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COPD and risk of venous thromboembolism and mortality in a general population

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ABSTRACT The relationship between chronic obstructive pulmonary disease (COPD) and risk of venous thromboembolism (VTE) has been scarcely studied in the general population. We aimed to investigate the association between COPD and risk of VTE and mortality in a population-based cohort.

Spirometry was conducted in 8646 males and females, participating in the fifth (2001–02) and sixth (2007–08) surveys of the Tromsø Study. Incident VTE events during follow-up were registered from the date of inclusion to December 31, 2011. Cox-regression models with COPD stages and confounders as time varying covariates were used to calculate hazard ratios with 95% confidence intervals for VTE and all-cause mortality.

During a median follow-up of 6.2 years, 215 subjects developed VTE. Subjects with COPD stage III/IV had a two-fold higher risk of secondary VTE compared to subjects with normal airflow (HR 2.05, 95% CI 1.02–4.10). COPD patients, particularly those with stage III/IV disease, with VTE had a higher mortality rate than COPD patients without VTE (50.2% *versus* 5.6% per year).

Our findings suggest that patients with severe COPD may have increased risk of secondary VTE, and that COPD patients with VTE have a higher mortality rate than COPD patients without VTE.

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Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) has increased dramatically in Western populations during the last few decades [1, 2], and has become a major challenge to public health and healthcare systems due to frequent hospitalisations, severe comorbidities and a high mortality rate [2, 3]. Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with complications such as the post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension and death [4, 5]. COPD is considered a moderate risk factor of VTE [6]. Moreover, there is a high prevalence of acute PE (15–30%) in COPD patients interpreted as acute exacerbation [7–10]. In COPD patients, it has been assumed that the risk of VTE, and PE in particular, is mediated by concomitant risk factors such as immobilisation, bronchial superinfection, right ventricular failure and venous stasis [8].

Knowledge on the impact of COPD on VTE risk in the general population relies exclusively on results from registry-based studies reporting a two- to five-fold increased risk of VTE in COPD patients [11–14]. In these studies the exposure (COPD) and outcome (VTE) were defined according to International Classification of Diseases codes and treatment with COPD medications. Previous studies have reported low validity of COPD diagnoses obtained from administrative databases [15, 16]. Similarly, a validation of VTE diagnoses in the Danish National Patient Registry reported positive predictive values for VTE diagnoses from emergency departments and hospitals of 44% and 67–77%, respectively [17]. Thus, it is not known whether risk ratios presented by previous registry-based studies are valid or suffer from a high degree of misclassification (*i.e.* false positive or false negative events) or confounding due to lack of important clinical information such as provoking factors for VTE.

Hospitalisation for acute COPD exacerbation is associated with 5–10% in-hospital mortality, increasing to >20% during the first year after hospital discharge [18, 19]. A concomitant VTE event is associated with prolonged hospital stay and higher 1-year mortality [9]. COPD patients frequently suffer comorbidities which are often adjudicated as the primary cause of death in nonsurvivors [12, 20]. Some comorbidities have been shown to augment the mortality rate in a cohort of 1664 COPD patients [21]. However, limited data exist on the prognostic impact of VTE on mortality in COPD patients recruited from a general population.

We therefore set out to investigate the association between stages of COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [22], and future risk of secondary (presence of one or more predisposing factors) and unprovoked VTE in a population-based cohort with well-recorded confounder information and validated VTE events. Furthermore, we aimed to assess the risk of mortality in COPD patients with and without VTE.

Methods

Study population

Study participants were recruited from the fifth (2001–02) and sixth (2007–08) surveys of the Tromsø Study [23]. Parts of the population aged ⩾30 years living in the municipality of Tromsø, Norway, were invited to participate in an extensive screening including spirometry. A detailed description of study participation has been published elsewhere [23]. The overall attendance rate was high: 85% (n=5918) of those invited participated in Tromsø 5 and 74% (n=7306) in Tromsø 6. 9577 unique individuals aged 32–89 years participated in at least one of the surveys, and of these, 3647 participated in both surveys. The regional committee of medical and health research ethics approved the study, and all subjects gave their written consent to participate. Subjects who were not officially registered as inhabitants of the municipality of Tromsø at date of study enrolment (n=12), subjects with VTE before baseline (n=113) and subjects with missing values for spirometry measures (n=806) were excluded. Accordingly, 8646 subjects were included in the study, and were followed from the date of inclusion until the end of follow-up, December 31, 2011 (fig. 1).

