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Chronic obstructive pulmonary disease and the development of atrial fibrillation☆

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) has been associated with atrial fibrillation (AF). More insight into the epidemiology and underlying mechanisms is required to optimize management.
Methods: The Rotterdam Study is a large, population-based cohort study with long-term follow-up. Time dependent Cox proportional hazard models were constructed to study the effect of COPD on incident AF, adjusted for age, sex and pack years of cigarette smoking, and additionally stratified according to exacerbation frequency, left atrial size and baseline systemic inflammatory levels.
Results: 1369 of 10,943 subjects had COPD, of whom 804 developed AF. The AF incidence rate was 14 per 1000 person years in COPD and 8 per 1000 person years in subjects without COPD. The adjusted hazard ratio (HR) for COPD subjects to develop AF as compared to subjects without COPD was 1.28 (95%CI [1.04, 1.57]). COPD subjects with frequent exacerbations had a twofold increased AF risk (HR 1.99 [1.42, 2.79]) and COPD subjects with a left atrial size ≥40 mm also had an elevated AF risk (HR 1.77 [1.07, 2.94]). COPD subjects with baseline systemic inflammatory levels above the median had significantly increased AF risks (hsCRP≥1.83 mg/L: HR 1.51 [1.13, 2.03] and IL6 ≥ 1.91 ng/L: HR 2.49 [1.18, 5.28]), whereas COPD subjects below the median had in both analyses no significantly increased AF risk.
Conclusions: COPD subjects had a 28% increased AF risk, which further increased with frequent exacerbations and an enlarged left atrium. The risk was driven by COPD subjects having elevated systemic inflammatory levels.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, having an estimated prevalence of 3% in adults aged ≥20 years, affecting 20.9 million men and 12.6 million women worldwide in 2010 [1–3]. AF is associated with increased rates of coronary artery disease, cerebrovascular accidents and other thromboembolic events, chronic heart failure, low quality of life, reduced exercise capacity and cognitive dysfunction [3–7]. Risk factors for AF include increasing age, male sex, hypertension, diabetes mellitus, myocardial infarction, valvular heart disease, heart failure, obstructive sleep apnea, chronic kidney disease, hyperthyroidism, obesity, heavy alcohol consumption and smoking [3–14]. Additionally, an enlarged left atrium due to structural remodeling in response to oxidative stress and inflammation, is a proven risk factor for developing AF [15].

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases worldwide characterized by progressive airflow

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limitation [16,17]. The number of COPD cases increased to 384 million in 2010, with a global prevalence of 11.7% and an overall prevalence in men aged ≥30 years of 14.3% compared to 7.6% in women [18]. Exacerbations contribute to the overall severity in individual patients, since they have a negative effect on quality of life, cause an accelerated decline in lung function, and are associated with significant mortality, especially in hospitalized patients [19]. COPD is associated with many co-morbidities and is considered an independent risk factor for cardiovascular morbidity and mortality [20–23]. Examining the potential association between COPD and incident AF, and identifying vulnerable patient groups can be useful for earlier detection of patients at risk for AF, by increasing awareness on risk factors and risk patients for clinical practice and by highlighting the opportunities for improved prevention and treatment of cardiovascular morbidity and mortality in COPD patients [24].

Previous studies have investigated the association between COPD and AF, but these studies are often limited in design (e.g. cross-sectional studies studying only the co-occurrence), sample size and follow-up time [22,25]. An association between reduced lung function and incident AF has been established longitudinally in the Copenhagen Heart Study in 2003, but this study did not evaluate COPD exacerbations or the effect of left atrial size on the association [22]. Identifying the effect of frequent COPD exacerbations and left atrial size on AF development in COPD patients is however useful for identifying a subset of patients at higher risk of incident AF. Furthermore, the role of systemic inflammation in COPD as a potential underlying pathophysiological mechanism of AF development has not been fully elucidated, but is important as it may improve therapeutic recommendations.

In this large prospective population-based study we aimed to determine the AF incidence in COPD subjects compared to subjects without COPD, as well as the effect of frequent COPD exacerbations and left atrial size on the association. Finally, this is one of the first studies with the aim to investigate the role of underlying systemic inflammation in COPD on AF development.

