ORIGINAL ARTICLE

Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality

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ABSTRACT

Background Coronary artery calcification is pathognomonic of coronary artery disease (CAD). Whether CAD in patients with COPD is linked to lung function, functional capacity and/or clinically relevant outcomes is unknown. The objective was to assess the association between CAD and disease severity, functional capacity and outcomes in patients with COPD.

Methods Coronary artery calcium score (CACS; Agatston score) was measured using chest CT in patients with COPD, smokers with normal spirometry and non-smokers from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.

Results CACS was measured in 942 subjects: 672 with COPD (mean age±SD, 63±7 years; FEV_1 49±16% predicted), 199 smokers with normal spirometry (54 ±9 years; FEV_1 110±12% predicted) and 71 non-smokers (55±9 years; FEV_1 114±14% predicted). CACS was higher in patients with COPD than smokers or non-smokers (median (IQR), 128 (492) vs 0 (75) vs 0 (3) Agatston units (AU), p<0.001). In patients with COPD, CACS correlated with age, pack-years, 6 min walking distance, modified Medical Research Council Dyspnoea score and circulating levels of interleukin (IL)-6, IL-8, Clara Cell protein 16, surfactant protein D and peripheral blood neutrophil count, but not with emphysema, exacerbation frequency, % predicted FEV_1 or decline in FEV_1. CACS was higher in patients with COPD who died than in those who survived until 3-year follow-up (CACS 406 vs 103 AU, p<0.001), and was associated with mortality in a Cox proportional hazards model (p=0.036).

Conclusions Patients with COPD have more CAD than controls and this is associated with increased dyspnoea, reduced exercise capacity and increased mortality. These data indicate that the presence of CAD in patients with COPD is associated with poor clinical outcomes.

Key messages

What is the key question?
- ▶ What is the relationship between coronary artery calcification and clinical outcomes in patients with COPD?

What is the bottom line?
- ▶ The extent of coronary artery calcification was substantially greater in patients with COPD than in smokers with normal spirometry or non-smokers, and was correlated with dyspnoea, exercise capacity and all-cause mortality, but not with FEV or exacerbations of COPD, indicating a link between coronary artery calcification and poor clinical outcome in COPD.

Why read on?
- ▶ The identification of patients with a high coronary artery calcium score is important to provide appropriate targeted therapy to modify cardiovascular risk by treating cardiovascular disease appropriately.

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INTRODUCTION

The relationship between COPD and coronary artery disease (CAD) is complex and remains poorly understood. Both diseases have a high worldwide prevalence and frequently coexist.[1] COPD is an independent risk factor for CAD and the presence of COPD is associated with an increased risk of CAD and cardiovascular mortality.[1 2] In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (SCO104960; NCT00292552), patients with COPD had an increased prevalence of self-reported CAD compared with smoker and non-smoker control subjects.[3] However, this increased prevalence is not solely attributable to shared risk factors, with COPD remaining an independent predictor for the development of CAD after adjustment for smoking and other cardiovascular risk factors.[4]

Coronary artery calcification can be identified by CT and is pathognomonic of coronary atherosclerosis. Coronary artery 'calcium scoring' methods, such as the Agatston score, quantify this calcification based on its extent and density on CT images.

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Coronary artery calcium score (CACS) is widely used to identify and stratify risk for CAD.[5] CACS correlates with increased mortality in smokers[6] and may provide additive prognostic information to that obtained from traditional methods of cardiovascular risk stratification such as the Framingham risk score.[7]

The pathogenic mechanisms linking COPD and CAD remain unknown, but are likely to involve a multifactorial process of systemic inflammation, oxidative stress, increased thrombogenicity, vascular dysfunction and hypoxia.[4 8–10] Although low-grade systemic inflammation occurs in a variety of conditions, including COPD and CAD,[11–13] the weak associations identified between inflammatory markers and CACS[14] or atherosclerotic plaque burden[15] suggest that the mechanisms of association may be distinct.

In patients with COPD, the relationship between CACS and clinically relevant long-term outcomes such as mortality, exacerbation rate or FEV_1 decline have not previously been evaluated. The aims of this study were to assess these associations in the ECLIPSE study cohort.

METHODS

Study population and ethics

We assessed coronary artery calcium on non-gated chest CT images in a subset of subjects recruited to the ECLIPSE study.[16] ECLIPSE is an international multicentre observational longitudinal cohort study of subjects with COPD, smokers with normal spirometry and non-smokers. Ethics committees of all participating institutions approved the study and written informed consent was obtained from all subjects.

Participants were aged 40–75 years and presence of significant lung disease was determined by history, physical examination and screening investigations. Patients with COPD were current or ex-smokers (≥10 pack years), with baseline post-bronchodilator FEV_1<80% of the reference value and FEV_1/FVC<0.7. Smokers with normal spirometry were free of significant lung disease, were current or ex-smokers (≥10 pack years), and had baseline post-bronchodilator FEV_1>85% and FEV_1/FVC>0.7. Non-smokers were free from significant lung disease, had smoking history of <1 pack year, and had baseline post-bronchodilator FEV_1>85% and FEV_1/FVC>0.7. Key exclusion criteria were the presence of respiratory disorders other than COPD and a reported COPD exacerbation within 4 weeks of enrolment. Comorbidities were not excluded, but these had to be clinically stable at the time of assessment.