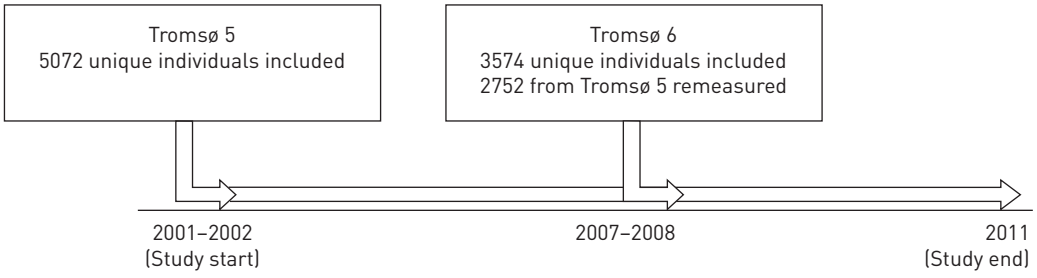

FIGURE 1 Overview of study inclusion. A total of 8646 unique individuals were included in the study. Of these, 2320 individuals participated in Tromsø 5 only, 3574 participated in Tromsø 6 only, and 2752 participated in both surveys, resulting in 11 398 observational periods.

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Baseline measurements

Data were collected using physical examination, blood samples and self-administrated questionnaires. Height and weight were measured with subjects wearing light clothes and no shoes, and body mass index (BMI) was calculated ($kg \cdot m^{-2}$). Baseline information on current smoking, self-reported history of cardiovascular disease (myocardial infarction, stroke or angina) and diabetes was collected from the questionnaire. Nonfasting blood samples were collected from an antecubital vein. Serum was prepared by centrifugation after 1 h respite at room temperature, and analysed at the Department of Clinical Chemistry, University Hospital of North Norway (Tromsø, Norway). Information on incidence of cancer before inclusion and during follow-up was obtained from the Cancer Registry of Norway [24].

Calibration of the spirometer was performed every morning and upon machine demand. The subjects were seated and using a nose clip, and were instructed to blow as long as possible and for ⩾6 s. At least three exhalations were required. The American Lung Association criteria for spirometry testing were followed [25]. Current drug therapy was not interrupted before the test. Reversibility tests were not performed. Predicted values of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC (FEV_1 % predicted) were calculated according to Langhammer *et al.* [26]. Spirometry was accepted in subjects who expired for >3 s. To avoid misclassification of healthy subjects as having obstructive lung disease, those with FEV_1/FVC <0.7 or FEV_1 <80% pred were excluded from the analyses if peak expiratory flow was <3× forced expiratory flow at 75% of FVC. Spirometry was performed using a SensorMedics VmaxLegacy 20 (Viasys Healthcare Respiratory Technologies, Yorba Linda, CA, USA) in Tromsø 5, and the Vmax Encore 20 (Viasys Healthcare Respiratory Technologies) in Tromsø 6. Use of different spirometers in longitudinal studies may introduce bias [27]. The change in spirometers caused an increase in FEV_1 of 2.5% and FVC of 5.2% from the Tromsø 5 to the Tromsø 6 survey [28]. Therefore, we adjusted the Tromsø 5 levels to accord with the Tromsø 6 levels.

The subjects were allocated into four groups based on lung function according to the GOLD guidelines [22]. Few subjects had severe obstruction, therefore participants with COPD stages III and IV (FEV_1/FVC ratio <0.7 combined with a FEV_1 <50% pred) were merged into one category for the analyses.

Outcome assessment

All incident VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway as previously described [29]. The University Hospital of North Norway is the only hospital in the region, and all diagnostic radiology and hospital care is provided exclusively by this hospital. The medical record for each potential case of VTE was reviewed by trained personnel, and a VTE was considered verified and recorded when the presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion–ventilation scan, pulmonary angiography or autopsy) and resulted in a VTE diagnosis that required treatment, as previously described in detail [29]. VTE cases derived from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or a significant condition associated with death. The VTEs were classified as unprovoked or secondary depending on the presence of provoking factors at the time of diagnosis, and the secondary events were further classified into provoked and cancer-related events. Provoking factors were recent surgery or trauma within the previous 8 weeks, acute medical conditions (acute myocardial infarction, ischaemic stroke or major infectious disease), immobilisation (bed rest >3 days, wheelchair use or long-distance travel of >4 h duration within the 14 days prior to the event) or other presumable provoking factor specifically described by a physician in the medical record (*e.g.* intravascular catheter). Cancer-related VTE was defined as VTE events occurring in patients with active cancer (*i.e.* patients with overt cancer who were receiving treatment or surveillance for their cancer diagnosis).

