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Relationship of Coronary Artery Calcium on Standard Chest Computed Tomography Scans with Mortality

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STRUCTURED ABSTRACT

Objectives—We aimed to determine the correlation between coronary artery calcium (CAC) scores on 3mm ECG-gated computed tomography (CT) scans and standard 6mm chest CT scans, and to compare relative strength of associations of CAC on each scan type with mortality risk.

Background—Coronary artery calcification predicts cardiovascular disease (CVD) and all-cause mortality, and is typically measured on ECG-gated 3mm CT scans. Patients undergo standard 6mm chest CTs for various clinical indications much more frequently, but CAC is not usually quantified. To better understand the usefulness of standard chest CTs to quantify CAC, we conducted a case-control study among persons who had both scan types.

Methods—Between 2000–03, 4,544 community-living individuals self- or physician-referred for "whole body" CT scans, had 3mm ECG-gated CTs and standard 6mm chest CTs, and were

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followed for mortality through 2009. In this nested case-control study, we identified 157 deaths and 494 controls frequency matched (1:3) on age and gender. The Agatston method quantified CAC on both scan types. Unconditional logistic regression determined associations with mortality, accounting for CVD risk factors.

Results—Participants were 68±11 years old and 63% male. The Spearman correlation of CAC scores between the two scan types was 0.93 ($p<0.001$); median CAC scores were lower on 6mm CTs compared to 3mm CTs (22 vs.104 Agatston units, $p<0.001$). Adjusted for traditional CVD risk factors, each SD higher CAC score on 6mm CTs was associated with 50% higher odds of death (OR=1.5; 1.2–1.9), similar to 50% higher odds on the 3mm ECG-gated CTs (OR=1.5, 1.1–1.9).

Conclusions—CAC scores on standard 6mm chest CTs are strongly correlated with 3mm ECG-gated CTs and similarly predict mortality in community-living individuals. Chest CTs performed for other clinical indications may provide an untapped resource to garner CVD risk information without additional radiation exposure or expense.

Keywords

Coronary artery calcium; Chest Computed Tomography; Mortality; Epidemiology

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality in the United States.(1) Detection of coronary artery calcification (CAC) is a strong predictor of CAD, cardiovascular events, and all-cause mortality,(2, 3) above and beyond the Framingham risk score.(2, 4) CAC is usually quantified on dedicated 3mm sliced computed tomography (CT) scans that are ECG gated, so as to minimize motion artifact from the beating heart and provide relatively fine cuts through the coronary arteries. These scans are done frequently in research settings, but uncommonly in clinical practice because most insurance providers do not cover the cost of the scan for preventive medicine and because the US Preventive Task Force currently does not recommend preventive CAC screening in individuals without a history of CAD.(5, 6) Standard chest CT scans are used for numerous clinical indications including lung cancer screenings, evaluation for pulmonary embolism, adenopathy, pleural diseases, and pneumonia, among others. Calcium within the coronary arteries can be easily recognized on these scans,(7) and prior studies have evaluated CAC on lung CTs for CAD screening in smokers at high risk for lung cancer.(8, 9) However, CAC screening may be most useful in persons at intermediate risk for CAD,(2) where presence and severity of CAC may modify the approach to preventive strategies such as use of statins and other interventions. In comparison to the approximate 600,000 3mm ECG-gated CT scans done in the US annually, it is estimated that over 7.1 million 6mm lung CT scans are done annually for other clinical indications.(10) While several studies have demonstrated agreement between 3mm ECG-gated CTs and standard chest CTs in their measurement of CAC (7, 9, 11), whether standard chest CTs can predict outcomes in the general population, and whether results are similar to 3mm EBCT scan data, despite the wider cuts and absence of ECG gating, is unknown.

To better understand the usefulness of standard chest CTs for this purpose, we conducted a case-control study among persons who had both scan types when they were seen in 2000–2003 and who were followed for mortality for approximately 8 years thereafter.