2. Methods

2.1. Setting

The Rotterdam Study is a prospective population-based cohort study in Rotterdam, the Netherlands, consisting of 14,926 subjects [26,27]. It consists of three independent cohorts, which are followed until present. Rotterdam Study I (RS-I) started with a baseline visit between 1990 and 1993, enrolling 7983 subjects aged ≥55 years; RS-II started between 2000 and 2001, enrolling 3011 subjects aged ≥55 years; and RS-III started between 2006 and 2007, enrolling 3932 subjects aged ≥45 years. There is a continuous follow-up for morbidity and mortality through linkage with digital medical records from general practitioners (GP) in the study area, collection of letters of medical specialists, discharge reports in case of hospitalization and municipal health authorities in Rotterdam. There are regular examination cycles every 3 to 5 years at the study center during which multiple tests, including spirometry and electrocardiography (ECG), are performed. Information on lifestyle factors, such as smoking, is obtained through systematic interviews and questionnaires. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All subjects provided written informed consent to participate in the study and to obtain information from their treating physicians.

2.2. AF assessment

Three methods were used for the assessment of prevalent and incident AF. Firstly, 10 s ECGs with 12 leads and stored digitally, were taken at baseline and during follow-up examinations [26,28]. All ECGs were analyzed by the Modular ECG Analysis System (MEANS). To verify the diagnosis of AF, all ECGs with a MEANS diagnosis of AF, atrial flutter or any other rhythm disorder were independently reviewed by two research physicians who were blinded to the MEANS diagnosis. In case of a persisting disagreement between the coding physicians, a cardiologist made the final diagnosis.

Secondly, additional medical information was obtained from the subject's GP. This information included investigations performed by the GP or by a physician in a hospital setting. AF was included in case of diagnosis by a specialist or by the GP with ECG evidence.

Thirdly, the national registry of hospital discharge diagnoses was searched for the diagnosis of AF. AF was not included as a case if AF developed during the process of dying while AF was not the cause of dying or if transient AF occurred during a hospitalization for myocardial infarction or cardiac operative procedures.

The incident AF date was either determined by incidence date in medical records or, when AF was first diagnosed at the research center, the incident date was the mean between the confirming ECG date and the last examination date within the Rotterdam Study which showed no AF. Subjects with AF at baseline or with missing data regarding AF were excluded.

2.3. COPD assessment

COPD was diagnosed by an obstructive spirometry at the research center, or, in absence of an interpretable spirometry at the research center, by a physician based on clinical history, physical examination or spirometry performed outside the investigations of the research center [27,29]. The diagnosis of COPD using spirometry at the study center was defined by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition: $FEV_1/FVC < 0.7$ based on pre-bronchodilator lung function testing which was available from 2002 onwards [20]. Subjects with physician diagnosed asthma were excluded. When the diagnosis of asthma or COPD was uncertain or overlapping, subjects were also excluded [27,29].

The incidence date of COPD was determined as whichever date came first: the date of obstructive lung function measurement at the research center, the date of COPD diagnosis by a physician or the date of first medication for obstructive lung disease. Subjects with frequent exacerbations were determined as subjects who had at least two moderate or severe exacerbations on average per year during the entire follow-up [30]. Moderate COPD exacerbations were defined as exacerbations treated with oral corticosteroids and/or antibiotics, whereas a severe COPD exacerbation was defined as a COPD worsening requiring hospitalization [31].

2.4. Assessment of systemic inflammation

Plasma interleukin 6 (IL6) and high-sensitivity C-reactive protein (hsCRP) levels were measured in RS-I during a stable state as previously described (33). IL6 plasma levels were measured in a 10% random subset who received venipuncture at the start of the study (1990–1993) by application of minimal stasis with a 21-gauge butterfly needle tube (Surflo winged infusion set, Terumo) (33). After nonfasting blood was collected in tubes containing 0.129 mol/L sodium citrate at 4 °C, plasma was yielded after centrifugation for 10 min at 3000 rpm and subsequently, platelet-free plasma was yielded by centrifugation for 10 min at 10000 rpm and immediately frozen in liquid nitrogen, and stored at −80 °C (33). Using a commercially available ELISA (Quantikine HS IL6 kit from R&D Systems Europe), IL6 levels were measured with an interassay coefficient of variation for IL6 of 8.7% (33).

2.5. Statistical analyses

For the descriptive statistics, median and interquartile range (IQR) are presented for continuous variables, and number and percentage for categorical variables. A non-parametric Mann-Whitney *U* test was performed to determine if continuous variables were different between subjects with or without COPD, and a Chi-Square test was used to determine significant differences in categorical variables.

