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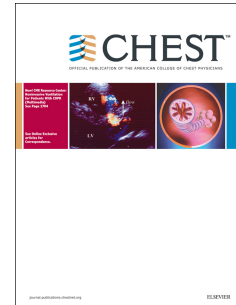Kazerooni, Ella A
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Visual estimate of coronary artery calcium predicts cardiovascular disease in COPD

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Some of the findings of this study were presented at an oral presentation at the European Respiratory Society (ERS) Conference, London, UK, Sep 2016.

Abbreviations

CAC: Coronary Artery Calcium

CAD: Coronary Artery Disease

CVD: Cardiovascular Disease

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

FEV_1: Forced Expiratory Volume in the first second

FVC: Forced Vital Capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HR = Hazards Ratio

HU = Hounsfield Units

Abstract

Background

COPD is associated with cardiovascular disease (CVD), and coronary artery calcification (CAC) provides additional prognostic information. With increasing use of non-gated CT scans in clinical practice, we hypothesized that the visual Weston CAC score would perform as well as Agatston score in predicting prevalent and incident coronary artery (CAD) and CVD in COPD.

Methods

We measured CAC using Agatston and Weston scores on baseline CT scans in 1875 current and former smokers enrolled in the COPDGene study. Baseline cardiovascular disease and incident cardiac events on longitudinal follow-up were recorded. Accuracy of the CAC scores were measured using receiver-operating characteristics analysis, and Cox Proportional hazards analyses were used to estimate the risk of incident cardiac events.

Results

CAD was reported by 133 (7.1%) subjects at baseline. 413 (22.0%) and 241 (12.9%) had significant CAC by Weston ($\geq$7) and Agatston ($\geq$400) respectively; the two methods correlated significantly (r=0.84;p<0.001). Over 5 years of follow-up, 127 (6.8%) developed incident CVD. For predicting prevalent CAD, c-indices for Weston and Agatston were 0.78 and 0.74 respectively, and for predicting incident CVD, 0.62 and 0.61 respectively. After adjustment for age, race, sex, smoking pack-years, FEV_1, percent emphysema and CT scanner type, Weston $\geq$7 was associated with time to first acute coronary event (HR = 2.16, 95%CI 1.32 to 3.53; p = 0.002), but not Agatston$\geq$400 (HR = 1.75, 95%CI 0.99 to 3.09; p = 0.053)

Conclusions

A simple visual score for CAC performs well in predicting incident CAD in smokers with and without COPD.

Abstract Word Count: 248

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States, and is associated with significant morbidity. Although primarily a disease that involves chronic inflammation of the lung, COPD is now recognized as a multisystem disease that is associated with accelerated atherosclerosis and cardiovascular disease.[1] Cardiovascular disease accounts for the majority of mortality in mild to moderate COPD,[1,2] and all manifestations of cardiovascular disease including coronary artery disease, ischemic stroke, peripheral arterial disease and the need for intervention are considerably greater in subjects with COPD, after adjustment for shared risk factors such as age and cigarette smoking.[3-5] Unfortunately, cardiovascular disease is silent and asymptomatic in a majority of patients, and this is exacerbated in patients with COPD in whom symptoms can be ascribed to underlying lung disease. Numerous approaches have been used to stratify patients at risk for adverse cardiovascular events, including scoring systems such as the Framingham coronary heart disease risk score.[6] Noninvasive surrogates for the presence of cardiovascular disease such as coronary artery calcification (CAC) on computed tomography (CT) have been demonstrated to offer risk assessments over that afforded by the scoring systems in the general population.[7,8] However, these scoring systems have not been specifically tested in populations with COPD.

