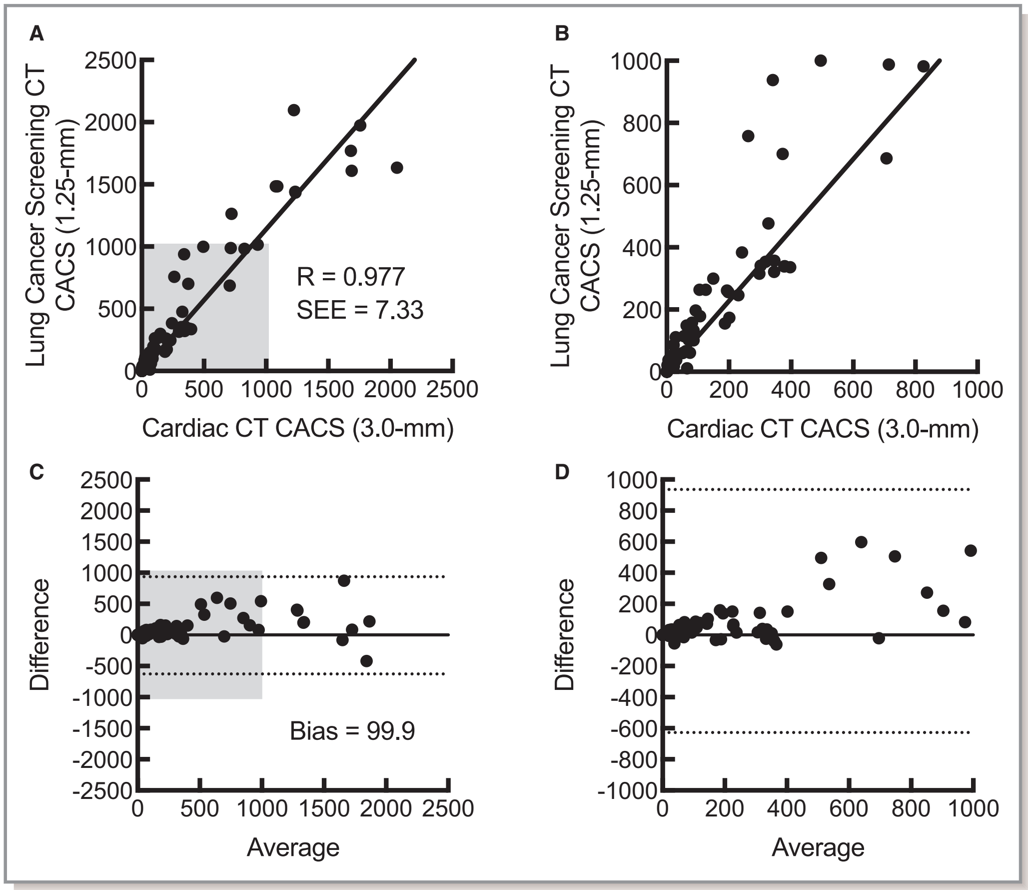

Figure 3. Scatter plot of Agatston CACS from CCT scans and 1.25-mm LCSCT scans along with corresponding Bland–Altman plots for agreement. **A**, Pearson correlation of CACS between CCT scans and LCSCT scans. **B**, Pearson correlation of CACS between CCT scans and LCSCT scans from shaded region of **(A)**. **C**, Bland–Altman plots for agreement between CCT scans (referent) and LCSCT scans (comparator). **D**, Bland–Altman plots for agreement between CCT scans (referent) and LCSCT scans (comparator) from shaded region of **(C)**. CACS indicates coronary artery calcium scoring; CCT, cardiac computed tomography; CT, computed tomography; LCSCT, lung cancer screening computed tomography; SEE, standard error of estimate.

value was 0.922. We next evaluated the agreement between 1.25- and 5.0-mm LCSCT for categorical risk ranges (Table 5). A far lower degree of association was observed between 1.25- and 5.0-mm LCSCT, with 62% of 5.0-mm LCSCT scores being in the same category as 1.25-mm LCSCT scores. Five percent of scores varied by more than 1 category. Overall Cohen's kappa value was much weaker at 0.610.