The association between COPD and incident AF was evaluated using a time dependent Cox proportional hazard model. The start of study follow-up was determined as either (1) the date of study entry if the participant had prevalent COPD at baseline, (2) the incidence date of COPD during follow-up, or (3) the date of study entry if the participant did not have prevalent COPD at baseline and did not develop COPD during follow-up. The last day of follow-up was determined as either (1) the incidence date of AF, (2) the date of death or (3) December 31, 2010, whichever came first. An additional time dependent Cox proportional hazard model was used to examine the association between COPD with or without frequent exacerbations and incident AF during the same follow-up. A stratified subset analysis was performed to explore the effect of left atrial size on the association between prevalent COPD at the date of echocardiography and incident AF. Left atrial size (in mm) was measured on echocardiography between 2002 and 2011. The start of study follow-up was the first date of echocardiography. The last day of follow-up was determined as previously stated.

Besides age (years) and sex, models were adjusted for the following covariates according to the previous literature when changing the risk estimate by >10%: smoking behavior (never, former, current smoker), pack years of cigarette smoking, alcohol use (g/day), height (cm), weight (kg), BMI (kg/m^2), total serum cholesterol (mmol/L), diabetes mellitus, hypertension, systolic and diastolic blood pressure (mmHg), acute myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, chronic heart failure and chronic kidney disease [3–10,29]. The information of the covariates was obtained through interview, laboratory tests, medical files or physical examination during the first visit of the study center at baseline [27]. Pack years of cigarette smoking were computed as the duration of self-reported smoking in years multiplied by the number of daily smoked cigarettes divided by 20 (1 pack). Blood pressure was measured in a sitting position at the right arm, taking the average of two consecutive measurements. A subject had baseline hypertension if having a systolic and/or diastolic blood pressure of ≥140 and/or ≥90 mm Hg or using antihypertensive medication. Myocardial infarction was defined using a combination of symptoms, ECG results and enzyme markers. Heart failure diagnosis was determined in accordance with the guidelines of the European Society of Cardiology. The estimated glomerular filtration rate (eGFR) was calculated with the MDRD formula. Chronic kidney failure as a dichotomous variable was defined as having an eGFR of <60 ml/min/1.73 m^2. Diabetes mellitus was defined as either fasting glucose

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>6.9 mmol/l, non-fasting glucose >11.0 mmol/l, the use of blood glucose lowering medication, or a previous diagnosis of diabetes mellitus. SPSS statistics 22 (IBM Corp., Somers, NY, USA) was used for the analyses.

3. Results

After exclusion of subjects due to AF at baseline, missing AF data or asthma, 10,943 subjects were included (Fig. 1). Table 1 demonstrates the baseline characteristics of the study population. The 1369 subjects with COPD were more frequently male, older and had smoked more pack years. Myocardial infarction was significantly more prevalent in COPD subjects.

Regarding the association between COPD and incident AF, 131 of 1369 COPD developed AF during 9569 person years (PY) of follow-up (incidence rate (IR) 13.7/1000 PY), whereas 673 of 9574 subjects without COPD had incident AF during 89,673 PY of follow-up (IR 7.5/1000 PY).(Fig. 2) Of the 131 COPD subjects who developed AF, 41 (31%) COPD subjects developed AF within eight weeks from the start of an exacerbation, and 8 (20%) of those exacerbations were severe requiring hospitalization. The analysis for confounding variables besides age and sex showed that only pack years of cigarette smoking had a pronounced effect (>10%) on the association between COPD and AF. The increased risk during follow-up for COPD subjects to develop AF as compared to subjects without COPD was 1.28 (95%CI [1.04, 1.57], p value 0.018) adjusted for age, sex and pack years of cigarette smoking.

Regarding the effect of COPD exacerbations (Fig. 3), the adjusted HR for COPD subjects with frequent exacerbations to develop AF as compared to subjects without COPD was 1.99 (95%CI [1.42, 2.79], p value <0.001) (Table 2). Stratified for sex, the adjusted risk of incident AF was more pronounced in females with frequent exacerbations (HR 2.46, 95%CI [1.48, 4.08], p value 0.001) than in males with frequent exacerbations (HR 1.67, 95%CI [1.06, 2.63], p value 0.026), both compared to subjects without COPD. When comparing the risk within COPD subjects, the additional adjusted risk for having frequent exacerbations to develop AF was 1.82 (95%CI [1.23, 2.69], p value 0.003).