METHODS

Study Population and Study Design

Study participants were recruited through a San Diego cardiovascular imaging clinic between 2000 and 2003, where 4544 community-living individuals who were mostly asymptomatic were self-referred or referred by primary care physicians for "whole body" CT scans. Participants were followed for mortality through 2009, during which 173 participants died. Using a nested case-control study design, each death (case) was frequency matched on gender and age within 1 year with 3 surviving controls, resulting in 518 controls, and totaling 691 participants.(12) Following the selection of cases and matching controls, we further excluded any participant who had undergone any angioplasty, stent, or bypass revascularization procedure (n=41), which resulted in a total of 651 participants – 157 deaths and 494 controls. Five of the oldest cases did not have age matches within 1 year. Thus, controls for these five cases were within 3 to 5 years of the ages of these 5 cases. A 3mm ECG-gated CT was obtained and scored for CAC at the time of the initial visit. A 6mm standard chest CT was also obtained and read for general lung pathology, but was not scored for CAC at the time of the baseline visit. Our case-control design, nested within a prospective cohort study allowed us a targeted approach to retrieve chest CTs and re-read them for CAC without significant loss of statistical power. All participants provided informed consent and the study was approved by the University of California, San Diego Human Research Protections Program.

Coronary Artery Calcification Imaging and Scoring

CT scans were performed using an Imatron C-150 scanner (San Francisco, California), which is an electron-beam CT (EBCT) scanner with a high resolution detector system. We used the standard single-section mode, which involves an image acquisition time of 100msec and 3mm section thickness. The 3mm ECG-gated CT scans were electrocardiographically triggered at 40% or 65% of the [0-9]-[a-z] interval, depending on the participant's heart rate, and resulted in 1.0 and 1.3 mSv of radiation for women and men, respectively.(13) For the 6mm chest CT scans, subjects were scanned from the sternal notch to base of the diaphragm without ECG gating. Radiation exposure for this type of scan, as presented in lung cancer screening literature for low-dose CT scan screening is approximately 1.5 mSv.(14) Methods for scoring CAC follow those described by Agatston et al. on both scan types. (15) The 3mm ECG-gated scans were read at the time of scan acquisition, while the 6mm scans were read for CAC in 2012. Readers were blinded to participant clinical data and to their 3mm CT CAC score.

Mortality

In 2009, we linked the data with the Social Security Death Index (SSDI) to identify individuals who had died in the intervening period. Potential deaths identified by the SSDI were cross-referenced with their patient clinical records to confirm identity.

Covariates

Height and weight were measured at clinic visits, and body mass index (BMI) was calculated (in kg/m^2). Age and sex were obtained through self-report, and a questionnaire was used to obtain a participant's medical history including smoking status (never, former, or current), prevalent hypertension, and cholesterol medication use. Non-fasting serum lipid and glucose levels were obtained via finger-stick using the Cholestec LDX system. Diabetes was defined as serum glucose > 200 mg/dL, or the use of glucose-lowering medications. Dyslipidemia was defined as total to high-density lipoprotein (HDL) cholesterol ratio > 5, or the use of cholesterol-lowering medication. Systolic and diastolic blood pressures were obtained from a trained technician after the participant rested for 5 minutes. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or the use of anti-hypertensive medications.

Statistical Analysis

We evaluated differences in demographics and traditional CVD risk factors in cases and controls using t-tests or Wilcoxon Rank Sum tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. We evaluated the correlation of CAC scores on the two scan types using Spearman correlations for continuous CAC scores, given skewed distributions, and Kappa statistics for categorical CAC scores. We also performed a Bland-Altman analysis to determine the bias and limits of agreement between the 3mm ECG-gated CT and the 6mm standard chest CT scans.(16) Next, we used unconditional logistic regression to examine associations of each scan type with mortality. Initial models were unadjusted. Subsequent models adjusted for demographics and traditional CVD risk factors (age, gender, diabetes, hypertension, dyslipidemia, BMI, smoking, and family history of CVD). We evaluated each CAC score as both a continuous and categorical variable. For analysis using a continuous CAC score, we added 1 to each CAC score (such that zero scores were not excluded from the analysis) and natural log transformed the distribution (Ln[CAC +1]) to approximate a normal distribution of CAC scores. We used standardized coefficients to compare strength of association per standard deviation of LnCAC+1 across the two scan types. For analysis using a categorical CAC score, we categorized patients into 4 groups according to standard 3mm Agatston CAC score cut-points, which facilitated comparisons across scan types.(17)