CT of the chest is performed frequently, and accounts for >20% of CT scans performed in the United States.[9] This number is expected to increase with the advent of low dose screening for lung cancer in smokers.[10] This offers an opportunity to easily screen and test for cardiovascular disease in patients at risk. CAC is traditionally measured using the semi-automated Agatston score on electrocardiographically gated CT scans, but standard and low dose non-gated scans have recently been shown to be reliable in scoring the presence of CAC in

patients with COPD.[11,12] Although the Agatston score performs well in the prediction of existing and incident cardiovascular disease and events, there are limited studies assessing CAC using this method in COPD.[13-15] Only one small study found a relationship between the presence of CAC and incident and recurrent cardiovascular events in subjects with COPD.[15] The applicability of the Agatston score is further limited by the need for special software, and often a separate work station.[16] With increasing use of non-gated CT scans in clinical practice, we hypothesized that a simple visual score (Weston) would perform as well as the Agatston score in predicting prevalent coronary artery disease (CAD) and incident cardiovascular disease in smokers with and without COPD.[17]

Methods

We analyzed subjects enrolled in a large multicenter cohort study (COPDGene) with current and former smokers aged 45 to 80 years. The details of this study have been previously published.[18] Participants with and without COPD were included, and those with known lung disease other than COPD and asthma were excluded. The diagnosis of COPD was made using post bronchodilator spirometry using the ratio of forced expiratory volume in the first second (FEV_1) to the forced vital capacity (FVC) of < 0.70.[19] Participants with $FEV_1/FVC \geq 0.70$ but with $FEV_1 < 80\%$ predicted were deemed to have Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD unclassifiable disease or Preserved Ratio Impaired Spirometry (PRISm).[20] Those without airflow obstruction on spirometry were categorized as smoking controls. Demographic data were recorded at enrollment, and prevalent cardiovascular disease was recorded as patient-reported physician-diagnosed conditions. Cardiovascular disease was

recorded to be present if participants had one or more of coronary artery disease, ischemic cerebrovascular disease and peripheral arterial disease. Participants at 7 centers who had visual CAC measured on-site were included in the current analyses.

Participants were prospectively followed for approximately 5 years by contacting them every 3 to 6 months using an automated telephone system, by internet data collection or by research coordinators.[21] Acute coronary events were recorded for time intervals rounded off to the nearest month. Information was obtained on incident diagnosis of cardiovascular disease, including procedures such as percutaneous cardiac interventions and coronary artery bypass grafting and recorded as present or absent at their follow-up visit for phase two of the COPDGene study at approximately 5 years after enrollment. We used 3D Slicer software (www.airwayinspector.org) to measure percent emphysema on inspiratory images.[18] Using a density mask analyses, we quantified emphysema as the percentage of voxels with attenuation < -950 HU. Written informed consent was obtained from all participants prior to study enrollment and the COPDGene study was approved by the institutional review boards of all participating centers (F070712014).

Measurement of coronary artery calcification

Thin section, helical CT scans were performed in all participants and inspiratory scans were used for measurement of CAC using two methods. The scans were obtained with an imaging protocol with collimation, 0-5mm; tube voltage, 120kV; tube current 200mAs; gantry rotation time of 0.5s; and pitch, 1.1. The images were reconstructed with a standard kernel with a slice thickness of 0.75 mm and a reconstruction interval of 0.5 mm. First, we measured the Agatston score using standard software (Heartbeat-CS, Extended Brilliance Workspace, Philips

Medical System, Best, The Netherlands).[22] To quantify CAC, a threshold was set for calcific lesions involving 3 contiguous voxels that had a CT density of 130 Hounsfield Units (HU) with an area ≥ 1 mm^2. As described by Agatston, a density factor was determined for each area of CAC: 1 = 130 to 199, 2 = 200 to 299, 3 = 300 to 399 and 4 = ≥ 400 HU. The lesion score for each area of CAC was calculated by multiplying the area of calcification by the density factor. The total Agatston score was then determined by summing individual lesion scores from each of four anatomic sites (left main, left anterior descending, circumflex and right coronary arteries). We defined Agatston score ≥ 400 as clinically significant.[23]

At each of the seven centers, experienced radiologists also visually analyzed the coronary arteries to calculate the visual Weston score.[17] The CT images were assessed visually using mediastinal soft tissue window settings (WW 400 and WL 40). The Weston score assigns values based on visual estimates for presence and degree of calcification in each of the major coronary arteries as follows: 0 - no visually detected calcium, 1 - only a single high density pixel detected, 3 – calcium dense enough to cause a blooming artifact and 2 – for calcium intermediate and between 1 and 3. All readers were blinded to the results of the Agatston scores and participants' demographic and clinical data. Based on the original description correlating Weston scores with Agatston scores, we defined Weston score ≥ 7 as clinically significant.[17]