Table 3. Categorical Agreement for CACS Between CCT and 1.25-mm LCSCT

	CCT			
	0	1 to 99	100 to 299	>300
1.25-mm LCSCT				
0	15			
1 to 99	1	22		
100 to 299		10	9	
>300			3	27

CACS indicates coronary artery calcium scoring; CCT, cardiac computed tomography; LCSCT, lung cancer screening computed tomography.

Effect of Slice Thickness on Cardiovascular Risk Assessment in LCSCT

In our patient population undergoing multiple slice thickness LCSCT, median follow-up time for MACE was 30 (IQI, 16.5, 37) months, and there was a total of 71 MACE events; 51 deaths, 14 non-ST-segment elevation myocardial infarctions, 0 ST-segment elevation myocardial infarctions, 1 coronary artery bypass graft surgery, and 5 percutaneous coronary interventions. Figure 6 demonstrates ROC curves for the 3 slice thicknesses, 1.25-, 2.5-, and 5.0-mm. AUC for ROC curves were 0.7040 (0.6307, 0.7772), 0.7063 (0.6327, 0.7799), and

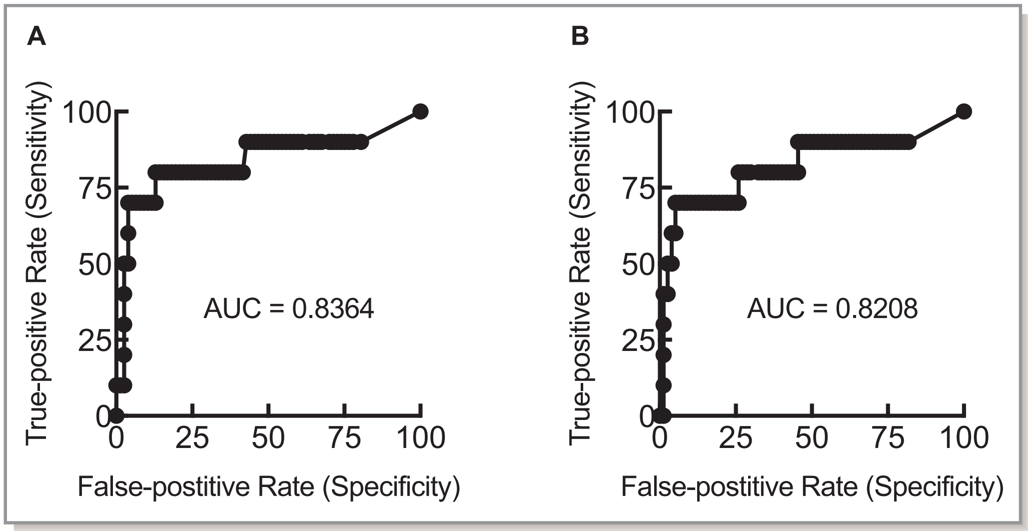

Figure 4. ROC curves for MACE of the CACS derived from CCT and LCSCT. **A**, ROC curve of CACS from CCT with AUC of 0.8364 (P=0.0006). **B**, ROC curve of CACS from LCSCT with AUC of 0.8208 (P=0.0010). AUC indicates area under curve; CCT, cardiac computed tomography; LCSCT, lung cancer screening computed tomography; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic.

0.7194 (0.6407, 0.7887), for 1.25-, 2.5-, and 5.0-mm LCSCTs, respectively. Comparison of AUCs revealed no significant differences between 1.25- and 2.5-mm (P=0.9002), 1.25- and 5.0-mm (P=0.5609), and 2.5- and 5.0-mm (P=0.6487). Despite comparable sensitivity and specificity among the 3 slice thicknesses, cut-off values for optimal test performance were different. At CACS of ≥1075, 1.25-mm scans had 64% sensitivity and 64% specificity with a likelihood ratio of 1.8 for MACE in this patient population. At CACS of ≥925, 2.5-mm scans had 66% sensitivity and 65% specificity with a likelihood ratio of 1.9 for MACE. At CACS of ≥475, 5.0-mm scans had 67% sensitivity and 67% specificity with a likelihood ratio of 2.1 for MACE.