Regarding the effect of left atrial size, the association between COPD and incident AF has been explored in the subset of subjects with left atrial echocardiographic measurement. 481 COPD subjects at date of echocardiography (median left atrial size 39 mm, IQR 36–43 mm), and 5374 subjects without COPD (median left atrial size 40 mm, IQR 36–43 mm) were followed within this analysis (p value 0.165). Median age was 66.5 years (IQR 58.8–74.2) at start of follow-up, which was the date of echocardiography. During 30,472 PY of follow-up, 172 subjects developed AF. Stratified on left atrial size, the adjusted incident AF risk was only significantly higher for COPD subjects compared to subjects without COPD in the stratum of subjects with a left atrial size ≥40 mm (HR 1.77, 95%CI [1.07, 2.94], p value 0.027; vs HR 1.15, 95%CI [0.50–2.62], p value 0.745, if left atrial size <40 mm).

Regarding the role of baseline systemic inflammatory levels, analyses were stratified below or above the median hsCRP and IL6 level, respectively. hsCRP was measured in 5545 of 5904 (94%) included RS-I subjects. Table 3 demonstrates that COPD subjects with hsCRP ≥ median of 1.83 mg/L, had a 1.5 significantly increased AF risk as compared to subjects without COPD (HR 1.51 [1.13, 2.03], p value 0.005). The AF risk in COPD subjects below the median hsCRP level was not significantly increased. Within the 10% random subset of the 5904 included RS-I subjects with baseline plasma IL6 measurement ($n = 599$), COPD subjects with IL6 ≥ median of 1.91 ng/L, had a 2.5 significantly increased AF risk as compared to subjects without COPD (HR 2.49 [1.18, 5.28], p value 0.017). The AF risk in COPD subjects below the median IL6 was not increased.

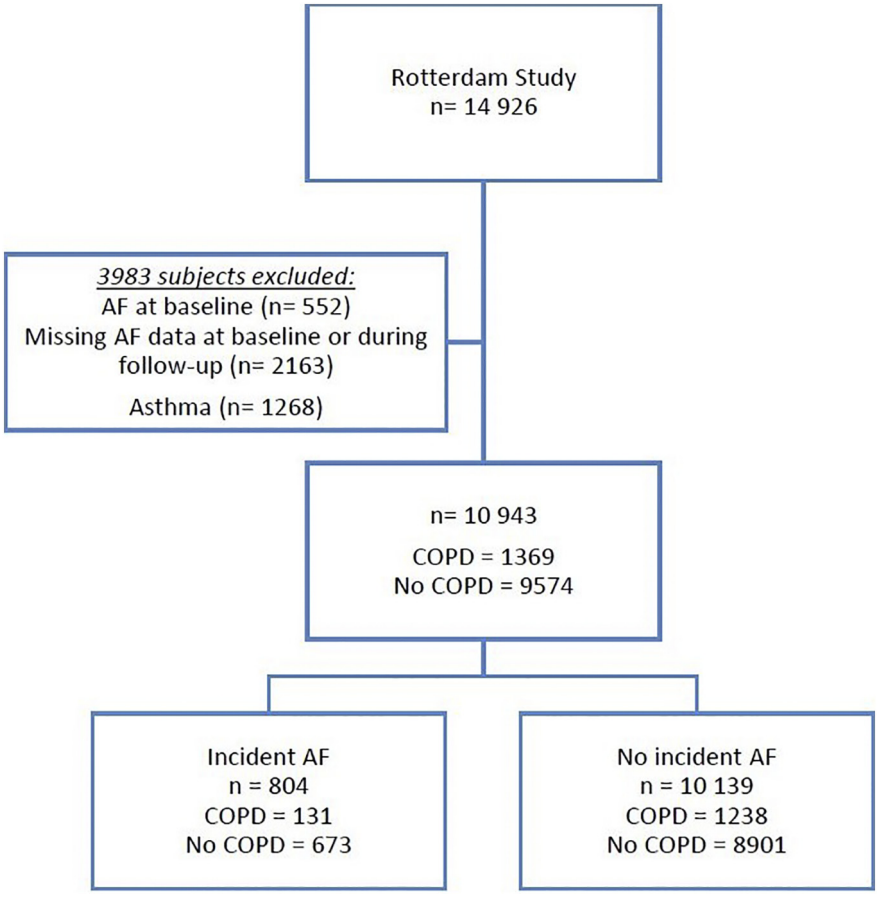

Fig. 1. Flowchart. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

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Table 1
Baseline characteristics table.