Information on date of death was obtained from the National Population Registry of Norway.

Statistical analyses

For each participant, person-years of follow-up were accrued from the date of enrolment to the date a VTE was diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or to the end of the study period (December 31, 2011). Subjects who died (n=914) or moved from Tromsø (n=318) during follow-up were censored at the date of migration or death. We used a time-varying analysis that allowed participants (n=2752) who were re-measured in Tromsø 6 to change their stage of COPD over time. Thus 8646 individuals contributed with 11 398 observational periods. This is graphically illustrated in figure 1.

Statistical analyses were performed using Stata (version 13.0; Stata Corporation, College Station, TX, USA). The significance level was 0.05. Crude incidence rates (IR) with 95% confidence intervals were calculated and expressed as number of events per 1000 person-years. Cox-proportional hazards regression models, with stages of COPD and potential confounders entered as time-varying covariates were used to estimate

hazard ratios (HR) with 95% CI for VTE across stages of COPD. Age was used as timescale, and the hazard ratios were estimated in sex-adjusted analyses, and in a multivariable model including sex, BMI, current smoking and history of cardiovascular disease. In addition, incidence rates and hazard ratios for PE and DVT, as well as provoked and unprovoked VTE were calculated separately. The proportional hazard assumption was tested using Schoenfeld residuals, and statistical interactions between COPD and sex were tested by including cross-product terms in the proportional hazards model. No statistical interactions between COPD and sex were found.

Hypothetically, death may prevent the observation of a future VTE during the follow-up period, and consequently the cause-specific hazard ratios may overestimate the risk of VTE in COPD patients. Since the overall risk of mortality was expected to be different across stages of COPD, we also calculated sub-hazard ratios taking competing risk of death into account by using the model described by Fine and Gray [30].

Finally, Cox-regression models were applied to investigate the impact of COPD stages on mortality in patients without and with VTE. In these analyses, both stages of COPD and VTE status were entered as time-varying covariates.

Results

The distribution of baseline characteristics across stages of COPD is shown in table 1. The frequency of self-reported symptoms of dyspnoea, daily cough and chest wheezing was higher in stage IV, as were the numbers of current smokers and pack-years among both current and former smokers. There were no differences in the distribution of comorbidities (cancer, cardiovascular disease and diabetes) between the different stages.

There were 215 validated VTEs during a median of 6.2 years of follow-up. In total, 50.5% presented with a clinically symptomatic PE with or without concurrent DVT, whereas 49.5% were DVTs only (table 2). Moreover, 37.2% of the events were unprovoked. Cancer was the most frequent provoking factor and 30.9% of the VTE patients had a cancer-related VTE.

The total follow-up time was 57 190 person-years, and the overall crude incidence rate was 3.76/1000 person-years (table 3). There was no linear increase in the risk of VTE across stages of COPD (multivariable p-value for trend=0.2). However, there was a threshold effect, and patients with COPD stage III/IV had a 1.6-fold higher risk of VTE than those without COPD (HR 1.61, 95% CI 0.90–2.93). Moreover, subjects with COPD stage III/IV

TABLE 1 Distribution of characteristics in 11 398 observation periods (generated by 8646 unique individuals) across stages of chronic obstructive pulmonary disease (COPD) according to Global Initiative for Chronic Obstructive Lung Disease guidelines