Statistical Analyses

All values are expressed as mean (standard deviation, SD). The correlation between Agatston and Weston CAC scores was analyzed using the non-parametric Spearman test. Intra- and inter-observer variability was tested using intra-class correlation coefficients. After categorizing participants into groups based on Agatston ≥ 400 and Weston ≥ 7, independent t-test and chi-

square test were used to compare differences between the groups, including differences in prevalent and incident cardiovascular disease between groups. Receiver operating characteristics (ROC) curves were used to assess accuracy of the two scores in predicting prevalent coronary artery disease and incident cardiovascular disease. The risk of acute coronary event on follow-up was assessed by time to first event using Cox Proportional hazards models, with adjustment for age, race, sex, smoking pack-years, FEV_1, percent emphysema, and CT scanner type. Associations between COPD parameters and CAC were tested with univariate and multivariable linear regression analyses. All tests of significance were two-tailed, with statistical significance deemed to be at an alpha level of 0.05. All analyses were performed using Statistical Package for the Social Sciences (SPSS 24.0, SPSS Inc., Chicago, IL, USA) and R statistical software (V 3.2).

Results

Demographics:

Visual CAC was measured in 1913 participants at seven centers. Of these, 10 were excluded due to unacceptable spirometry and 28 due to unavailable Agatston scores; the final sample size was 1875. The mean age of the cohort was 60.7 (8.1) years. 957 (51%) were males and 480 (25.6%) were of African American race. Participants had a significant cigarette smoking burden with mean pack-years of 43.4 (23.8); 869 (46.3%) were active smokers at the time of enrollment. 1017 (54.2%) had COPD, and participants spanned the spectrum of severity of airflow obstruction with 858 (45.8%), 184 (9.8%), 379 (20.2%), 179 (9.5%) and 42 (2.2%) having GOLD stages 0, 1, 2, 3 and 4 respectively. 233 (12.4) had GOLD unclassified or PRISm.

A large proportion of participants had significant cardiovascular comorbidities. The frequency of diabetes mellitus, hypertension and hyperlipidemia was 234 (12.5%), 820 (43.7%) and 798 (42.6%) respectively. 133 (7.1%) had coronary artery disease at enrollment. 40 (2.1%) had peripheral arterial disease and 46 (2.5%) had a history of ischemic stroke. The cumulative frequency of cardiovascular disease at baseline was 198 (10.6%). 103 (5.5%) had undergone percutaneous coronary interventions and 41 (2.2%) had undergone coronary artery bypass grafting.

Coronary artery calcification:

The intra- and inter-observer agreement for scoring visual CAC was excellent (intra-class correlation coefficient 0.98, 95%CI 0.95 to 0.99;p<0.001 and 0.97, 95%CI 0.94 to 0.99;p<0.001, respectively). The median Weston score was 3 (interquartile range 0 to 6). 507 (27.0%) had 0 CAC on visual analyses, and 413 (22%) had Weston score ≥7. The median Agatston score was 31 (interquartile range 0 to 191). 581(31%) had 0 Agatston CAC. 659 (35.1%) had CAC of at least 100, 306 (16.3%) had CAC ≥300 and 241 (12.9%) had CAC ≥400. **Table 1** shows a comparison of baseline demographics, comorbidities and cardiovascular disease in those with significant CAC by the two methods. The Agatston and Weston scores correlated significantly (Spearman r=0.84; p<0.001). On ROC analyses, the accuracy of CAC for prevalent coronary artery disease at baseline by Agatston and Weston were comparable: c-indices 0.74 (95%CI 0.70 to 0.79; p<0.001) and 0.78 (95%CI 0.74 to 0.82; p<0.001) respectively (**Figure 1A**). In those with COPD, the accuracy was comparable for the two scores: c-index 0.75 (95%CI 0.70 to 0.80; p<0.001) for Agatston and 0.76 (95%CI 0.70 to 0.81; p<0.001) for Weston score (**Figure 1B**). **Table 2** shows that cardiovascular comorbidity at baseline was significantly greater in those with COPD compared with smoking controls. The prevalence of cumulative cardiovascular disease

was 134 (13.2%) in those with COPD compared with 64 (7.5%) in those without COPD (p<0.001). Agatston ≥400 was present in more patients with COPD [147(14.5%)] than in controls [94(11.0%)]; p=0.024. There was a similar difference in the prevalence of Weston ≥7: 254(25%) vs. 159 (18.5%); p=0.001. Based on Agatston and Weston thresholds, there were 192 (10.2%) and 333 (17.8%) participants with undiagnosed CAD, respectively. Compared with controls, there were more participants with COPD who had undiagnosed CAD based on both Agatston and Weston thresholds [80 (9.3%) v. 112 (11.0%); p=0.007 and 199 (19.6%) vs. 134 (15.6%); p = 0.001, respectively].