Baseline characteristics of subjects with or without COPD			
	COPD	No COPD	*p*-value
	n = 1369	*n* = 9574	
Demographics			
Male - no. (%)	757 (55.3)	3893 (40.7)	<0.001
Age (IQR) – year	69.6 (62.3–76.2)	62.2 (57.7–71.4)	<0.001
BMI (IQR) - kg/m^2	25.8 (23.5–28.3)	26.4 (24.2–29.0)	<0.001
Height (IQR) - cm	170.0 (163.0–176.5)	167.2 (161.0–174.8)	<0.001
Weight (IQR) - kg	74.7 (66.9–83.6)	74.8 (66.2–84.1)	0.613
Pack years of cigarette smoking (IQR)	26.3 (7.7–44.0)	3.5 (0–22.0)	<0.001
Smoking status			<0.001
Never smoker - no. (%)	208 (15.5)	3503 (37.4)	
Former smoker - no. (%)	578 (43.2)	4089 (43.6)	
Current smoker - no. (%)	553 (41.3)	1785 (19.0)	
Alcohol (IQR) - g/day	2.9 (0–7.1)	1.6 (0–7.1)	0.625
Sex-specific eGFR (IQR) - ml/min/1.73 m^2	74.9 (66.2–85.5)	73.8 (64.9–83.7)	0.001
Cholesterol (IQR) - mmol/l	6.2 (5.4–7.0)	6.1 (5.3–6.9)	0.076
IL6 (IQR) – pg/ml	2.0 (1.4–3.4)	1.9 (1.2–3.0)	0.132
hsCRP (IQR) - mg/l	1.9 (0.9–3.8)	1.5 (0.6–3.1)	<0.001
Systolic blood pressure (IQR) - mm Hg	136.0 (123.0–151.0)	136.0 (123.0–152.0)	0.372
Diastolic blood pressure (IQR) - mm Hg	76.0 (68.0–84.0)	77.0 (69.0–85.0)	<0.001
Pulse pressure (IQR) - mm Hg	59.0 (49.0–71.0)	58.0 (47.0–71.0)	0.111
Comorbidities			
Chronic kidney disease (<60 ml/min/1.73m^2) - no. (%)	131 (12.0)	1201 (15.2)	0.005
Myocardial infarction - no. (%)	91 (6.7)	431 (4.5)	0.001
Coronary artery bypass graft - no. (%)	28 (2.1)	165 (1.8)	0.410
Percutaneous coronary intervention - no. (%)	16 (1.2)	123 (1.3)	0.707
Heart failure - no. (%)	30 (2.2)	143 (1.5)	0.054
Diabetes mellitus - no. (%)	128 (9.3)	903 (9.4)	0.923
(Treated) hypertension - no. (%)	639 (52.9)	4517 (53.8)	0.546

AF, atrial fibrillation; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range;
BMI was missing in 217, height in 210, weight in 207, pack years of cigarette smoking in 482, smoking status in 227, alcohol in 3081, eGFR in 1925, cholesterol in 218, IL6 in 10,524, CRP in 602, systolic blood pressure in 126, diastolic blood pressure in 126, pulse pressure in 126, atrial size in 4542, chronic kidney disease in 1925, myocardial infarction in 54, coronary artery bypass graft in 218, percutaneous coronary intervention in 218, heart failure in 36 and (treated) hypertension data in 1335 subjects.