Clinical, physiological and biochemical measurements

Participants underwent detailed phenotypic characterisation and follow-up over 3 years, including lung physiology, imaging, biomarkers, health outcomes and mortality, as reported previously[3] (see online supplement).

Computed tomography

All subjects underwent a low-dose CT of the chest using multidetector scanners with a minimum of four rows (GE Healthcare or Siemens Healthcare). Imaging was performed in the supine position, at suspended full inspiration, without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mAs and images were reconstructed using 1.0 mm (Siemens) or 1.25 mm (GE) contiguous slices and a low spatial frequency reconstruction algorithm (GE: Standard; Siemens: b35f). Quantitative assessment of the percentage of low attenuation areas (%LAA), representing the presence of emphysema, was performed using a threshold of −950 Hounsfield units.

Coronary artery calcium score

CACS was assessed on the standard images used for analysis of the lungs and no additional reconstructions were performed. CT scans were assessed by a trained observer (MCW), who was blinded to subject characteristics. One hundred randomly selected scans were reassessed (by MCW and JM) to assess intra-observer and inter-observer variability. Images were analysed on a dedicated workstation using dedicated analysis software (VScore, Vitrea Fx, V.3.1.0, Vital Images, Minnetonka, Minnesota, USA).

Image quality was assessed on a five-point Likert scale (1, excellent; 2, mild artefact; 3, moderate artefact; 4, severe artefact; 5, non-diagnostic) for each of the three main coronary arteries. Image quality scores from individual vessels were summed to calculate the total image quality score. Images with a total image quality score of 15 were excluded from further analysis.

CACS was assessed using the Agatston scoring method.[17] Coronary calcification was defined as an area in the course of a coronary artery that had an attenuation threshold of ≥130 Hounsfield units and was ≥1 mm^2. On each axial slice the area of calcification that met these requirements was measured and then multiplied by a weighting factor dependent on the peak attenuation within the region. These weighted areas were summed to produce the total Agatston CACS. For the interpretation of Agatston score in asymptomatic patients the absolute value can be used or it can be considered as low (<100 Agatston units (AU)), intermediate (101–400 AU), high (401–1000 AU) or very high (>1000 AU).

Normal ranges for Agatston scores in healthy asymptomatic individuals stratified by age, gender and ethnicity have been published.[18] These can be used to calculate the CACS percentile (CACSP) for individual patients. A CACSP above 90% can be used as an indication to commence primary preventative therapy.

Statistical analysis

Results are shown as mean (SD), median (IQR), frequency distribution or proportions. Comparisons between subject groups were carried out using analysis of variance, Kruskal–Wallis tests, van Elteren tests or Cochran–Mantel–Haenszel tests, adjusting for age, gender and smoking pack-years. Pack-year-adjusted CACSP medians and IQRs were calculated from quantile regression models based on 1000 bootstrap samples. Linear associations were assessed by Spearman correlation coefficients due to non-normality of the CACS and CACSP; 95% CIs were calculated by the Fisher z-transformation method. To adjust for effects of covariates on CACS, multiple regression was conducted on the log-transformed values; estimates were back-transformed for presentation. The CACSP did not respond to log transformation, so the analysis was two-stage; a logistic regression model to describe the effect of covariates on a zero versus non-zero percentile and multiple regression on the log-transformed non-zero values. Cox proportional hazard models were constructed to compare mortality between subject groups. For all models, covariates that were expected to impact the dependent variables or showed differences among the cohorts were included, including age, sex and pack-years. Two-sided $p<0.05$ values were considered significant with no adjustment for multiple testing. Analyses were conducted with SAS V.9.1 (SAS Institute, Cary, North Carolina, USA). Intra-observer and inter-observer agreement were assessed via concordance correlation coefficients.[19]

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Table 1 Demographic and baseline details of the study population

Characteristic	Study cohort		
	COPD subjects	Smokers	Non-smokers
N	672	199	71
Age years	63.2 (7.0)	54.1 (8.5)*	54.7 (9.2)*
Men	422 (63%)	115 (58%)	21 (30%)*
Pack-years	47.4 (25.1)	30.7 (19.9)*	0.1 (1.0)*
Body mass index, kg/m^2	26.5 (5.6)	26.7 (4.3)	28.3 (6.9)*
Post-bronchodilator FEV_1, litres	1.36 (0.54)	3.46 (0.71)*	3.19 (0.79)*
Post-bronchodilator FEV_1% predicted	48.7 (16.1)	110.0 (11.5)*	114.4 (13.8)*
Post-bronchodilator FEV_1/FVC ratio	44.1 (11.5)	79.2 (4.8)*	81.0 (5.9)*
Patient-reported cardiovascular disease	357 (53%)	45 (23%)*	24 (34%)*
%LAA	15.6 [19.2]	0.8 [1.9]*	2.8 [4.4]*

Mean (SD), median [IQR] or n (%).
Cohorts were compared via analysis of variance, Kruskal–Wallis tests or Cochran–Mantel–Haenszel tests, as appropriate.
*p Value <0.05 versus patients with COPD.
%LAA, per cent low attenuation areas <−950 Hounsfield units.