In evaluating the 6mm Agatston scores, 34% had Agatston scores of zero, whereas 24% had scores of zero using the 3mm CT scans. Using standard cut-points proposed by Detrano and colleagues, we defined 4 categories of CAC for both 3mm ECG-gated and 6mm chest CT scans: CAC=0, CAC=1–100, CAC=101–300, and CAC>300.(17) All analyses were conducted using Stata version 11.0SE (Stata Corp., College Station, TX) and SAS version 9.4 (SAS Corp, Cary, NC), and p-values < 0.05 were considered statistically significant.

RESULTS

The 651 participants in this study had mean age of 68 years, and 63% were male. Cases and controls had similar BMI, total cholesterol, HDL cholesterol, and use of lipid lowering medications. However, a greater proportion of cases had diabetes and hypertension, were former or current smokers, and had a family history of CVD. Cases also had higher median CAC scores on both the 3mm CT and 6mm CT scans compared to controls at baseline (Table 1). Race/ethnicity was not required to obtain a CT scan, thus it was provided by 199 individuals in this study. Of these 199 individuals with reported ethnicity, 100% (43) of deaths occurred in Caucasians. This subsample of 199 included 0.6% Asian, 12% Hispanic and 2% Other – the remaining 85% were Caucasian.

The correlation between CAC scores on the 3mm ECG-gated CT and the 6mm standard chest CT was 0.93 ($p < 0.001$; Figure 1). However, the median CAC scores were significantly lower on the 6mm CT scan than on the 3mm ECG-gated scan (22 vs. 104 Agatston units, respectively, $p < 0.001$). The Kappa statistic for agreement between CAC score categories on the 3mm ECG- gated CT compared to the 6mm standard chest CT was 0.41, and the weighted Kappa statistic was 0.62, indicating moderate to substantial agreement between the two scans using the cut-points specific to the 3mm ECG- gated CT scans. Bland-Altman analysis presents a mean bias of 3.23, with limits of agreement between 0.6 and 17.3, as shown in Figure 2, suggesting that Agatston scores on 3mm ECG-gated CT scans were, on average, approximately 323% higher than Agatston scores on the 6mm standard chest CT scan.(16) As illustrative examples of the difference in sensitivity, Figure 3 presents CAC measured on 3mm ECG-gated CT (CAC=372.09) and 6mm chest CT (CAC=116.58) at approximately the same location within an individual. In a participant with more advanced CAC, Figure 4 presents 2 consecutive slices within the same individual where CAC measured on 3mm ECG-gated CT totaled to 3212.75 and CAC measured on 6mm chest CT totaled to 1044.00. Both examples demonstrate that, while CAC is present and quantifiable on both the 3mm and 6mm scans, the clarity and amount of CAC scored by the Agatston method is higher using a 3mm ECG-gated CT scan.

Table 2 shows the associations of CAC scores on the two scan types with mortality. When evaluating CAC on the 6mm chest CT scans, compared to the CAC=0 reference, there was a graded relationship of higher CAC score with odds of mortality such that those with CAC scores between 1 and 100 had 1.9-fold higher odds of mortality, between 101 and 300 had 2.3 fold higher odds of mortality, and those with CAC greater than 300 had 2.6-fold higher odds for mortality in models adjusted for demographics and traditional CVD risk factors. In comparison, with the 3mm ECG-gated scans, compared to the CAC=0 reference, participants with CAC scores between 1 and 100 had 2.1-fold higher odds of mortality, between 101 and 300 had 2.9-fold higher odds of mortality, and those greater than 300 had 3.2-fold higher odds of mortality in adjusted models. These associations have been plotted in Figure 5. When CAC scores were evaluated as a continuous variable, each SD higher CAC score on the 6mm chest CTs was associated with 1.5-fold higher odds of mortality. Similarly, each SD higher score on the 3mm ECG-gated scans was associated with 1.5-fold higher odds of mortality. All of these results were statistically significant.