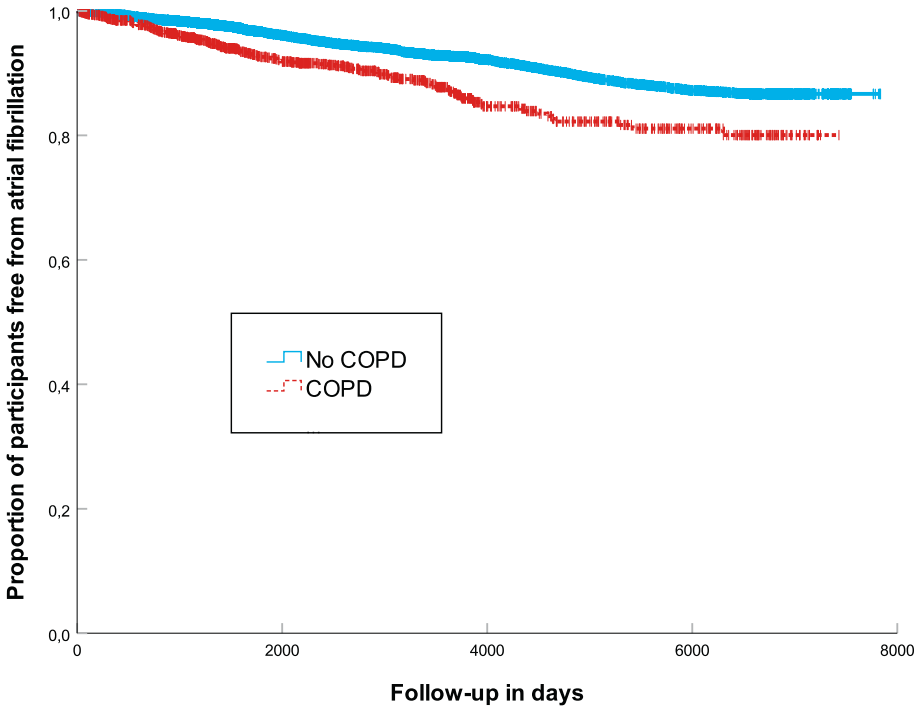

Fig. 2. Kaplan–Meier plot of the proportion of participants free from atrial fibrillation over the follow-up time in days. Blue line, subjects without COPD; red dotted line, subjects with COPD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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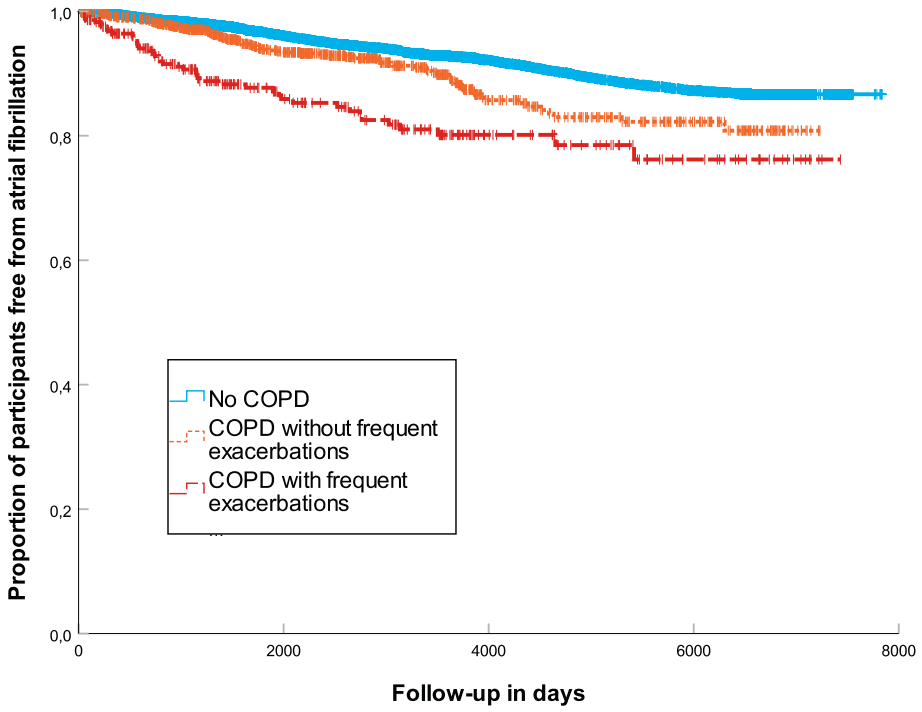

Fig. 3. Kaplan-Meier plot of the proportion of participants free from atrial fibrillation over the follow-up time in days. Blue line, subjects without COPD; orange dotted line, subjects with COPD without frequent exacerbations; red striped line, subjects with COPD with frequent exacerbations (at least two per year). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Hazard ratios for association between no COPD, COPD without (<2/y) and with frequent exacerbations (≥2/y), and incident AF.

	Total n	Events	Median follow-up time in years (IQR)	HR (95% CI)	*p*-value
Crude model					
No COPD	9574	673	9.1 (11.4)	Reference	
COPD without freq. ex.	1076	88	6.1 (6.8)	1.54 (1.24–1.93)	<0.001
COPD with freq. ex.	290	43	5.3 (8.0)	2.87 (2.11–3.91)	<0.001
Adjusted model[*]					
No COPD	9153	630	9.1 (11.2)	Reference	
COPD without freq. ex.	1034	81	6.0 (6.8)	1.11 (0.87–1.40)	0.407
COPD with freq. ex.	271	37	5.2 (8.0)	1.99 (1.42–2.79)	<0.001

AF, atrial fibrillation; CI, Confidence interval; COPD, chronic obstructive pulmonary disease; Freq. ex., frequent exacerbations; HR, Hazard Ratio; IQR, interquartile range.
[*] Adjusted for age, sex and pack years of cigarette smoking.