Follow up:

Participants were prospectively followed for a median duration of 5.8 years (interquartile range 4.9 to 6.3 years). At the 5-year return visit, an additional 127 (6.8%) participants had a new diagnosis of cardiovascular disease. A greater number of COPD patients developed incident cardiovascular disease [80(8.1%)] compared to controls [47(5.7%)]; p = 0.041. For predicting incident cardiovascular disease, both measures performed modestly with c-indices of 0.61 for Agatston (95%CI 0.56 to 0.66; p<0.001) and 0.62 for Weston (95%CI 0.57 to 0.68; p<0.001). Compared to participants with known CAD who developed additional CVD events, both Weston≥7 and Agatston≥400 identified patients with undiagnosed CAD who developed incident CVD [71 (5.2%) vs. 33 (10.2%); p=0.001 for Weston, and 79(5.3%) vs. 25(13.2%); p<0.001].

We also compared the utility of the two scores in estimating time to first acute coronary event on follow-up. Compared to Agatston <400, a score ≥400 was associated with a shorter time to first event (unadjusted hazards ratio HR 2.18, 95%CI 1.30 to 3.65;p=0.003), but not after adjustment for age, race, sex, smoking pack-years, FEV_1, percent emphysema and CT scanner

type, HR = 1.75, 95%CI 0.99 to 3.09; p = 0.053). In contrast, compared to Weston score <7, a score $\geq$7 was associated with a shorter time to first coronary event (unadjusted HR = 2.40, 95%CI 1.53 to 3.76; p <0.001, and adjusted HR = 2.16, 95%CI 1.32 to 3.53; p = 0.002) (**Figure 2**).

Association with COPD parameters:

After multivariable adjustment for age, race, sex, smoking pack years and CT scanner type, FEV_1 was inversely associated with Weston CAC (adjusted beta co-efficient = -0.264, 95%CI -0.481 to -0.046; p=0.017), but not with Agatston CAC (adjusted beta co-efficient = -3.86, 95%CI -24.37 to 16.66; p=0.712). CT emphysema was not associated with either Agatston CAC (adjusted beta co-efficient = -1.15, 95%CI -3.03 to 0.73; p=0.230) or with Weston CAC (adjusted beta co-efficient = -0.003, 95%CI -0.023 to 0.017; p=0.739) after adjustment for age, race, sex, smoking pack-years and CT scanner type.

Visual CAC at 5-year follow up:

To test repeatability, we also assessed accuracy of Weston scores at the 5-year follow-up visit. Weston score was scored in 1869 (99.7%) participants and increased from a median of 3 (IQR 0 to 6) at baseline to 4 (IQR 1 to 7) at follow-up. The accuracy of Weston $\geq$7 for prevalent CAD at follow-up was 0.73 (95%CI 0.69 to 0.77; p<0.001), and for prevalent CVD was 0.69 (95%CI 0.65 to 0.72; p<0.001).

Discussion

In a cohort of current and former smokers, with and without COPD, we demonstrated that CAC predicts incident cardiac events, and also that a simple visual method of estimating CAC performs well in predicting prevalent coronary artery disease and incident cardiovascular disease. The visual score was equally accurate as the Agatston score for prevalent CAD and performed better than the Agatston score in predicting incident cardiac events. With COPD increasingly recognized as a cardiovascular risk factor, the early recognition of CAC is especially important for both the diagnosis of cardiovascular disease and for prognostication. Agatston CAC scores rely on relatively complex methodologies and the Weston CAC score can provide equivalent prognostic information.