RESULTS

Demographic details

Of the 2746 subjects enrolled in ECLIPSE, 2574 patients had scans available for analysis. From a random sample of 1001 scans, CACS was measured in 942 scans after the exclusion of duplicate scans and five scans (0.5%) with poor image quality (image quality score of 15). The demographic details of the study population are show in table 1 and differences between the ECLIPSE cohort and CACS cohort are shown in online supplement table Si. Consistent with the total ECLIPSE cohort, subjects with COPD were older, had a higher pack-year history, a lower post-bronchodilator % predicted FEV_1 and a higher % LAA. Patients with COPD also had a higher frequency of diabetes mellitus, hypertension, statin therapy and patient-reported cardiovascular disease than smoker or non-smoker controls (table 2).

Coronary artery calcium score

Intra-observer and inter-observer agreement for CACS were excellent (concordance correlation coefficients 0.992 and 0.956, respectively, p<0.001 for both).

The median CACS was higher in subjects with COPD than control smokers and non-smokers (128 (492) vs 0 (75) vs 0 (3) AU, p<0.001, online supplement table Sii). The CACS was also higher in men than women and in those who reported cardiovascular disease, diabetes mellitus, hypertension or treatment with statin therapy (see online supplement tables Siii–Sv). The absence of coronary artery calcification was more frequent in non-smokers (72%) than for smokers (53%) or patients with COPD (23%). High (>400 AU) or very high (>1000 AU) CACS were more frequent in patients with COPD (see online supplement table Svi).

The CACSP was greater in patients with COPD than in smokers or non-smokers (71% (60%) vs 0 (78%) vs 0 (43%), respectively, p<0.001). When further corrected for pack-years, the CACSP remained greater in patients with COPD than in smokers and non-smokers.

Spearman correlation analysis showed that CACS in patients with COPD was associated with age and pack-years (see online supplement table Svii). CACS also correlated with markers of functional capacity and symptoms, including the 6 min walking distance, modified Medical Research Council Dyspnoea score and BODE index.[20] CACS in patients with COPD was weakly correlated with the extent of emphysema and with borderline statistical significance and with FEV_1 /FVC ratio. However, there were no significant correlations with FEV_1, FEV_1% predicted, decline in FEV_1 or reported exacerbation frequency. When stratified into the four patient types proposed by the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document (A, B, C and D),[21] there were no differences in CACS (p=0.681) or CACSP (p=0.398).

CACS in subjects with COPD correlated with several circulating inflammatory biomarkers (see online supplement table Svii), including interleukin (IL)-6, IL-8, Clara cell secretory protein 16, surfactant protein D and peripheral blood neutrophil count. It did not correlate with high-sensitivity C-reactive protein (CRP), fibrinogen, tumour necrosis factor α, chemokine ligand 18, sRAGE or total white blood cell count. There was a higher CACS and CACSP in patients with persistent systemic inflammation (defined as two or more elevated biomarkers on two occasions)[12] compared with patients who had no elevated biomarkers (see online supplement table Sviii). This difference was statistically significant for CACS but not CACSP.

Multivariate analysis of CACS and percentiles

Multiple regression analysis showed that CACS score was associated with age, gender, pack-years, % predicted FEV_1 and patient-reported cardiovascular disease. CACSP was associated

Table 2 Cardiovascular risk factors

Location	Patients with COPD	Smokers	Non-smokers	p Value			
				Overall	Patients with COPD vs smokers	Patients with COPD vs non-smokers	Smokers vs non-smokers
Diabetes	66 (10%)	14 (7%)	3 (4%)	0.158	0.213	0.115	0.402
Hypertension	260 (41%)	31 (17%)	17 (25%)	<0.001	<0.001	0.015	0.115
Statin therapy	173 (26%)	27 (14%)	8 (11%)	<0.001	<0.001	0.007	0.621
Patient-reported cardiovascular disease*	357 (53%)	45 (23%)	24 (34%)	<0.001	<0.001	0.002	0.064

Number (%).
Cohorts were compared via Cochran–Mantel–Haenszel tests.
*'Heart trouble', angina or 'heart attack'.

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Table 3 Multivariate analysis for calcium score and coronary artery calcium score percentile (CACSP) based on age, gender and ethnicity

	Agatston score			CACSP based on age, gender and ethnicity		
Parameter	**Effect estimate* (SE)**	**p Value**	**Model R^2**	**Effect Estimate* (SE)**	**p Value**	**Model R^2**
Age (per 10 years)	4.67 (1.18)	<0.001	0.242	0.88 (1.02)	<0.001	0.153
Women	0.51 (1.27)	0.005		1.20 (1.03)	<0.001	
Pack-years (per 20 years)	1.22 (1.09)	0.026		0.99 (1.01)	0.320	
FEV_1% predicted (post bronchodilator) (per 10%)	0.85 (1.08)	0.029		1.01 (1.01)	0.590	
CVD	2.37 (1.25)	<0.001		1.06 (1.03)	0.046	
6MWD (per 100 m)	1.00 (1.10)	0.990		0.97 (1.01)	0.017	
IL-6 (per 1 SD)	0.99 (1.11)	0.953		1.02 (1.02)	0.221	
Clara cell protein (per 1 SD)	1.01 (1.12)	0.951		1.02 (1.02)	0.132	
Surfactant protein D (per 1 SD)	1.15 (1.12)	0.199		1.02 (1.02)	0.177	

*The effect estimate represents the change in score per 1 unit change in the parameter after adjusting for all other terms in the model. Note: the dependent variables (Agatston score and CACSP) were log transformed in this multiple regression model and the exponentiated values of the coefficients and SEs are provided here. For example, a coefficient of 2.37 for CVD corresponds to a 137% higher Agatston score for those with CVD compared with those without, when all other predictors are held fixed.
6MWD, 6 min walking distance; CVD, cardiovascular disease; IL-6, interleukin 6.

with age, gender, patient-reported cardiovascular disease and the 6 min walking distance (table 3).