Based on the AUC derived from the ROC curves, patients were divided into high- and low-risk groups, using the above cut-off values for optimal test performance. Figure 7 demonstrates the Kaplan–Meier plots for MACE outcomes (CACS high-risk cutoffs of ≥1075 for 1.25-mm, ≥925 for 2.5-mm, and ≥475 for 5.0-mm LCSCTs). Plots for the low- versus high-risk groups were not statistically significant between slice thicknesses. When low-risk plots were compared between 1.25-, 2.5-, and 5.0-mm LCSCTs, there were no statistical differences (P=0.9132) between slice thicknesses. Likewise, when high-risk plots were compared between slice thicknesses, there were no differences (P=0.8695).

Discussion

We evaluated a total of 258 patients, who had undergone 1.25-, 2.5-, and 5-mm slice thickness LCSCT, and we evaluated the impact of slice thickness on Agatston-based CACS derived from LCSCT scans in an elevated risk population as well as its predictive value for MACE. To accomplish this, CACS derived from 1.25-mm slice thickness LCSCT was first compared with CACS from CCT in the same patients, and these scores were found to correlate well with good agreement. We have previously shown that CACS values from 2-mm slice thickness LCSCT also correlate well with good agreement to CACS from CCT.[14] In this study, whereas there was good correlation and agreement in CACS between 1.25- and 2.5-mm scans, the 5-mm scan consistently tended to underidentify coronary calcium.

CACS from CCT is a well-established predictor of coronary events, and although it is particularly useful in patients who fall into the Framingham intermediate-risk cohort, it can also play a role in further risk stratification of low- and high-risk patients.[15,16,34–37] CACS is one of the best-performing tools in terms of risk prediction in asymptomatic individuals and correlates very well with overall atherosclerotic burden.[23,38] Furthermore, addition of CACS to traditional risk algorithms in the MESA (Multi-Ethnic Study of Atherosclerosis) improved risk stratification.[23,39] The Agatston-derived CACS is a summed score based on calcified plaque area and maximal density of individual calcified lesions, and has been the standard CACS metric. It is typically derived from ECG-gated, noncontrast CT studies at 2.5- to 3.0-mm slice thickness, using 120 kVp.[8] Agatston scoring is fast, programmed into imaging software, and is highly correlative with total burden of atherosclerosis.[40] In spite of the clinical utility of CACS from CCT for cardiac risk stratification, use of the technology remains limited, in part because of concerns over radiation exposure, lack of insurance coverage, and cost.[15,20,41,42]