DISCUSSION

In this population of free-living individuals who self-referred or were referred by their primary care physicians for “whole body” CT scans, CAC scores on standard 6mm chest CTs were strongly correlated to those on the 3mm ECG-gated CT scans specifically designed for CAC measurement. Scores on either scan type were strongly associated with all-cause mortality, and the relative strength of association was similar irrespective of the scan type.

CAC screening has been considered useful for prevention of CVD because it can further risk-stratify persons who are considered intermediate risk for incident CVD events by the Framingham risk score. Several investigators have reported that standard chest CT scans used for lung cancer screening can also detect and quantify CAC.(3, 4, 9, 11, 18, 19) Our study confirms these results, and extends them to a community-living population for the first time. Moreover, to our knowledge, this is the first study to compare the correlation and relative strengths of association of CAC on the standard chest CT and the 3mm ECG-gated CT with mortality.

Our results may have important implications for preventive cardiology clinical practice. In 2007, approximately 7.1 million chest CT scans were performed in the US, compared to 600,000 CT scans for calcium scoring, presumably using 3mm ECG-gated CTs.(10) There is concern that radiation exposure from CT scans may increase cancer risk.(20, 21) In addition, many health insurance plans do not cover the expense of CT scanning for CAC measurement for preventive care purposes. Given that chest CTs are done frequently for numerous other clinical indications, many individuals may already have scans that can be scored for CAC, which may guide preventive cardiology care. Thus, if our results are confirmed, health care providers may consider utilizing previously obtained CT scans to assess CAC while avoiding the potential risks and expense of repeat CT scans designed specifically for CAC measurement.

Currently, CAC observed on standard chest CT scans is not routinely reported by radiologists, and use of the Agatston method is even less common. For example, Williams et al. reported that CAC on chest CTs was recorded in the final radiology report in only 44% of patients with known CAC.(22) Jacobs and colleagues demonstrated that, by using simple visual grading to measure CAC on standard chest CT, CAC was strongly associated with future CVD events.(23) Thus, by simple visual grading system evaluated by others,(23, 24) or by the Agatston method used here, the detection of CAC on standard chest CT has prognostic implications. As it has important implications for preventive care, we believe it should be systematically reported.

The median CAC scores on the 6mm CT scans were substantially lower on average than on the 3mm CT scans. This may be because there are fewer slices to evaluate and score on the 6mm scan. With fewer slices, there may also be volume averaging in plaque based on interpolation algorithms from slice to slice. Also, small plaques may be missed between 6mm cuts. Therefore, 6mm chest CT scans may be less sensitive for low levels of CAC, and the good prognosis provided by a 3mm ECG-gated scan showing zero CAC may not be as robust for a 6mm chest CT with zero CAC. Absence of any CAC on an ECG-gated 3mm scan has been associated with low risk for incident CVD, and relatively standard CAC cut-points (for example, 0–100; 101–300; and > 300) have been used frequently in prior studies. In this study, we have extended these cut-points to 6mm standard chest CT scans, which were similarly associated with mortality risk, but the implication of a specific CAC score may differ across scan types. For example the median 6mm standard chest CT scan CAC scores were 3, 46, and 286 in individuals in the 3mm CT scan CAC categories of 1–100, 101–300, and >300, respectively. Establishing applicable cut-points for Agatston CAC scores on 6mm standard chest CT scans warrant further development. However, our data suggest that lower CAC scores on 6mm chest CT scans may underestimate the CAC burden compared to 3mm ECG-gated CT scores.