CACS and mortality

Patients with COPD who died (n=63) during 3 years of follow-up had a higher CACS, CACSP and CACSP adjusted for pack-years than subjects who survived (see online supplement table Six). As a single predictor of mortality, CACS had a HR of 1.55 (95% CI 1.26 to 1.92) and CACSP greater than 90% had a HR of 1.66 (95% CI 0.98 to 2.81). After adjustment for age, gender and pack-years, CACS had a HR of 1.42 (CI 1.12 to 1.78) and CACSP had a HR of 1.77 (95% CI 1.04 to 3.01). In Cox proportional hazards models the CACS adjusted for age, gender and pack-years was associated with increased mortality in all subjects (p=0.005) and in patients with COPD (p=0.007). The same was found for a CACSP greater than 90% (p=0.051 for all subjects, and p=0.072 for patients with COPD) (figure 1 and online supplement figure Si). The addition of hypertension or statin therapy had little effect on the HRs and neither was significant in the models. CACS and patient-reported cardiovascular disease were predictive of mortality, but the two assessments together did not improve the prediction of mortality.

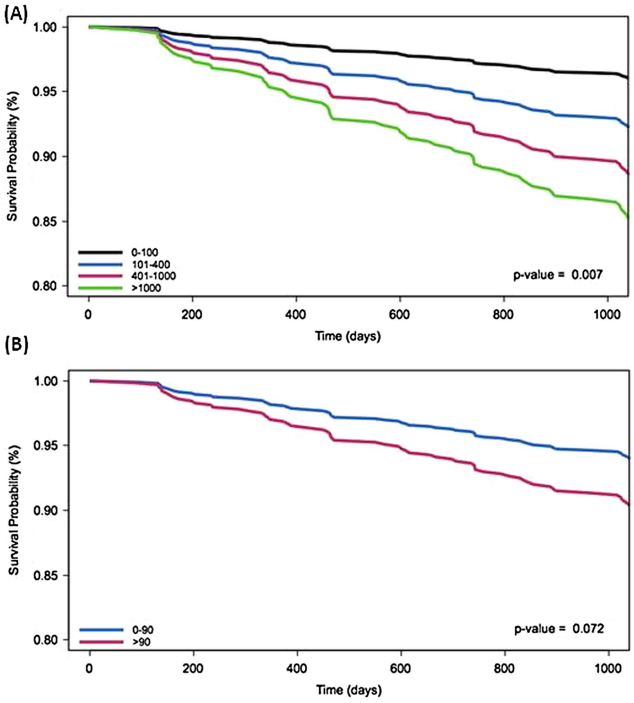

Figure 1 Cox proportional hazards model for patients with COPD and (A) coronary artery calcium score (CACS) (Agatston score)adjusted for age, gender, pack-years, severity of COPD and self-reported cardiovascular disease and (B) CACSP adjusted for pack-years.

DISCUSSION

In a large cohort of well characterised subjects, we have shown that patients with COPD had a higher CACS corrected for age, gender, ethnicity and pack-year smoking history than smokers with normal spirometry or non-smokers. Moreover, a higher CACS is associated with adverse functional capacity and increased mortality in these patients. We conclude that patients with COPD have a disproportionately greater burden of CAD that causes increased morbidity and mortality.

Low-level chronic inflammation is believed to play an important role in COPD and cardiovascular disease.[12] Coronary artery calcium and atherosclerotic plaque burden are associated with increased systemic inflammatory markers such as CRP, IL-6 and fibrinogen in population studies.[14 15] However, in our study these associations were weak, suggesting that inflammatory markers and coronary artery calcium may reflect different disease mechanisms. Recently a pattern of systemic inflammation with raised levels of CRP, IL-6, white blood cell count and fibrinogen has been associated with COPD.[12] Persistent inflammation (defined as elevation in two systemic biomarkers) occurred in a proportion of patients who had significantly worse outcomes.[12] In our study the systemic inflammatory phenotype was associated with a small increase in CACS. We therefore believe that it is unlikely that inflammation alone can account for the association between COPD and CAD.

In the multiple regression analysis CACS was associated with the degree of airflow limitation. However, whether lung disease per se has a direct influence on the initiation or progression of CAD remains unclear. Due to overlap in the diagnostic symptoms, it can be difficult to establish whether CAD is present in patients with COPD. Indeed, acute coronary syndromes and stable angina are under-diagnosed in patients with COPD.[22–24]

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The association between CACS and dyspnoea, quality of life and exercise capacity suggests that some symptoms and functional impairment may be attributable to occult CAD rather than COPD. Thus, the identification of coronary artery calcification by CT may aid in the diagnosis and treatment of occult CAD in patients with COPD.