Table 3
Hazard ratios for association between COPD and incident AF, stratified according to baseline systemic inflammatory levels.

	Total n	Events	Median follow-up time in years (IQR)	HR (95% CI)[*]	*p*-value
hsCRP < 1.83 mg/L					
No COPD	2242	255	17.2 (9.0)	Reference	
COPD	353	37	7.6 (8.6)	1.04 (0.72–1.49)	0.852
hsCRP ≥ 1.83 mg/L					
No COPD	2108	241	12.5 (11.9)	Reference	
COPD	426	62	7.6 (8.2)	1.51 (1.13–2.03)	0.005
IL6 < 1.91 ng/L					
No COPD	239	29	17.8 (9.1)	Reference	
COPD	38	3	8.3 (10.1)	0.53 (0.14–1.97)	0.341
IL6 ≥ 1.91 ng/L					
No COPD	231	33	10.9 (11.6)	Reference	
COPD	47	11	7.6 (6.0)	2.49 (1.18, 5.28)	0.017

AF, atrial fibrillation; CI, Confidence interval; COPD, chronic obstructive pulmonary disease; hsCRP, high-sensitivity C reactive protein; HR, Hazard Ratio; IL6, Interleukin 6; IQR, interquartile range.
[*] Adjusted for age, sex and pack years of cigarette smoking.

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4. Discussion

In this large population-based cohort study, we demonstrate that COPD subjects have an increased risk of developing AF, even after adjusting for the relevant confounding variables. Importantly, only COPD subjects with elevated hsCRP and IL6 plasma levels had a significantly increased risk, suggesting the potential role of systemic inflammation on AF development present in a subset of COPD patients. Increasing evidence supports the role of systemic inflammation, characterized by elevation of various inflammatory mediators such as CRP, IL6 and tumor necrosis factor α, in the pathophysiology of AF development and progression [32–35]. Likewise, COPD and its disease severity have been associated with elevated levels of several inflammatory markers including IL6 and CRP, potentially linking systemic inflammation to various extra-pulmonary complications of COPD such as cachexia, osteoporosis, muscle wasting, diabetes mellitus and cardiovascular disease [36–40]. The role of systemic inflammation might provide new therapeutic options for preventing the occurrence and recurrence of AF in COPD, but potentially also a practical prognostic marker for incident AF in COPD by measuring baseline IL6. Further research is needed to examine these therapeutic interventions such as statins, ACE-inhibitors and corticosteroids, as well as new therapies specifically targeting IL6 in COPD.

Furthermore in terms of COPD severity, the risk was most pronounced in COPD subjects with frequent exacerbations. Because COPD exacerbations usually require medical assistance, such occasions provide ideal opportunities for detecting potential incident AF. Still, further research is needed to investigate whether screening for AF in high risk COPD patients provides an additional benefit on clinical outcomes, such as hospitalizations and survival. However, it is known that earlier AF detection might facilitate faster therapeutic interventions, protect against potential AF complications and slow down its progression [4,22].

Moreover, COPD patients with an enlarged left atrium were significantly more at risk of developing AF. Atrial size has already been linked to hyperuricemia and alcohol consumption in new-onset AF, but an association between COPD and atrial enlargement as a potential intermediate phenotype along the causal pathway to AF development has not been clearly investigated [41,42]. This could be used as an echocardiographic parameter in predicting incident AF in COPD patients. Still, further research is needed to investigate the clinical significance of these findings.

Our results that COPD subjects have a significantly increased AF risk, are in line with previous findings. For example, Buch et al. found an inverse relationship between FEV_1% predicted and AF [22]. Chahal et al. also found that reduced lung function as measured by FEV_1 was significantly associated with incident AF [43]. Additionally, Konecny et al. found that incident AF occurred significantly more among COPD subjects [25].