	Normal	COPD		
		Stage I	Stage II	Stage III/IV
Observation periods	77.8 (8869)	9.2 (1051)	10.8 (1226)	2.2 (252)
Male	41.4 (3323)	48.9 (549)	49.7 (722)	57 (156)
Age years	63.0±9.5	67.7±9.2	67.8±8.4	69.3±7.6
FEV_1 L	2.7±0.7	2.6±0.7	1.9±0.5	1.1±0.3
FVC L	3.6±1.0	3.9±1.0	3.1±0.8	2.3±0.7
FEV_1/FVC %	76.6±4.0	66.4±3.5	62.6±6.0	49.9±10.1
FEV_1 % predicted	93.5±14.2	91.3±9.5	67.5±8.3	40.2±8.4
Dyspnoea[#]	2.8 (146)	3.9 (31)	5.9 (61)	19.5 (38)
Daily cough	16.7 (917)	21.6 (183)	31.0 (342)	49.2 (102)
BMI kg·m^{-2}	27.3±4.1	25.5±3.7	26.2±4.2	26.1±4.2
Smoking				
Current	18.0 (1582)	29.6 (308)	41.7 (501)	47.2 (119)
Former	42.7 (3784)	47.7 (499)	42.2 (518)	39.7 (100)
Pack-years current	19.7±12.6	21.5±12.7	23.5±14.8	26.0±16.1
Pack-years former	12.7±12.6	16.6±15.9	19.5±15.9	27.7±18.3
History of cancer	7.7 (616)	10.5 (118)	10.0 (145)	13.9 (38)
History of CVD	13.6 (1092)	16.5 (185)	24.4 (354)	28.2 (77)
Diabetes	5.3 (307)	3.76 (34)	5.1 (59)	6.2 (14)

Data are presented as mean±SD or % (n). COPD stages III and IV are combined. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; CVD: cardiovascular disease. [#]: dyspnoea when walking calmly.

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TABLE 2 Characteristics of the venous thromboembolism (VTE) events during follow-up

Events	215
Male	47.3 (101)
Deep vein thrombosis	49.5 (106)
Pulmonary embolism	50.5 (109)
Unprovoked events	37.2 (79)
Clinical risk factors	
Oestrogen[#,¶]	1.9 (4)
Pregnancy/puerperium[¶]	0 (0)
Heredity[+]	1.9 (4)
Other medical conditions[§]	17.3 (37)
Provoking factors	
Surgery	16.4 (35)
Trauma	8.4 (18)
Acute medical conditions	17.1 (37)
Cancer	30.9 (68)
Immobility[f]	18.4 (42)
Other[##]	6.9 (15)

Data are presented as n or % (n). [#]: current use of oestrogens or oral contraceptives; [¶]: proportion of female subjects; [+]: VTE in first-degree relative aged <60 years; [§]: myocardial infarction, ischaemic stroke, heart failure, chronic obstructive pulmonary disease, myeloproliferative disorders, inflammatory bowel disease and chronic infections within the last year; [f]: bed rest >3 days in the previous 14 days, confinement to wheelchair, travel by car, boat, train or by air lasting >4 h within the previous 14 days, or other type of immobilisation; [##]: other provoking factor specifically described in the medical record (*e.g.* intravascular catheter).

had a two-fold higher risk of secondary VTE compared to subjects with normal airflow (HR 2.05, 95% CI 1.02–4.10) and similar risk estimates were found in subgroup analyses of provoked VTE (HR 1.71, 95% CI 0.60–4.88) and cancer-related VTE (HR 2.28, 95% CI 0.88–5.91). The hazard ratio of PE in subjects with COPD stage III/IV *versus* normal airflow was 1.83 (95% CI 0.83–4.02) (table 3).

When competing risk of death was taken into account, the relative risk estimates were attenuated, but still, subjects with COPD stage III/IV had ∼40% increased risk of VTE compared to those with normal airflow (multivariable subdistribution HR 1.39, 95% CI 0.76–2.55) (online supplementary table 1).

The mortality rates and hazard ratios of mortality according to stages of COPD and VTE status are shown in table 4. Overall, COPD patients with VTE had a five-fold (HR 5.54, 95% CI 4.01–7.66) higher risk of dying than those without VTE. Moreover, within the different stages of COPD both the absolute risks and the relative risks of mortality were higher in VTE patients than in patients without VTE (table 4 and fig. 2). Patients with COPD stage III/IV and VTE had a mortality rate of 50.2% per year and an 11-fold (HR 10.88, 95% CI 5.26–22.52) higher risk of death compared to those without VTE (table 4).