This study has important limitations. Our study population was mostly older non-Hispanic white adults, many of whom self-referred for "whole body" CT scans for preventive care. Such individuals may be particularly motivated to prevent chronic diseases. Future studies in other settings are required to confirm these findings. As discussed previously, although the associations of either scan type with mortality were similar, there are absolute differences in the CAC scores across scan types, which may impact sensitivity to detect low level CAC and will influence specific cut-points. Thus, specific CAC values should be interpreted with knowledge about the scan type.

In conclusion, despite the absence of ECG gating and wider slice thickness, CAC scores on standard 6mm chest CTs are highly correlated with those on 3mm ECG-gated CT scans, and are similarly associated with mortality risk in community-living individuals. Most insurance providers do not routinely cover the expense of 3mm ECG-gated scans for CAC scoring, and conversely approximately 7 million chest CT scans are done annually in the US for other clinical indications.(10) Persons who have chest CTs for other clinical indications may benefit from systematic reading of CAC to garner additional information on CVD risk without the added expense and radiation exposure required for dedicated 3mm ECG-gated scans.

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ABBREVIATIONS

CAD	Coronary Artery Disease
CAC	Coronary Artery Calcium
CT	Computed Tomography
ECG	Electrocardiogram/Electrocardiography
EBCT	Electron Beam Computed Tomography
CVD	Cardiovascular Disease
HDL	High Density Lipoprotein
SD	Standard Deviation

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Clinical Perspectives

Competency in Medical Knowledge

Standard chest CT scans are often not read for CAC severity by radiologists when reading scans obtained for other clinical indications. We show that detection of CAC on standard chest CT scans is closely correlated with CAC on the ECG-gated CT scans, and similarly predicts mortality. Therefore, chest CT scans obtained for various clinical indications can also inform CVD risk through measurement of CAC.

Translational Outlook

While similarly predictive of events, a CAC score on a standard chest CT was lower than on an ECG-gated CT on the same individual. Future studies are required to determine applicable cut-points for CAC scores on standard CT scans relative to the ECG-gated CT.

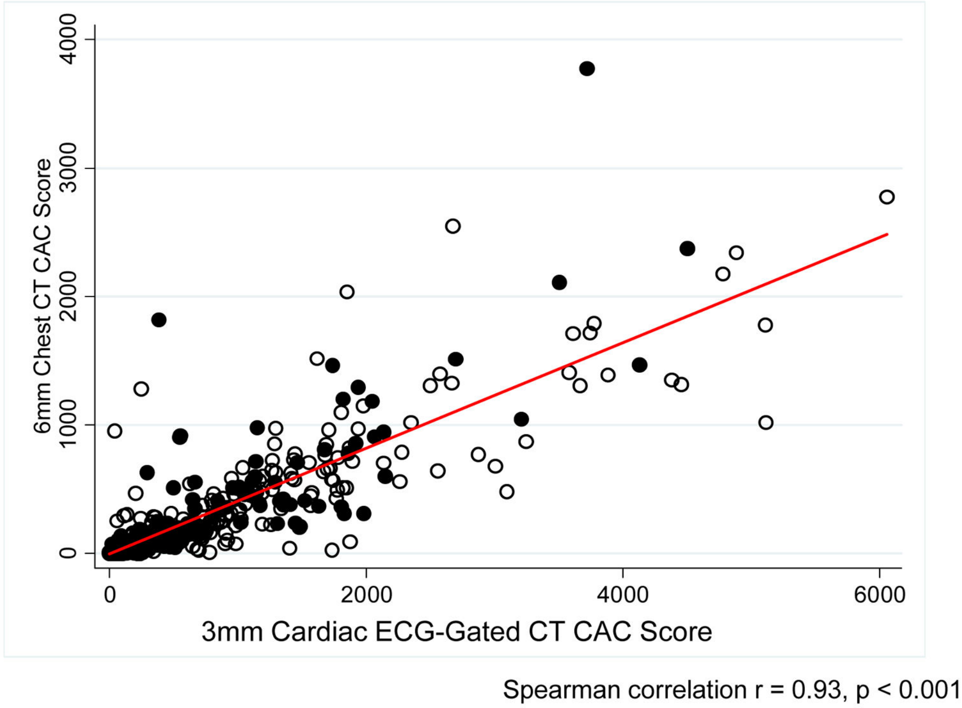

Figure 1. Scatter Plot Agatston CAC Score on 6mm Chest CT and 3mm Cardiac ECG-Gated CT Scans