Cardiovascular disease is an important cause of morbidity and mortality in patients with COPD, accounting for up to 50% of deaths.[25] Furthermore, patients with more severe COPD have higher cardiovascular morbidity and mortality.[1] This association may indicate a shared pathogenesis, a synergistic impact on disease progression or an under diagnosis or under treatment of concomitant CAD in patients with COPD. In addition, there may be common responses to smoking-induced tissue injury, such as inflammation, oxidative stress or tissue remodelling.[26] The association between CACS and cardiovascular events or mortality has been established in asymptomatic individuals,[27–29] subjects at intermediate[30] or high[6] likelihood of cardiovascular disease, and patients with hypertension[31] or diabetes mellitus.[32] An association between CACS and mortality has also been identified in lung cancer screening studies.[33] Our results extend these findings to show, for the first time, that CACS is also associated with increased morbidity and mortality in patients with COPD. Clinical intervention trials are now warranted to ascertain whether screening and treatment for occult CAD may improve the clinical outcome of patients with COPD.

Study limitations

Coronary artery calcification is a surrogate marker of coronary atherosclerosis and a higher CACS is associated with increased risk of significant coronary artery stenosis.[34] However, in the absence of coronary artery calcification, haemodynamically significant non-calcified plaques may be present in between 0.8% and 0.9% of asymptomatic individuals.[35] Thus a zero calcium score in our study is likely to be associated with an underestimation of the prevalence of CAD.

The standard reconstruction parameters for calcium scoring utilises 3 mm non-overlapping slices.[36] However, coronary artery calcium can be identified using non-gated chest CT images.[33 37] Good correlations have been identified between standard reconstructions and CACS calculated using chest CT[38] or non-gated images.[37] However, the absolute Agatston numbers may not be the same as those calculated using standard reconstructions. Nevertheless, this technique can be used to investigate associations between subgroups within this study.

Cigarette smoking is a major and common risk factor for COPD and CAD. Any association between COPD and CAD could therefore be explained by this shared risk factor. In our study patients with COPD had higher pack-years than smoking controls. We adjusted for linear effects of pack-years in the regression models, but there could be non-linear effects that could contribute to the observed differences.

A further limitation is that cardiovascular events were not recorded and cardiovascular risk scores such as the Framingham risk score could not be calculated. Confounding factors such as hypertension and hyperlipidaemia could also affect the study results, as could other unmeasured cardiovascular risk factors. The ECLIPSE study excluded patients with respiratory disorders other than COPD and thus these results are not necessarily generalisable to other respiratory disorders. Participants with acute exacerbations within 4 weeks of enrolment were also excluded. However, coronary artery calcium develops over a prolonged period of time, thus this is unlikely to affect the results.

CONCLUSION

This is the first large cohort study to identify the presence of a higher CACS in patients with COPD and to show an association of this with poor clinical outcomes in these patients, including all-cause mortality.

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Collaborators See online supplementary appendix for the principal investigators and centres participating in ECLIPSE.

Contributors The study was conceived and conducted by WM, AA, PB, PMAC, BC, HOC, CC, DAL, BEM, SR, EKS, RT-S, JV, EW and JCY with additional patient recruitment from the Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study investigators. Images were assessed by MCW, JTM and EvB. Data were analysed by MCW, LDE and WM. The manuscript was prepared by MCW, WM, JTM, DEN and LDE. Critical revision of the manuscript was provided by AA, PB, PMAC, BC, HOC, CC, DAL, BEM, SR, EKS, RT-S, EvB, JV, EW and JCY. MCW and WM were responsible for the overall content of the manuscript as guarantors.

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Patient consent Obtained.

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Provenance and peer review Not commissioned; externally peer reviewed.

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APPENDIX 1

PRINCIPAL INVESTIGATORS AND CENTERS PARTICIPATING IN ECLIPSE (NCT00292552, SC0104960)

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APPENDIX 2

Methods: Clinical, physiological and biochemical measurements in the ECLIPSE study

The American Thoracic Society (ATS) respiratory questionnaire, the modified Medical Research Council (mMRC) questionnaire and the COPD-specific version of the St. George's Respiratory Questionnaire (SGRQ-C) were used to record data related to symptoms, disease history and quality of life. Exacerbations requiring treatment with antibiotics, oral corticosteroids or hospitalization (moderate or severe exacerbations respectively) in the year prior to the study were also recorded. Co-morbidities were self-reported using the ATS-DLD-78 questionnaire. Nutritional status was assessed by body mass index (BMI) and fat-free mass index (FFMI) measured by bioelectrical impedance. Spirometry and the 6-minute walking distance (6MWD) were performed according to international guidelines.(1) Spirometric reference values were obtained from the European Community for Coal and Steel (ECCS) tables.(2) The BODE index was calculated according to Celli *et al*.(3) Peripheral venous blood was collected in the morning after an overnight fast on all study visits. White blood cell (WBC) count was measured in a central clinical laboratory. Serum was prepared by centrifugation of whole blood at 1500 *g* for 10-15 min and plasma (anticoagulated with ethylene-diamine tetra-acetate) was obtained by centrifugation at 2000 *g* for 10-15 min. Samples were stored at -80ºC until analyzed centrally. Serum interleukin (IL)-6, IL-8 and tumour necrosis factor alpha (TNF-α) concentrations were determined by validated enzyme-linked immunosorbent assays (ELISAs; SearchLight Array Technology, Thermo Fisher Scientific, Rockford, IL, USA). Serum surfactant protein D (SP-D) was measured using a colorimetric sandwich immunoassay method (BioVendor, Heidelberg, Germany). Chemokine ligand 18 (CCL-18) concentrations were measured using a human CCL18/PARC DuoSet ELISA kit (R&D systems). Soluble receptor for advanced glycation endproducts (sRAGE) was measured using the