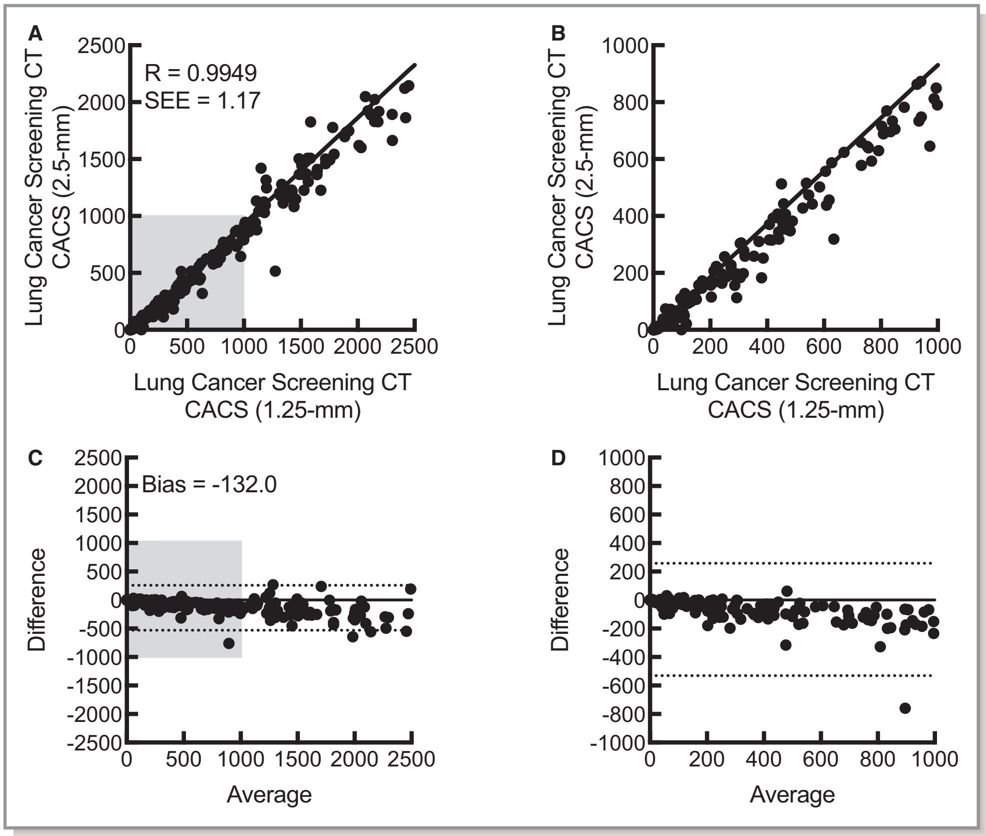

Figure 5. Scatter plot of Agatston CACS from LCSCT scans of differing slice thickness along with corresponding Bland–Altman plots for agreement. **A**, Pearson correlation of CACS between 1.25- and 2.5-mm slice thickness LCSCT scans. **B**, Pearson correlation of CACS between 1.25- (referent) and 2.5-mm (comparator) slice thickness LCSCT scans from shaded region of **(A)**. **C**, Bland–Altman plot for agreement of CACS between 1.25- (referent) and 2.5-mm (comparator) slice thickness LCSCT scans. **D**, Bland–Altman plots for agreement between 1.25- (referent) and 2.5-mm (comparator) slice thickness LCSCT scans from shaded region of **(C)**. **E**, Pearson correlation of CACS between 1.25- and 5.0-mm slice thickness LCSCT scans. **F**, Pearson correlation of CACS between 1.25- (referent) and 5.0-mm (comparator) slice thickness LCSCT scans from shaded region of **(E)**. **G**, Bland–Altman plot for agreement of CACS between 1.25- (referent) and 5.0-mm (comparator) slice thickness LCSCT scans. **H**, Bland–Altman plots for agreement between 1.25- (referent) and 5.0-mm (comparator) slice thickness LCSCT scans from shaded region of **(G)**. CACS indicates coronary artery calcium scoring; CT, computed tomography; LCSCT, lung cancer screening computed tomography; SEE, standard error of estimate.

Recently, it has been recognized that the requirements for 120 kVp, ECG gating, and 2.5- to 3.0-mm slice thickness are somewhat arbitrary, and that alternative calcium metrics, including a visual ordinal system, which more simply take into account total atherosclerotic burden may work just as well as the Agatston score.[22,23] Moreover, the Agatston score assumes that scoring should be upwardly weighted for calcium density, and recent studies have called this into question.[40,43]

There are an estimated 72 million noncontrast chest CTs done each year in the United States.[44] With the recent US Preventative Services Task Force recommendations for lung cancer screening with low-dose CT in adults who have a long-standing history of smoking, use of LCSCT has grown tremendously; it is estimated that as many as 94 million US adults are current or former smokers.[12,13,44–47]

Therefore, demonstrating the ability to obtain comparable data about CACS from LCSCT may help fulfill an unmet clinical need while taking advantage of already-existing information. Our current study assessed the utility of reporting CACS from these studies to provide cardiovascular risk assessment with negligible added expense or radiation exposure. With increasing recognition that this information may be valuable to cardiovascular risk assessment and preventive treatment strategies, the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology published a guideline for coronary calcium scoring in all noncontrast and noncardiac chest CT scans, regardless of the indication.[23] They recommend reconstruction of all LCSCT scans at 2.5- or 3-mm slice thickness for reporting of CACS, as well as reporting of CACS with every LCSCT scan. More recently, the Society of