Spearman Correlation r = 0.93, p < 0.001

● = Cases (n=157)

○ = Controls (n=494)

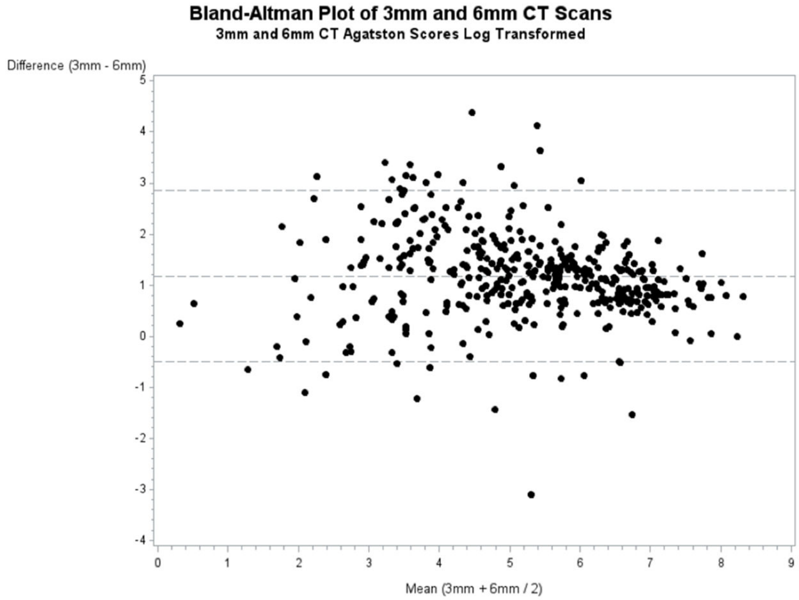

Figure 2. Bland-Altman Plots for Agreement Between 3mm ECG-Gated CT Scans and 6mm Standard Chest CT Scans

*Log transformed mean bias (center line) was 1.17 (±0.855), which back transforms to 3.23, with limits of agreement ranging from 0.6 to 17.3 (top and bottom dashed lines).