Discussion

We have investigated the impact of COPD on risk of VTE, and the impact on VTE on all-cause mortality in COPD patients, in a cohort recruited from the general population with validated exposures and outcomes. Subjects with severe COPD had a 1.6-fold higher risk of VTE compared to those with normal airflow. The risk of VTE, particularly PE, by COPD was driven by secondary events, and no association was found between COPD and unprovoked VTE events. However, the confidence intervals were wide, and the risk estimates derived from the association between COPD and VTE should therefore be interpreted with caution. Additionally, we found that VTE was a strong predictor of all-cause mortality in COPD patients, particularly among those with severe COPD.

A few registry-based studies have previously investigated the relationship between COPD and VTE. In general, low specificity of COPD diagnosis, limited information on important confounders and lack of objective outcome validation may limit the validity of studies based on administrative registry data only. Our risk estimates for PE were lower than those from the UK General Practice Research Database (GPRD) study [11], the US healthcare database study [12], Taiwan's National Health Insurance Database [14] and the Saskatchewan database [13] which reported a 2.5-fold, 2.7-fold, 3.5-fold and five-fold higher risk of PE, respectively. These studies treated COPD as a dichotomous variable and were therefore unable to look at the degree of airflow obstruction and risk of VTE, while we found a threshold effect at stage III/IV according to the GOLD criteria. Similar to the UK GPRD study [11], we found that those with severe COPD had a 1.4-fold higher risk of DVT, although this association was not statistically significant.

TABLE 3 Incidence rates and hazard ratios for total, unprovoked and secondary venous thromboembolism (VTE) by stage of chronic obstructive pulmonary disease (COPD) according to Global Initiative for Chronic Obstructive Lung Disease guidelines

	Person-years	VTE	Incidence rate (95% CI)[#]	HR (95% CI)[¶]	HR (95% CI) [+]
All VTE					
Normal	41744	137	3.3 (2.8–3.9)	1 (reference)	1 (reference)
Stage I	5912	26	4.4 (3.0–6.3)	0.98 (0.64–1.50)	1.02 (0.66–1.57)
Stage II	8008	40	5.0 (3.7–6.8)	1.09 (0.76–1.56)	1.12 (0.78–1.62)
Stage III/IV	1526	12	7.9 (4.5–13.8)	1.61 (0.90–2.93)	1.60 (0.88–2.92)
p-value for trend				0.2	0.2
Unprovoked VTE					
Normal	41744	55	1.3 (1.0–1.7)	1 (reference)	1 (reference)
Stage I	5912	6	1.0 (0.5–2.3)	0.55 (0.24–1.29)	0.62 (0.26–1.46)
Stage II	8008	15	1.9 (1.1–3.1)	1.00 (0.56–1.78)	1.07 (0.59–1.95)
Stage III/IV	1526	3	2.0 (0.6–6.1)	0.99 (0.31–3.25)	1.04 (0.32–3.39)
p-value for trend				0.8	1.0
Secondary VTE					
Normal	41744	82	2.0 (1.6–2.4)	1 (reference)	1 (reference)
Stage I	5912	20	3.4 (2.2–5.2)	1.28 (0.78–2.10)	1.27 (0.76–2.12)
Stage II	8008	25	3.1 (2.1–4.6)	1.16 (0.73–1.82)	1.14 (0.72–1.83)
Stage III/IV	1526	9	5.9 (3.1–11.3)	2.05 (1.02–4.10)	1.97 (0.97–3.99)
p-value for trend				0.1	0.1
Provoked VTE					
Normal	41744	39	0.9 (0.7–1.3)	1 (reference)	1 (reference)
Stage I	5912	12	2.0 (1.0–3.4)	1.39 (0.71–2.74)	1.53 (0.76–3.06)
Stage II	8008	14	1.7 (1.0–3.0)	1.27 (0.68–2.35)	1.25 (0.66–2.37)
Stage III/IV	1526	4	2.6 (1.0–7.0)	1.77 (0.63–5.00)	1.71 (0.60–4.88)
p-value for trend				0.2	0.3
Cancer-related VTE					
Normal	41744	43	1.0 (0.8–1.4)	1 (reference)	1 (reference)
Stage I	5912	8	1.4 (0.7–2.7)	1.05 (0.49–2.25)	1.04 (0.49–2.25)
Stage II	8008	11	1.4 (0.8–2.5)	1.03 (0.53–2.03)	1.04 (0.52–2.07)
Stage III/IV	1526	5	3.3 (1.4–7.9)	2.33 (0.91–5.95)	2.28 (0.88–5.91)
p-value for trend				0.3	0.3
PE					
Normal	41744	68	1.6 (1.3–2.1)	1 (reference)	1 (reference)
Stage I	5912	15	2.5 (1.5–4.2)	1.12 (0.64–1.96)	1.21 (0.68–2.14)
Stage II	8008	19	2.4 (1.5–3.7)	1.01 (0.60–1.69)	1.01 (0.60–1.72)
Stage III/IV	1526	7	4.6 (2.2–9.6)	1.83 (0.83–4.02)	1.80 (0.81–3.99)
p-value for trend				0.4	0.4
DVT					
Normal	41744	69	1.7 (1.3–2.1)	1 (reference)	1 (reference)
Stage I	5912	11	1.9 (1.0–3.4)	0.84 (0.44–1.60)	0.82 (0.41–1.61)
Stage II	8008	21	2.6 (1.7–4.0)	1.18 (0.72–1.93)	1.22 (0.73–2.04)
Stage III/IV	1526	5	3.3 (1.4–7.9)	1.38 (0.55–3.45)	1.39 (0.55–3.51)
p-value for trend				0.5	0.4