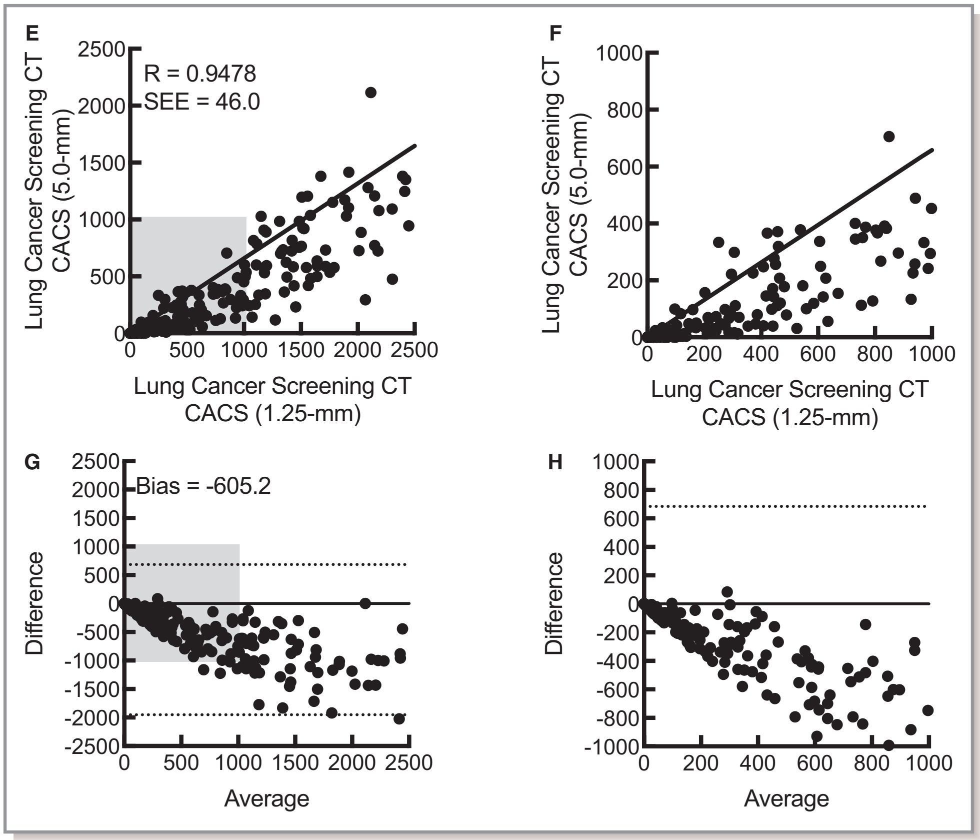

Figure 5. Continued.

Cardiovascular Computed Tomography published the Coronary Artery Calcium Data and Reporting System, recommending a categorical classification system that incorporates either Agatston-based scoring or visual ordinal scoring.[22] The reason for this slice thickness recommendation is because of the fact that risk-prediction models are based on CACS obtained at 2.5- to 3-mm slice thickness CCT. However, reconstruction at these thicknesses is not routinely done for all LCSCT scans at all institutions, and widespread implementation of these guidelines has not yet been achieved.

Our study found that CACS values obtained at the 1.25-mm slice thickness correlate well with good agreement to both CCT and the recommended 2.5-mm slice thickness and therefore could be reported directly. Though there is a positive bias for CACS derived from this narrower slice thickness, prognostic value for outcomes remains comparable with similar threshold values for elevated risk as to CCT. Within LCSCT comparisons, slice thicknesses of 1.25 and 2.5 mm maintained a good correlation and agreement and predicted outcomes based on very similar threshold values for high risk. Moreover, categorical ranges that determine

Table 4. Categorical Agreement for CACS Between 1.25-mm LCSCT and 2.5-mm LCSCT

	1.25-mm LCSCT			
	0	1 to 99	100 to 299	>300
2.5-mm LCSCT				
0	16	3		
1 to 99		30	6	
100 to 299		1	25	7
>300				170

CACS indicates coronary artery calcium scoring; LCSCT, lung cancer screening computed tomography.