The utility of CAC in diagnosing cardiovascular disease and predicting incident disease has been extensively debated. Although early studies showed that CAC provides additional information over risk scores such as the Framingham Risk Score, recent studies have struggled to identify a distinct threshold for CAC as measured traditionally using the Agatston scores. Whether any score above 0 implies presence of occult coronary artery disease is not clear. In addition, Agatston CAC scores have not been validated in COPD. One small case control study of 162 subjects found that COPD patients experienced greater coronary events despite no difference in CAC, suggesting that the excess risk could not be explained by CAC.[15] The Multi-Ethnic Study of Atherosclerosis (MESA) Lung study that excluded patients with known cardiac disease found that airflow obstruction was associated with subclinical atherosclerosis in the carotid and peripheral circulation, but not when assessed by Agatston CAC.[13] Rasmussen et al found a relationship between COPD and CAC but no dose-response relationship between COPD severity and CAC.[24] In contrast, we found that Agatston CAC is associated with lower FEV_1.

Our findings are in line with two studies from Korea that found an inverse relationship between FEV$_1$ and Agatston CAC,[14,25] and supports the findings of multiple epidemiologic studies showing an association between lower FEV$_1$ and coronary artery disease.[3] We included patients across the spectrum of COPD severity and included patients with a high burden of cardiac disease. Results from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study suggest that the presence of CAC in COPD is associated with greater dyspnea, reduced exercise tolerance as well as increased all-cause mortality; however this study did not examine cardiovascular events.[26] We extend the literature by demonstrating that Agatston CAC in COPD is associated with incident cardiovascular events.

Similarly, using CAC measured on an ordinal visual scale, O'Hare et al found that visual CAC >4 in patients with COPD is associated with emphysema severity, myocardial infarction and all-cause mortality.[27] We also found that visually scored CAC was associated with airflow obstruction as well as with incident cardiovascular events. The visual score performed better than the Agatston score in predicting incident cardiovascular disease over 5 years, and we contend that the visual score is simpler and easier to adapt in daily clinical practice. The reasons for this difference in cardiac risk prediction are unclear. The Agatston score is a combination of plaque volume as well as density and it is weighted more towards density.[28] Calcification volume is likely a stronger predictor of cardiovascular disease,[28] and hence the visual method might improve prediction by relying more on the size of the lesions detected than on the density. In addition, participants with early disease may have small or trace levels of calcification that may be less than 3 contiguous voxels, or slightly less than the 130 HU threshold, and these lesions may end up being classified as undetectable. The original Agatston protocol usually has 3 mm collimation since the validation came from early CT studies that used the Imatron electron beam

scanner that had a minimum collimation of 3 mm. The current study protocol used submillimeter z-axis collimation and slice thickness. With the high rate of use of clinical CT scans of the lung for other indications, and an expected increase in the number of these scans for lung cancer screening in patients who share the same risk factors for COPD, the visual score can be easily adapted into clinical practice.[29,30]

Our study has a number of limitations. The CAC scores were estimated by experienced radiologists and hence these findings may not be generalizable. However, the visual scoring system is very simple, and has excellent intra- and inter-observer agreement, and with increasing recognition of the clinical importance of coronary calcification many radiologists already report the presence of calcification. Although other visual scoring methods exist,[29,30] we chose the Weston score as representative of easy to use scoring methods. The CT scans were not electrocardiographically gated. However, recent studies have shown a strong correlation between gated and non-gated scans, and CAC measured on non-gated scans has been shown to be independently associated with clinical outcomes.[11,31,32] It is possible some events were not captured on follow-up, but this bias would likely impact both scores equally as the scores were estimated in the same participants. The study also has a number of strengths. Our analyses included participants from the COPDGene study, a well characterized cohort with participants with all stages of COPD severity, included a high percentage of African Americans, had rigorous CT and spirometry quality control, and included participants with a high burden of cardiovascular disease.

With increasing recognition of cardiovascular disease as a major comorbidity in COPD, the use of a simple visual scale to identify and prognosticate patients adds to the clinical

evaluation of these patients. There is considerable merit in using readily available clinical CT

scans to screen for cardiovascular disease in this high risk COPD population.