Data are presented as n, unless otherwise stated. PE: pulmonary embolism; DVT: deep vein thrombosis. [#]: per 1000 person-years; [¶]: age was timescale; adjusted for sex; [+]: adjusted for age, sex, current smoking, body mass index and self-reported cardiovascular diseases (myocardial infarction, angina or stroke).

Data from clinical registries have shown that PE presents more frequently than DVT in patients with COPD [31] or asthma [32]. Accordingly, we observed higher risk estimates of PE than DVT in subjects with severe COPD. A COPD patient with an exacerbation would symptomatically resemble a patient with an acute PE, and in many cases the two conditions cannot be distinguished clinically. This may result in either an overdiagnosis or an underdiagnosis of PE. Awareness of a high prevalence of PE in hospitalised COPD patients among clinicians [1, 10], may entail a preponderance to impose diagnostic procedures for detecting this disease. Presence of detection bias would lead to an overestimation of the association and could potentially explain the higher risk estimates for nonvalidated PEs observed in the registry-based studies [11–14] compared to our study and clinical registries [31, 32]. Moreover, detection bias could also partly explain the strong association of COPD with PE rather than with DVT as found in most studies.

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TABLE 4 Mortality rates per 100 person-years and hazard ratios of death according to stage of chronic obstructive pulmonary disease (COPD) and venous thromboembolism (VTE) status according to Global Initiative for Chronic Obstructive Lung Disease guidelines

	VTE	Person-years	Deaths	Mortality rate (95% CI)	HR (95% CI)#	HR (95% CI)#
COPD		15 654	431	2.8 (2.5–3.0)	1.00 (reference)	
COPD and VTE		194	41	21.2 (15.6–28.7)	5.54 (4.01–7.66)	
COPD stage						
I	No	5947	118	2.0 (1.7–2.4)	1.00 (reference)	1.00 (reference)
I	Yes	70	12	17.1 (9.7–30.1)	7.02 (3.83–12.85)	7.45 (4.10–13.5)
II	No	8170	227	2.8 (2.4–3.2)	1.00 (reference)	1.37 (1.09–1.72)
II	Yes	104	19	18.3 (11.7–28.7)	4.18 (2.60–6.73)	5.57 (3.41–9.09)
III/IV	No	1537	86	5.6 (4.5–6.9)	1.00 (reference)	2.54 (1.92–3.36)
III/IV	Yes	20	10	50.2 (27.0–93.3)	10.88 (5.26–22.52)	24.60 (12.73–47.55)

Data are presented as n, unless otherwise stated. #: age is timescale, adjusted for sex.

Any association between COPD and risk of VTE may be affected by confounders. Smoking is the leading cause of COPD [33] and is also associated with risk of VTE in some [34, 35], but not all [36, 37], cohort studies. In our study, the impact of COPD on the risk of VTE remained unchanged after adjustment for smoking. Smoking is associated with both COPD and cancer, and cancer is a strong risk factor for VTE. Thus, the observed association between COPD and VTE could be confounded by a higher rate of cancer in COPD patients during follow-up. Using cause-specific analyses, we showed that the risk of VTE in severe COPD patients was not explained by cancer. Our finding of a relationship between the severity of COPD and risk of VTE could be biased by poorer prognosis of patients with severe COPD. When competing risk of death was taken into account, the risk estimates were only slightly attenuated, from 1.6 to 1.4.