Postulated mechanisms as an explanation for the association between COPD and AF are multiple and can be differentiated in pathophysiological mechanisms leading to right and/or left atrial changes. In case of AF originating in the right atrium in COPD patients, the following mechanisms are proposed: hypoxia, hypercapnia and acidosis due to ventilation perfusion mismatching can lead to pulmonary hypertension due to pulmonary arteriolar constriction, resulting in right ventricular hypertrophy and diastolic dysfunction, which in turn can increase right atrial diameter, transmural pressure and myocardial stretching [22,23,44–47]. In acute exacerbations, impaired lung function, hypercapnia and increased pulmonary artery systolic pressure are proven to be independent predictors of incident AF [47]. Moreover, acute exacerbations lead to increased levels of IL6, hsCRP, and fibrinogen [48]. Since up to a third of all AF onsets among COPD subjects were registered in our study during the eight week period of a COPD exacerbation, COPD subjects seem particularly prone to develop AF during this unstable condition. These results are in line with observations that COPD subjects are at the highest risk of developing an adverse cardiovascular event during or shortly after an exacerbation [36,37,47]. Moreover, as recommended by the GOLD guidelines, severe COPD exacerbations are treated with high dose systemic corticosteroids, which have been associated with an increased risk of incident AF [49], while low dose corticosteroids had previously shown to prevent AF recurrence post cardioversion by significantly reducing CRP [50].

Besides inducing oxidative stress triggering ectopic firing foci (often originating in the walls of pulmonary veins) and aggravating left ventricle systolic dysfunction in the acute setting [51], COPD-related systemic inflammation might also play a role in AF originating in the left atrium in COPD patients by facilitating atrial structural remodeling on the long-term [47]. Persistent systemic inflammation is not a constant feature of COPD, as described by Agusti et al., but when present for at least one year, it is associated with worse outcomes after three years of follow-up [37]. Moreover, our results within the subset with left atrial size measurement also indicate that COPD subjects with an enlarged left atrium, which may be the consequence of structural remodeling due to systemic inflammation, may be particularly prone to develop AF. This correlates with the findings of Psychari et al. who found that left atrial diameter was positively related to CRP and IL6 [52].

Lastly, medication use, such as β-agonists, anticholinergic drugs, methylxanthine agents and oral corticosteroids, has recently been proposed as a potential pathophysiological mechanism for AF development in COPD [22,23,44–47].

This study has many strength such as the population-based setting, the large number of subjects, the long-term follow-up and the blinded assessment of the determinant (COPD) and the outcome (AF). Still, some limitations should be mentioned. First, the exact date of AF incidence was difficult to determine, even more because AF can be asymptomatic and paroxysmal. Because subjects with known AF at start of follow-up were excluded, latency might have underestimated this amount of subjects. Furthermore, we could not distinguish between paroxysmal and persistent AF, as our large population-based cohort design did not allow regular Holter monitoring in all patients to determine underlying paroxysmal AF. In future research, it would be of interest to follow-up the incident AF cases over multiple center visits to distinguish between paroxysmal and persistent AF, and evaluate whether COPD is associated with paroxysmal versus persistent atrial fibrillation compared to controls. Second, spirometric data was not available in all subjects. However, asthmatic patients were excluded. Third, COPD subjects differed from subjects without COPD in many demographic, lifestyle and co-morbid characteristics, all of which could have an influence on the association. Despite the fact that we evaluated the effect of almost twenty potential confounders, still some potential confounding factors - including valvular heart disease, hyperthyroidism and obstructive sleep apnea - have not been taken into account. Neither has the effect of COPD disease duration been taken into account. Covariates were moreover adjusted for their baseline level, whereas COPD subjects were followed since diagnosis if not present at baseline. This leaves the possibility for residual confounding, since the confounders were not treated time-varying. Fourth, the subgroup with available data on IL6 was rather small, because IL6 was only measured in a 10% random subset who received venipuncture at baseline. Nevertheless, results from adding the IL6 data in this smaller subsample were in line with the results from the hsCRP data, which we have measured in almost all participants. Since CRP is an acute-phase protein which increases following IL6 secretion, it is biologically reasonable that the AF risk associated with increased IL6 levels was higher. Therefore, IL6 might be an interesting biomarker to predict AF risk in COPD patients, although the shorter half-life of IL6 compared to hsCRP complicates its utility. Finally, exacerbations were measured during follow-up, implicating that reverse causation might theoretically still be present in this analysis.

In conclusion, we observed a significant association between COPD and incident AF. After adjusting for the relevant confounding variables, COPD subjects still had a 28% increased risk of developing AF. This risk

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was even more pronounced in COPD subjects with frequent exacerbations and with an enlarged left atrium. Importantly, this risk was driven by COPD subjects with elevated hsCRP and IL6 plasma levels, suggesting the important role of systemic inflammation in COPD on AF development. This may provide new therapeutic strategies targeting underlying systemic inflammation in COPD for primary and secondary prevention of AF.

Conflict of interest

None declared.

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