Author Contributions:

Study design: SPB, HN. Acquisition of data: All authors. Measurement of CAC: EAK, JDN, MJB, CAD, FLJ, AY, CF, JHT and HN. Statistical analyses: SPB. Data interpretation: All authors. Manuscript writing: SPB, MTD, HN. Critical review of the manuscript for important intellectual content: All authors. SPB is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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Figure Legend:

Figure 1: shows that the accuracy of CAC for prevalent coronary artery disease at baseline by Agatston and Weston scores were comparable using receiver operating characteristics analyses: c-indices 0.74 (95%CI 0.70 to 0.79; p<0.001) and 0.78 (95%CI 0.74 to 0.82; p<0.001) respectively (Figure 1A). In those with COPD, the accuracy was comparable for the two scores: c-index 0.75 (955CI 0.70 to 0.80; p<0.001) for Agatston and 0.76 (95%CI 0.70 to 0.81; p<0.001) for Weston score (Figure 1B).

Figure 2: shows Kaplan-Meier curves comparing the Weston visual score with the Agaston score for acute coronary event free follow-up. After adjustment for age, race, sex, smoking pack-years, FEV_1, percent emphysema and CT scanner type, Weston score ≥ 7 compared with <7 was associated with a shorter time to first coronary event (adjusted HR = 2.16, 95%CI 1.32 to 3.53; p = 0.002). In contrast, in comparison with Agatston <400, a score ≥ 400 was not associated with a shorter time to first event (adjusted HR = 1.75, 95%CI 0.99 to 3.09; p = 0.053).

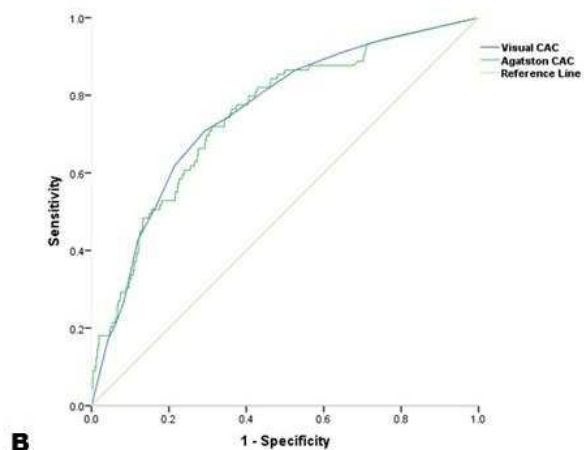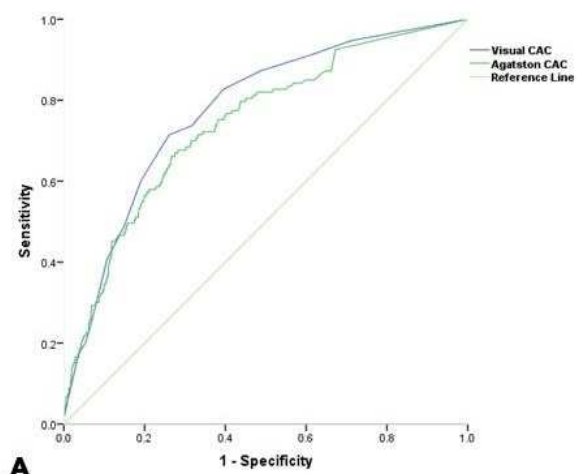**Table 1: Comparison of baseline demographics and cardiovascular disease by CAC scores**