Immobilisation, bronchial superinfection, right ventricular failure and repeated hospitalisations have been suggested as precipitating risk factors for VTE in COPD patients. Previous registry-based studies [11–14] have not been able to differentiate between VTE occurring in the absence (unprovoked VTE) or presence (provoked VTE) of such factors. We found a higher risk of provoked VTE, which suggests that the risk of VTE in patients with COPD was most likely caused by concomitant provoking factors such as immobilisation for acute exacerbation of COPD or infections.

Even though it is well known that COPD is associated with several comorbidities and poor prognosis, limited knowledge exists on how these diseases contribute to the prediction of mortality in COPD patients. Recent results from a cohort of COPD patients with simultaneous registration of comorbidities revealed that some of these diseases predicted mortality in COPD patients [21]. In our study, we found that occurrence of a VTE was associated with higher all-cause mortality in COPD patients, particularly among those with severe COPD. Our findings suggest that a VTE event has prognostic impact in COPD patients.

Strengths of our study include the recruitment of subjects from the general population, long-term follow-up with repeated measurements of exposure and confounders, and thorough identification and validation of

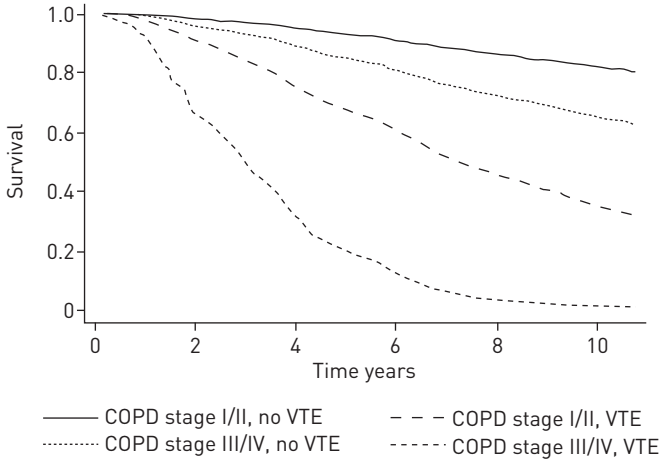

FIGURE 2 Age and sex-adjusted survival curves according to stages of chronic obstructive pulmonary disease (COPD) and venous thromboembolism (VTE) status.

outcomes. Measuring airflow using spirometry allowed us to grade an individual's stage of COPD according to GOLD guidelines. Status on potential confounders was assessed each time spirometry was (re-)measured, and we adjusted for these in the time-dependent analyses. The cohort design ensured a clear temporal sequence between exposure and outcome, and that potential exposure misclassification would be nondifferential (*i.e.* not related to the outcome and thereby diluting the observed effect). Some limitations merit consideration. The statistical power was low in some subgroups, resulting in wide confidence intervals. We detected a HR of 1.6 in severe COPD *versus* normal airflow. However, due to the low prevalence of severe COPD, the statistical power of this analysis was only 20%, indicating a high chance of type II error (failure to reject a false null hypothesis). To be able to detect a hazard ratio of 1.6 with 80% power, we would have needed a cohort of ~40 000 individuals. COPD exacerbations are related to hospitalisation, immobilisation, infections and other conditions that may predispose for VTE. Unfortunately, we did not have detailed information on hospital-related factors during follow-up for all individuals, and could therefore not investigate the role of these factors with regard to VTE risk in COPD patients. Finally, our spirometry measures were carried out without a test of reversibility. Consequently, some subjects with asthma may have been misclassified as having COPD. This potential misclassification would be nondifferential, and would most likely lead to an underestimation of the true association due to regression dilution bias.

In conclusion, severe COPD was associated with increased risk of secondary VTE, implying that the association was dependent upon the presence of provoking factors of VTE or cancer in COPD patients. Although our results were obtained from a relatively large population cohort, the number of events was low in some subgroups, and the risk estimates for the association between COPD and VTE should therefore be interpreted with caution. Additionally, we found that VTE was a strong predictor of all-cause mortality among COPD patients.

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