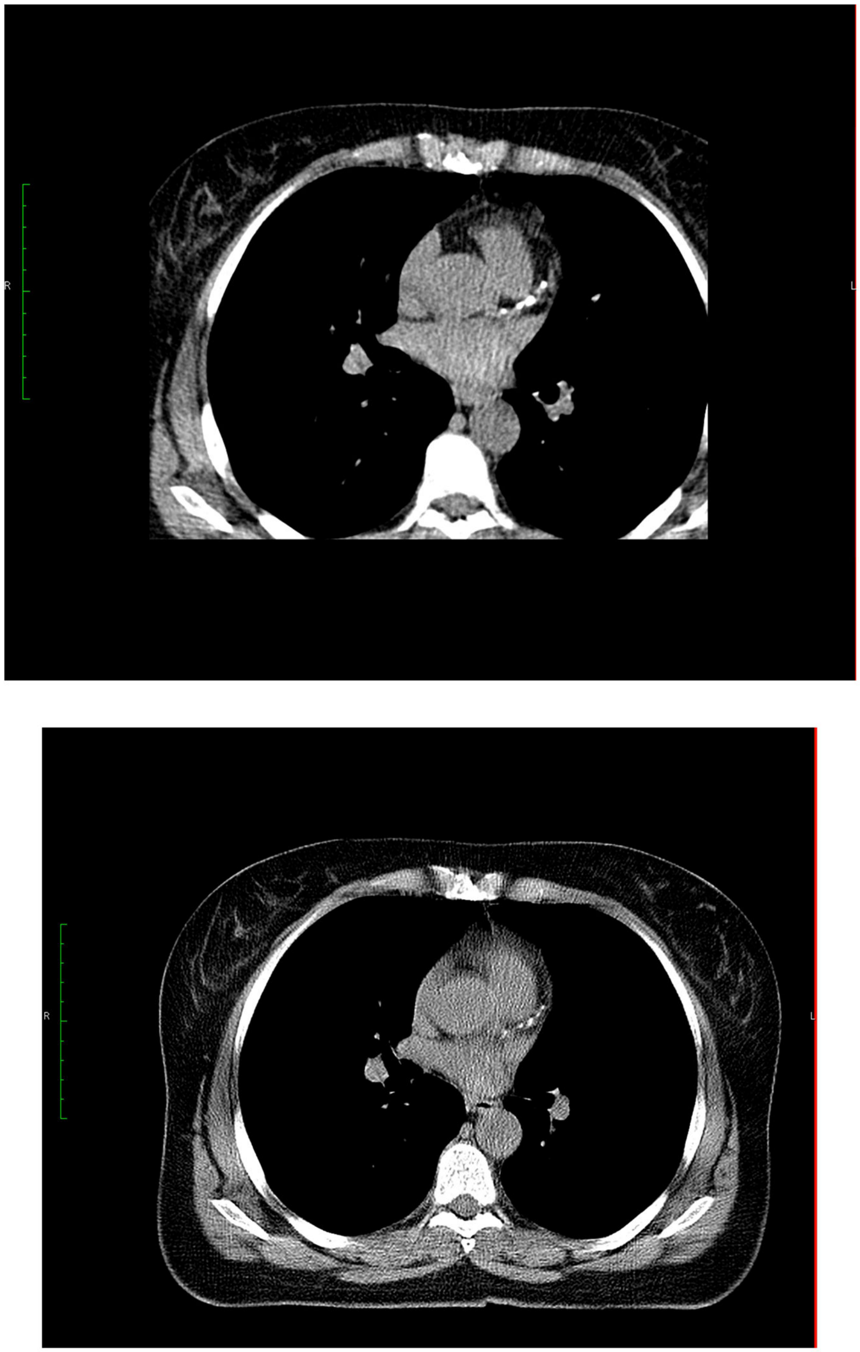

Figure 3. Illustrative Example of the Difference in Sensitivity between 3mm ECG-Gated CT Scans and 6mm Chest CT Scans in a Single Slice within an Individual

A. 3mm ECG-gated CT (Agatston CAC Score = 372.09)

B. 6mm Chest CT (Agatston CAC Score = 116.58)


R
L


R
L

Figure 4. Illustrative Example of the Difference in Sensitivity between 3mm ECG-Gated CT Scans and 6mm Chest CT Scans in Two Consecutive Slices within an Individual

A.1, A.2 Two consecutive slices from 3mm ECG-gated CT within an individual (Agatston CAC Score = 3212.75)

B.1, B.2 Two consecutive slices from 6mm Chest CT within an individual (Agatston CAC Score = 1044.00)