Table 5. Categorical Agreement for CACS Between 1.25-mm LCSCT and 5.0-mm LCSCT

	1.25-mm LCSCT			
	0	1 to 99	100 to 299	>300
5.0-mm LCSCT				
0	16	20		
1 to 99		14	28	13
100 to 299			2	35
>300			1	129

CACS indicates coronary artery calcium scoring; LCSCT, lung cancer screening computed tomography.

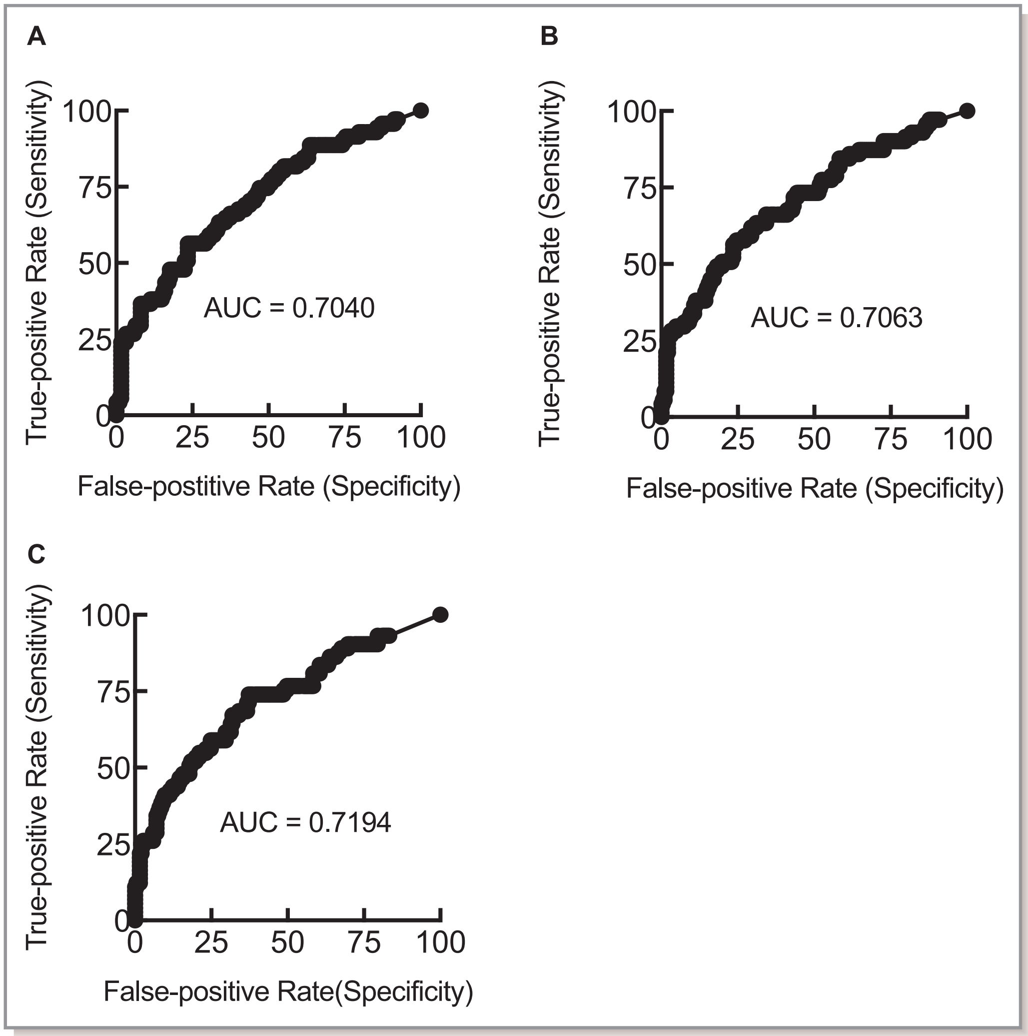

Figure 6. ROC curves for MACE of the CACS derived from LCSCT scans of differing slice thicknesses. **A**, ROC curve for 1.25-mm slice thickness with AUC of 0.7040 (P<0.0001). **B**, ROC curve for 2.5-mm thickness with AUC of 0.7063 (P<0.0001). **C**, ROC curve for 5.0-mm slice thickness with AUC of 0.7194 (P<0.0001). AUC indicates area under curve; CACS, coronary artery calcium scoring; LCSCT, lung cancer screening computed tomography; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic.

relative risk assessment and potential therapeutic recommendations remained in agreement between CCT and 1.25-mm LCSCT, despite the general trend toward positive bias. It is important to note that despite the 84% agreement in categorical ranges, almost one-third of CCT values in the 1 to 99 (mild) range were categorized upward to the 100 to 299 range on CACS derived from 1.25-mm LCSCTs, which may potentially have implications in risk assessment and treatment for patients in the mild calcification group.