	Agatston CAC			Visual CAC		
	<400 (n=1634)	**≥400 (n=241)**	**p value**	**<7 (n= 1462)**	**≥7 (n=413)**	**p value**
Age (years)	60.0 (8.0)	65.6 (7.2)	<0.001	59.6 (8.0)	64.8 (7.3)	<0.001
Sex (%male)	783 (47.9)	174 (72.2)	<0.001	687 (47.0)	270 (65.4)	<0.001
Race (%Non-Hispanic White)	1191 (72.9)	204 (84.6)	<0.001	1044 (71.4)	351 (85.0)	<0.001
Body-mass-index (kg/m2)	29.1 (6.0)	29.8 (5.6)	0.106	29.2 (6.2)	29.2 (5.3)	0.971
Smoking packyears	42.2 (23.3)	51.6 (25.6)	<0.001	42.0 (22.9)	26.5 (22.6)	<0.001
Current smoker (%)	786 (48.1)	83 (34.4)	<0.001	715 (48.9)	154 (37.3)	<0.001
Diabetes mellitus (%)	186 (11.4)	48 (19.9)	<0.001	163 (11.1)	71 (17.2)	0.001
Hypertension (%)	675 (41.3)	145 (60.2)	<0.001	584 (39.9)	236 (57.1)	<0.001
Hyperlipidemia (%)	658 (40.3)	140 (58.1)	<0.001	568 (38.9)	230 (55.7)	<0.001
Coronary artery disease (%)	84 (5.1)	49 (20.3)	<0.001	53 (3.6)	80 (19.4)	<0.001
Ischemic cerebrovascular disease (%)	34 (2.1)	12 (5.0)	0.007	29 (2.0)	17 (4.1)	0.013
Peripheral arterial disease (%)	27 (1.7)	13 (5.4)	<0.001	22 (1.5)	18 (4.4)	<0.001
Percutaneous coronary intervention (%)	68 (4.2)	35 (14.5)	<0.001	36 (2.5)	67 (16.2)	<0.001
Coronary artery bypass grafting (%)	24 (1.5)	17 (7.1)	<0.001	10 (0.7)	31 (7.5)	<0.001
GOLD stage			0.211			<0.001
0	764 (46.8)	94 (39.0)		699 (47.8)	159 (38.5)	
1	159 (9.7)	25 (10.4)		138 (9.4)	46 (11.1)	
2	317 (19.4)	62 (25.7)		266 (18.2)	113 (27.4)	
3	155 (9.5)	24 (10.0)		132 (9.0)	47 (11.4)	
4	36 (2.2)	6 (2.5)		32 (2.2)	10 (2.4)	
PRISm	203 (12.4)	30 (12.4)		195 (13.3)	38 (9.2)	
FEV_1 (L)	2.33 (0.83)	2.34 (0.82)	0.854	2.35 (0.82)	2.28 (0.84)	0.164
FEV_1 %pred	80.1 (22.4)	77.5 (21.2)	0.090	80.5 (22.1)	77.0 (22.6)	0.005
FVC (L)	3.37 (0.96)	3.51 (0.96)	0.028	3.37 (0.96)	3.47 (0.98)	0.042
FVC %pred	89.1 (16.5)	87.8 (16.3)	0.244	89.0 (16.3)	88.7 (16.9)	0.741
FEV_1/FVC	0.69 (0.14)	0.66 (0.14)	0.009	0.69 (0.14)	0.65 (0.14)	<0.001
%Emphysema	5.4 (7.7)	6.4 (8.1)	0.069	5.1 (7.6)	6.8 (8.2)	<0.001

CAC = Coronary artery calcification. GOLD = Global Initiative for Chronic Obstructive Lung Disease. PRISm = Preserved Ratio Impaired Spirometry. FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity.

Table 2: Comparison of baseline demographics in participants with and without COPD

	COPD (n=1017)	Smoking Controls (n=858)	p value
Age (years)	61.8 (8.0)	59.5 (8.2)	<0.001
Sex (%male)	528 (51.9)	429 (50.0)	0.408
Race (%Non-Hispanic White)	762 (74.9)	633 (73.8)	0.570
Body-mass-index (kg/m2)	29.1 (6.4)	29.2 (5.5)	0.772
Smoking packyears	48.0 (25.3)	37.9 (20.7)	<0.001
Current smoker (%)	476 (46.8)	393 (45.8)	0.665
Diabetes mellitus (%)	126 (12.4)	108 (12.6)	0.897
Hypertension (%)	475 (46.7)	345 (40.2)	0.005
Hyperlipidemia (%)	430 (42.3)	368 (42.9)	0.790
Coronary artery disease (%)	89 (8.8)	44 (5.1)	0.002
Ischemic cerebrovascular disease (%)	34 (3.3)	12 (1.4)	0.007
Peripheral arterial disease (%)	29 (2.9)	11 (1.3)	0.019
Percutaneous coronary intervention (%)	67 (6.6)	36 (4.2)	0.024
Coronary artery bypass grafting (%)	26 (2.6)	15 (1.7)	0.233
Agatston CAC			
≥100	396 (38.9)	263 (30.7)	<0.001
≥300	197 (19.4)	109 (12.7)	<0.001
≥400	147 (14.5)	94 (11.0)	0.024
Weston CAC ≥7	254 (25.0)	159 (18.5)	<0.001

CAC = Coronary artery calcification.