Quantikine human RAGE ELISA kit (R&D). High-sensitivity C-reactive protein (hs-CRP) (Roche Diagnostics, Mannheim, Germany) and fibrinogen (K-ASSAY fibrinogen test, Kamiya Biomedical Co., Seattle, WA, USA) concentrations were measured using immunoturbidometric assays validated for use with EDTA plasma.

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Figure caption

Figure i: Cox proportional hazards model for all subjects and (A) CACS (Agatston score) adjusted for age, gender, pack-years, severity of COPD and self-reported cardiovascular disease and (B) CACSP adjusted for pack-years.

Table i: Demographic and baseline details of the study population and the full ECLIPSE cohort.

	Full ECLIPSE Cohort			Study Cohort			p-value for study cohort		
Characteristic	**COPD Subjects**	**Smoker**	**Non-smokers**	**COPD Subjects**	**Smokers**	**Non-smokers**	**COPD subjects vs smokers**	**COPD subjects vs Non-smokers s**	**Smokers vs Non-smokers**
N	2164	337	245	672	199	71			
Age years	63.4 (7.1)	55.4 (9.0)	54.1 (9.0)	63.2 (7.0)	54.1 (8.5)*	54.7 (9.2)	<0.001	<0.001	0.554
Male (%)	1412 (65%)	187 (55%)	92 (38%)	422 (63%)	115 (58%)	21 (30%)	0.202	<0.001	<0.001
Pack years	48.6 (27.1)	31.6 (21.5)	0.2 (1.1)	47.4 (25.1)	30.7 (19.9)	0.1 (1.0)	<0.001	<0.001	<0.001
Body mass index kg/m^2	26.5 (5.7)	26.8 (4.6)	27.7 (5.4)	26.5 (5.6)	26.7 (4.3)	28.3 (6.9)	0.753	0.010	0.031
post-bronchodilator FEV_1 litres	1.35 (0.52)	3.33 (0.77)	3.29 (0.79)	1.36 (0.54)	3.46 (0.71)*	3.19 (0.79)	<0.001	<0.001	0.001
post-bronchodilator FEV_1 % Predicted	48.3 (15.8)	108.6 (12.0)	114.8 (13.9)	48.7 (16.1)	110.0 (11.5)	114.4 (13.8)	<0.001	<0.001	0.039

	Full ECLIPSE Cohort			**Study Cohort**			**p-value for study cohort**		
Characteristic	**COPD Subjects**	**Smoker**	**Non-smokers**	**COPD Subjects**	**Smokers**	**Non-smokers**	**COPD subjects vs smokers**	**COPD subjects vs Non-smokers s**	**Smokers vs Non-smokers**
post-bronchodilator FEV_1/FVC Ratio	44.8 (11.6)	79.2 (5.2)	81.1 (5.2)	44.1 (11.5)	79.2 (4.8)	81.0 (5.9)	<0.001	<0.001	0.203
Patient reported cardiovascular disease	1201 (55%)	106 (31%)	75 (31%)	357 (53%)	45 (23%)*	24 (34%)	<0.001	0.002	0.064
%LAA **	15.6 [17.8]	1.1 [2.7]	2.7 [4.2]	15.6 [19.2]	0.8 [1.9]*	2.8 [4.4]	<0.01	<0.01	<0.01

[* p-value <0.05 vs the full ECLIPSE cohort]

[Mean and (Standard deviation) or ** median and (interquartile range) or %]

Table ii: Vessel and total coronary artery calcium score (Agatston score) for COPD subjects, smokers and non-smokers.

Location	COPD Subjects	Smokers	Non-smokers	p-value			
				Overall	COPD Subjects vs Smokers	COPD Subjects vs Non-smokers	Smokers vs Non-smokers
Left anterior descending artery	52 [0, 259]	0 [0, 48]	0 [0, 1]	<0.001	<0.001	<0.001	0.007
Left circumflex coronary artery	0 [0, 31]	0 [0, 0]	0 [0, 0]	<0.001	<0.001	<0.001	0.780
Left main stem	0 [0, 13]	0 [0, 0]	0 [0, 0]	<0.001	<0.001	<0.001	0.585
Right coronary artery	0 [0, 119]	0 [0, 0]	0 [0, 0]	<0.001	<0.001	<0.001	0.030
Total	128 [2, 494]	0 [0, 75]	0 [0, 3]	<0.001	<0.001	<0.001	0.003

[Median and [25th and 75th percentile]]

Cohorts were compared via Kruskal-Wallis tests.

Table iii: Coronary artery calcium score (Agatston score) and cardiovascular risk factors.