In contrast, 5.0-mm slice thickness consistently underidentified calcium as evidenced by degree of negative bias. Moreover, categorical value agreement was much worse, with 62% of 5.0-mm LCSCT scores being in the same category as the 1.25-mm LCSCT scores and a far lower kappa of 0.610. Despite the lack of agreement, 5-mm slice thickness CT still provided prognostic information. Our data suggest that although we cannot currently apply the Coronary Artery Calcium Data and Reporting System categorical system to Agatston CACS values derived from 5.0-mm LCSCT, we may be able to individualize the threshold values that determine the differing categories of risk within this slice thickness. However, this would require additional research and prospective validation, using the 5-mm slice thickness. One reasonable and more-practical alternative to designing slice-specific threshold values for 5.0-mm scans would be to validate the visual qualitative scoring system, which is already recommended by the new Coronary Artery Calcium Data and Reporting System guidelines, for use in 5.0-mm slice thickness LCSCTs in future studies.[22] This would still require slice-specific training and education to avoid subjective variability

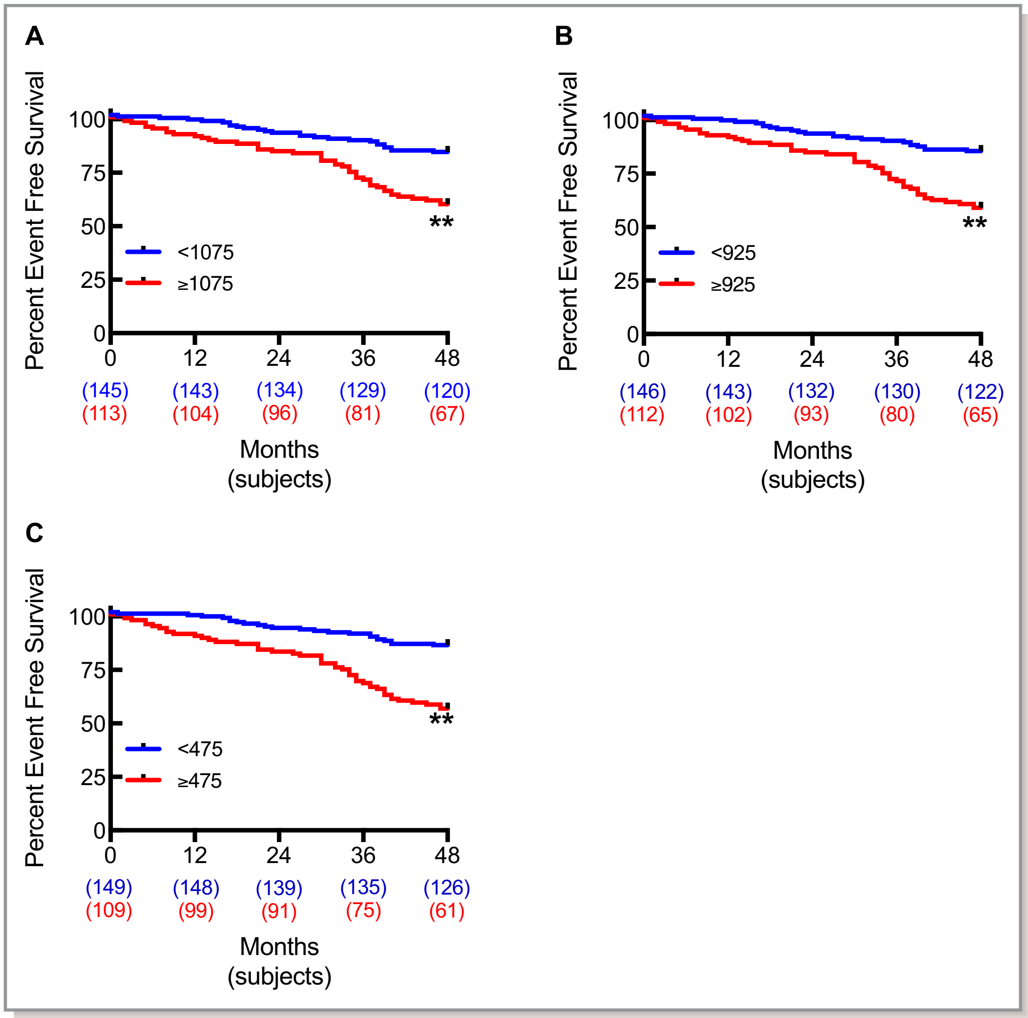

Figure 7. Kaplan–Meier plots for MACE of the CACS derived from LCSCT scans of differing slice thicknesses. **A**, 1.25-; **B**, 2.5-; and **C**, 5.0-mm derived CACS divided into high-risk calcium burden as determined by thresholds derived from their respective ROC curves (**P<0.01, log-rank test). CACS indicates coronary artery calcium scoring; LCSCT, lung cancer screening computed tomography; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic.

in ordinal categorization by less-experienced users, but has potential to be a very effective alternative solution. In summary, quantifying calcium scores from 1.25- and 2.5-mm slice thickness LCSCT scans is a simple, fast, and inexpensive way to profile patient risk, demonstrating comparable agreement and prediction of outcomes to traditional CCT. Though additional prospective, multicenter studies are required, it appears reasonable to report Agatston-based CACS values from 1.25- and 2.5-mm slice thickness LCSCT scans in order to help assess cardiovascular risk.