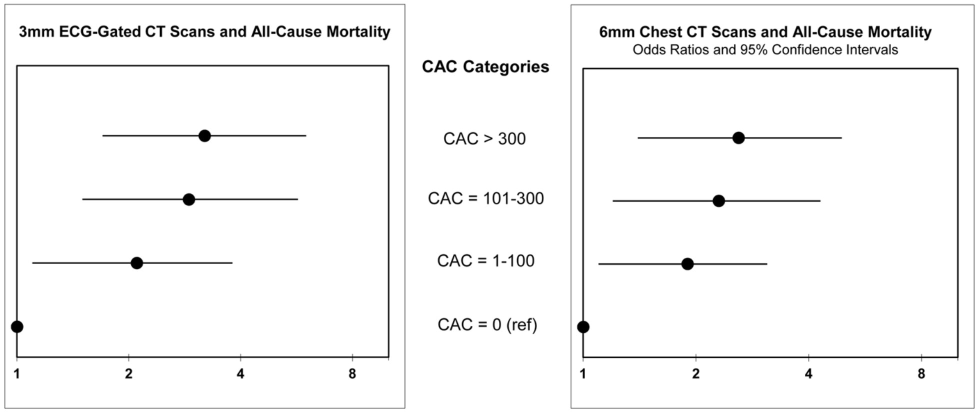

Figure 5. Forest Plots of Odds Ratios and 95% Confidence Intervals for the Associations between 3mm ECG-Gated CT Scans and Mortality and 6mm Chest CT Scans and Mortality

*Adjusted for age, sex, diabetes, hypertension, hyperlipidemia, BMI, smoking, and family history of CVD

Table 1

Participant Characteristics by Case-Control Status

Characteristics	Case	Controls	P-value
	(n=157)	(n=495)	
Age, years	67.74 ± 11.71	67.84 ± 10.76	0.92
Body Mass Index	26.68 ± 4.66	26.84 ± 4.22	0.70
Total Cholesterol	203.5 ± 42.51	201.9 ± 40.03	0.67
HDL Cholesterol	52.45 ± 17.92	51.79 ± 16.90	0.70
Female	67 (43%)	186 (38%)	0.26
Diabetes	13 (8%)	16 (3%)	0.01
Hypertension	64 (41%)	188 (38%)	0.53
Lipid Medication Use	9 (6%)	38 (8%)	0.41
Smoking Status			
Never Smoked	70 (45%)	269 (54%)	0.03
Former Smoker	67 (43%)	195 (39%)	0.47
Current Smoker	20 (13%)	32 (6%)	0.01
CVD Family History	43 (27%)	87 (18%)	0.01
3mm EBCT CAC Score (Median; 25th, 75th Percentile)	210 (14, 608)	84 (0, 484)	0.01
6mm Chest CT CAC Score (Median; 25th, 75th Percentile)	55 (0, 230)	15 (0, 146)	0.00

[*] Used Wilcoxon-Rank Sum Test to determine differences between cases and controls.

Table 2

Association of 6mm Standard Chest CT vs. 3mm ECG-Gated EBCT CAC scores with All-Cause Mortality

6mm Non-Gated Chest CT					
Agatston Score Range	< 1.0	1–100	101–300	> 300	Continuous Model Per SD Ln [CAC +1]
# Deaths/# Controls	41/192	53/152	29/70	34/80	
Unadjusted OR (95% CI)	1.00 (Ref)	1.6 (1.0, 2.6)	1.9 (1.1, 3.4)	2.0 (1.2, 3.4)	1.3 (1.1, 1.6)
p-value		0.037	0.018	0.01	0.002
Adjusted* OR (95% CI)	1.00 (Ref)	1.9 (1.1, 3.1)	2.3 (1.2, 4.3)	2.6 (1.4, 4.9)	1.5 (1.2, 1.9)
p-value		0.017	0.009	0.004	0.001
3mm ECG-Gated EBCT					
Agatston Score Range	<1.0	1–100	101–300	>300	Continuous Model Per SD Ln [CAC +1]
# Deaths/# Controls	26/139	35/120	31/77	65/158	
Unadjusted OR (95% CI)	1.00 (Ref)	1.6 (0.9, 2.7)	2.2 (1.2, 3.9)	2.2 (1.3, 3.7)	1.3 (1.1, 1.6)
p-value		0.122	0.011	0.002	0.005
Adjusted* OR (95% CI)	1.00 (Ref)	2.1 (1.1, 3.8)	2.9 (1.5, 5.7)	3.2 (1.7, 6.0)	1.5 (1.1, 1.9)
p-value		0.022	0.002	0.000	0.002

* Adjusted for age, sex, diabetes, hypertension, hyperlipidemia, BMI, smoking, and family history of CVD.