Location	COPD Subjects			Smokers			Non-smokers		
	Yes	No	p value	Yes	No	p value	Yes	No	p value
Diabetes	66, 205 [22, 708]	587, 119 [1, 475]	0.021	14, 293 [0, 549]	182, 0 [0, 57]	0.002	3, 4 [0, 724]	67, 0 [0, 1]	0.146
Hypertension	260, 219 [27, 686]	380, 72 [0, 373]	<0.001	31, 46 [0, 164]	156, 0 [0, 61]	0.009	17, 0 [0, 12]]	50, 0 [0, 0]	0.075
Statin Therapy	173, 281 [42, 1111]	499, 87 [0, 386]	<0.001	27, 314 [35, 872]	172, 0 [0, 41]	<0.001	8, 401 [0, 901]	63, 0 [0, 0]	0.002
Patient reported cardiovascular disease, “heart trouble”, angina or “heart attack”	357, 217 [28, 667]	315, 52 [0, 332]	<0.001	45, 75 [0, 427]	154, 0 [0, 40]	<0.001	24, 0 [0, 9]	47, 0 [0, 0]	0.193

[number, median and [25th and 75th percentile]

Table iv: Coronary artery calcium score (Agatston score) and gender.

Gender	COPD Subjects	Smokers	Non-smokers
Male	179 [659]	15 [120]	12 [270]
Female	54 [353]	0 [6]	0 [0]
p-value	<0.001	<0.001	<0.001

[median and [interquartile range]

Table v: Agatston score and coronary artery calcium score percentile (CACSP) for patients with and without self-reported cardiovascular disease at baseline.

	Cardiovascular disease				No cardiovascular disease			
Characteristic	**COPD Subjects**	**Smoker Controls**	**Non-smoker Controls**	**p-value**	**COPD Subjects**	**Smoker Controls**	**Non-smoker Controls**	**p-value**
N	357	45	24		315	154	47	
Agatston Score	217 [28, 667]	75 [0, 427]	0 [0, 9]	<0.001	52 [0, 332]	0 [0, 40]	0 [0, 0]	<0.001
CACSP based on age, gender and ethnicity	77 [49, 92]	63 [0, 90]	0 [0, 67]	<0.001	63 [0, 88]	0 [0, 75]	0 [0, 0]	<0.001
CACSP based on age, gender and ethnicity adjusted for pack years	76.7 [2.5]	63.8 [18.4]		0.001	59.4 [10.1]	18.7 [22.3]		<0.001
Age (years)	65 [61, 69]	57 [53, 65]	55 [49, 64]	<0.001	62 [57, 67]	51 [46, 59]	55 [45, 61]	<0.001
Pack-years	45 [32, 60]	36 [20, 42]	0 [0, 0]	<0.001	41 [29, 55]	24 [17, 35]	0 [0, 0]	<0.001
Female	126 (35%)	14 (31%)	16 (67%)	<0.001	124 (39%)	70 (45%)	34 (72%)	<0.001

[Median [25th and 75th percentile] or number (%)].

Table vi: Coronary artery calcium score (Agatston score) frequency.

Agatston score	COPD Subjects	Smokers	Non-smokers	p-value			
				Overall	COPD Subjects vs Smokers	COPD Subjects vs Non-smokers	Smokers vs Non-smokers
0	155 (23%)	105 (53%)	51 (72%)	<0.001	<0.001	<0.001	0.070
1-10	40 (6%)	14 (7%)	6 (8%)				
11-100	121 (18%)	37 (19%)	8 (11%)				
101-400	158 (24%)	21 (11%)	2 (3%)				
401-1000	110 (16%)	14 (7%)	3 (4%)				
>1000	88 (13%)	7 (4%)	1 (1%)				

[Number (%)]

Table vii: Correlations in COPD subjects between Agatston calcium score and coronary artery calcium score percentile (CACSP) based on age, gender and ethnicity and baseline characteristics, functional assessments, physiological assessments, imaging and biomarkers.

	Agatston Score				CACSP based on age, gender and ethnicity			
Variable	**n**	**Spearman Correlation Coefficient**	**95% Confidence interval**	**p-value**	**n**	**Spearman Correlation Coefficient**	**95% Confidence interval**	**p-value**
Age	672	0.403	(0.338, 0.464)	<0.001	672	0.112	(0.036, 0.186)	0.004
Pack-years	672	0.199	(0.125, 0.270)	<0.001	672	0.113	(0.038, 0.187)	0.003
BMI	672	-0.014	(-0.090, 0.061)	0.710	672	-0.072	(-0.147, 0.003)	0.060
post-bronchodilator FEV_1	670	-0.052	(-0.128, 0.024)	0.176	670	-0.107	(-0.181, -0.032)	0.005
post-bronchodilator FEV_1 % Predicted	670	-0.070	(-0.145, 0.005)	0.069	670	-0.070	(-0.145, 0.006)	0.071
post-bronchodilatorFEV_1/FVC Ratio	670	-0.086	(-0.161, -0.011)	0.026	670	-0.065	(-0.140, 0.011)	0.093
Decline in FEV_1	672	0.045	(-0.031, 0.120)	0.249	672	0.016	(-0.060, 0.091)	0.683
Exacerbations/year	664	0.012	(-0.064, 0.088)	0.748	664	0.011	(-0.065, 0.087)	0.772
Severe Exacerbations/year	664	0.093	(0.017, 0.168)	0.016	664	0.064	(-0.012, 0.139)	0.101
GOLD Stage	672	0.091	(0.015, 0.165)	0.019	672	0.075	(-0.001, 0.149)	0.053
6MWD	657	-0.132	(-0.206, -0.056)	<0.001	657	-0.116	(-0.191, -0.040)	0.003
SGRQ-C Total score	641	0.074	(-0.003, 0.151)	0.060	641	0.079	(0.002, 0.156)	0.045
SGRQ-C Activity score	652	0.064	(-0.013, 0.140)	0.104	652	0.069	(-0.008, 0.145)	0.078
SGRQ-C Impacts score	647	0.076	(-0.001, 0.152)	0.052	647	0.084	(0.007, 0.160)	0.033
SGRQ-C Symptoms score	667	0.019	(-0.057, 0.095)	0.617	667	0.021	(-0.055, 0.097)	0.588
mMRC Dyspnea score	646	0.108	(0.031, 0.183)	0.006	646	0.074	(-0.004, 0.150)	0.061
BODE Index	630	0.124	(0.047, 0.201)	0.002	630	0.112	(0.035, 0.189)	0.005