There are a number of limitations to this study that should be acknowledged. This was a retrospective study that took place at a single institution with the resultant biases inherent to this study design. This study took place in the VA, and thus the population was mostly men. Cardiovascular events were mainly driven by death, so it will be important to confirm findings in a larger, prospective study powered for cardiovascular events. Moreover, the total number of events in the comparison between 1.25-mm LCSCT and CCT was relatively low. Additionally, the concept of an individualized risk group thresholding of CACS values from 5.0-mm slice thickness LCSCTs must be validated in a larger, prospective cohort powered for cardiovascular events.

Conclusion

Agatston-based CACS obtained from LCSCT scans represent a readily available and as yet underutilized resource to help stratify cardiovascular risk for patients. Here, we have presented evidence that supports the importance of taking slice thickness into consideration when carrying out quantitative Agatston-based calcium scoring methodology. Despite the absence of ECG gating, CACS from 1.25-mm slice thickness LCSCT scans correlate well with good agreement when compared with CACS from CCT, yet may present challenges in patients with mild coronary calcification because of the tendency toward increased identification of calcium. Overall, both 1.25- and 2.5-mm slice thickness LCSCT scans demonstrate very similar prognostic information, and it appears reasonable to report Agatston-derived CACS values from these slice thicknesses. Whereas CACS derived from 5.0-mm slice thickness scans appear to provide some prognostic information, the absolute thresholding values for elevated risk are significantly lower secondary to the underidentification of calcium, thus currently limiting the practical use of Agatston-based CACS values from 5.0-mm LCSCTs.

Sources of Funding

This work was supported by Career Development Award Number 7IK2BX002527 from the U.S. Department of Veterans Affairs Biomedical Laboratory Research and Development (Morrison), R01 Research Project Grant Award from National Heart, Lung, and Blood Institute of the National Institutes of Health under grant number 1RO1HL139795 (Morrison), Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103652 (Morrison), R01 Research Project Grant Award from National Heart, Lung, and Blood Institute of the National Institutes of Health under grant number 5R01HL128661 (Choudhary), and Summer Research Experience Program Awards from National Heart, Lung, and Blood Institute of the National Institutes of Health under grant number R25HL088992 (Neverson).

Disclosures

None.

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