	Agatston Score				CACSP based on age, gender and ethnicity			
Variable	**n**	**Spearman Correlation Coefficient**	**95% Confidence interval**	**p-value**	**n**	**Spearman Correlation Coefficient**	**95% Confidence interval**	**p-value**
%LAA	632	0.078	(-0.000, 0.155)	0.050	632	0.042	(-0.036, 0.120)	0.292
Lowest 15th Percentile	632	-0.074	(-0.151, 0.004)	0.063	632	-0.041	(-0.119, 0.037)	0.298
Radiologist score	663	0.056	(-0.021, 0.131)	0.153	663	0.063	(-0.013, 0.139)	0.103
High Sensitivity CRP	643	0.039	(-0.038, 0.116)	0.323	643	0.004	(-0.073, 0.082)	0.915
Fibrinogen	663	0.063	(-0.013, 0.138)	0.106	663	0.029	(-0.047, 0.105)	0.454
IL-6	595	0.176	(0.097, 0.252)	<0.001	595	0.093	(0.013, 0.172)	0.023
IL-8	646	0.083	(0.006, 0.159)	0.035	646	0.053	(-0.024, 0.130)	0.176
TNF-alpha	649	0.028	(-0.049, 0.104)	0.483	649	0.001	(-0.076, 0.078)	0.981
CC-16	652	0.184	(0.109, 0.257)	<0.001	652	0.046	(-0.031, 0.122)	0.245
Surfactant Protein-D	652	0.108	(0.032, 0.183)	0.006	652	0.051	(-0.025, 0.128)	0.189
CCL-18	597	0.078	(-0.003, 0.157)	0.058	597	-0.001	(-0.081, 0.079)	0.983
sRAGE	581	-0.005	(-0.086, 0.077)	0.912	581	-0.017	(-0.098, 0.064)	0.680
WBC	661	0.058	(-0.019, 0.133)	0.139	661	0.017	(-0.059, 0.093)	0.665
Neutrophils	661	0.089	(0.012, 0.164)	0.023	661	0.025	(-0.051, 0.102)	0.513

(BMI, body mass index; FEV, forced expiratory volume; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; 6MWD, six minute walking distance; SGRQ-C, St George Respiratory questionnaire; mMRC, modified Medical Research Council, BODE index, Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity; %LAA, per cent low attenuation area; CRP, C-reactive protein; IL-6, interleukin 6; IL-8, interleukin 8; TNF-alpha, tumour necrosis factor-alpha; CC-16, clara cell protein 16; CCL-18, chemokine ligand 18; sRAGE, soluble receptor for advanced glycation endproducts; WBC, white blood cell)

Spearman correlation coefficients are presented; 95% confidence intervals have been calculated by the Fisher z-transformation method.

Table viii: Agatston score and coronary artery calcium score percentile (CACSP) for patients with and without two or more elevated biomarkers measured on two occasions.

	Number of elevated biomarkers at both visits		
	0	**2+**	**p-value**
N	148	66	
Agatston Score	95 [2, 390]	232 [41, 694]	0.024
Number with a zero Agatston score	34 (23%)	13 (20%)	0.594
CACSP based on age, gender and ethnicity	71 [30, 89]	78 [42, 93]	0.347

[Median [25th and 75th percentile] or number (%)].

Table ix: Agatston score and coronary artery calcium score percentile (CACSP) for COPD subjects and smoker and non-smoker controls who did or did not die during 3 years follow up.

	COPD Subjects			**Smoker controls**			**Non-smoker controls**		
	Yes	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
N	63	609	-	2	197	-	0	71	-
Agatston Score	406 [97, 1076]	103 [1, 453]	<0.001	228 [0, 455]	0 [0, 75]	0.659	-	0 [0, 3]	-
CACSP based on age, gender and ethnicity	83 [52, 95]	70 [23, 89]	0.009	47 [0, 94]	0 [0, 78]	0.689	-	0 [0, 43]	-
CACSP based on age, gender and ethnicity adjusted for pack years	83.0 [74.8, 85.1]	69.3 [67.7, 70.8]	0.003	-	-	-	-	-	-

[Median [25th, 75th percentile]]

CACSP adjusted for pack years was compared using quantile regression. All other comparisons were done by Kruskal-Wallis tests.