



Incidence of venous thromboembolism in COPD: linking inflammation and thrombosis?

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Impact of systemic inflammation to an increased prevalence and incidence of VTE in COPD patients <http://ow.ly/UgU1a>

Chronic obstructive pulmonary disease (COPD) is a major health burden and expected to become the third leading cause of death by 2030 [1, 2]. Acute exacerbations with aggravation of respiratory symptoms are associated with an acceleration of progressive lung function decline and significant worsening of prognosis (in-hospital mortality rate, 10%; 3-year mortality rate, 49%) [2]. Management of patients with COPD presenting with worsening dyspnoea remains challenging and, in approximately one-third of cases, the underlying cause cannot be identified [2]. Importantly, evidence is accumulating that, in a relevant proportion of patients presenting with symptoms of an exacerbation of COPD, the underlying condition is an acute episode of pulmonary embolism. Of all the studies published over the past 10 years, which investigated the prevalence of pulmonary embolism in patients hospitalised for exacerbation of COPD [3–12] (table 1), those with a prospective study design including a standardised protocol for pulmonary embolism examination (highlighted in bold in table 1 [3, 5–7, 9–11] reported a high prevalence of pulmonary embolism (14.4% (203 of 1406 patients); range 3.3–29.1%). On the other hand, retrospective population data from 58 392 000 patients hospitalised with COPD from 1979 to 2003 registered in the United States National Hospital Discharge Survey suggest that, in patients with COPD, both deep vein thrombosis (632 000 patients (1.08%)) and pulmonary embolism (381 000 patients (0.65%)) are generally underdiagnosed in clinical practice [13]. Furthermore, in a retrospective observational study including 436 consecutive patients with acute pulmonary embolism, COPD was identified as an independent predictor of a delayed diagnosis [14]. Given the therapeutic and prognostic implications of a (missed) diagnosis of acute pulmonary embolism, it appears crucial to increase awareness of this clinical condition [15], identify predictors of pulmonary embolism in patients with COPD exacerbation [11] and incorporate pulmonary embolism into the differential diagnosis work-up of COPD patients presenting with worsening dyspnoea.

In the present issue of the *European Respiratory Journal*, BØRVIK *et al.* [16] provide an analysis of 8646 men and women included in the Tromsø study in 2001/2002 and 2007/2008 followed until the end of 2011 (giving a total follow-up time of 57 190 person-years) [16]. The reported incidence of venous thromboembolism was slightly higher (215 events in a median follow-up time of 6.2 years; overall incidence rate, 3.8 per 1000 person-years) compared with previous reports [17, 18], probably explained by the inclusion of patients at least 30 years of age in the Tromsø study and with a mean age of >60 years in the present cohort. Recently, the incidence rate of venous thromboembolism in the general population was

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TABLE 1 Prevalence of pulmonary embolism in patients hospitalised for exacerbation of COPD

First author [ref.]	Year	Country	Observation period	Study design	Patients n	Prevalence of pulmonary embolism n (%)
SHAPIRA-ROOTMAN [3]	2015	Israel	Feb 2010–Aug 2010	Prospective, single centre, standardised protocol for pulmonary embolism examination (patients with D-dimer levels >500 µg·L⁻¹ underwent CTPA on admission)	49	9 (18.4)
Bahloul [4]	2015	Tunisia	5-year period	Retrospective, single centre, critical ill patients admitted to intensive care unit were investigated (51 patients [38.9%] underwent CTPA)	131	23 (17.5)
Akpinar [5]	2014	Turkey	May 2011–May 2013	Prospective, single centre, standardised protocol for pulmonary embolism examination (all patients underwent CTPA with 24 h of admission)	172	50 (29.1)
CHOI [6]	2013	South Korea	Aug 2008–July 2011	Prospective, single centre, standardised protocol for pulmonary embolism examination (all patients underwent CTPA within 24 h of admission)	103	5 (4.9)
RISTIĆ [7]	2013	Serbia	Jan 2011–Nov 2012	Prospective, single centre, patients admitted to intensive respiratory care unit were investigated, standardised protocol for pulmonary embolism examination (patients with D-dimer levels >500 µg·L⁻¹ underwent CTPA)	631	68 (10.8)
DUTT and UDWADIA [8]	2012	India	Feb 2005–Feb 2007	Prospective, single centre, standardised protocol for deep vein thrombosis examination only	100	2 (2.0)
GUNEN [9]	2010	Turkey	Not provided	Prospective, single centre, standardised protocol for pulmonary embolism examination (all patients underwent CTPA within 24 h of admission)	131	18 (13.7)
RUTSCHMANN [10]	2007	Switzerland	Feb 2003–Dec 2004	Prospective, two centres, standardised protocol for pulmonary embolism examination (patients with D-dimer levels >500 µg·L⁻¹ underwent CTPA)	123	4 (3.3)
TILLIE-LEBLOND [11]	2006	France	April 1999–Dec 2002	Prospective, single centre, standardised protocol for pulmonary embolism examination (all patients underwent CTPA within 48 h of admission)	197	49 (24.9)
AKGUN [12]	2006	Turkey	Oct 2004–Feb 2005	Prospective, single centre, standardised protocol for deep vein thrombosis examination only	120	4 (3.3)

Only studies published during the past 10 years are displayed. Prospective studies using standardised protocol for pulmonary embolism examination are highlighted in bold. COPD: chronic obstructive pulmonary disease; CTPA: computed tomography pulmonary angiography.

found to range between 0.8 and 2.7 per 1000 person-years in a review of studies from Western Europe, North America, Australia and Southern Latin America [15] on the occasion of World Thrombosis Day 2014. Additionally, a strong and consistent association of increasing incidence of venous thromboembolism with increasing age was observed with an annual venous thromboembolism incidence between 2 and 7 per 1000 population among those ≥70 years of age.

Predisposing factors for venous thromboembolism include patient-related (permanent) and setting-related (temporary) risk factors and allow discrimination of “provoked” (in the presence of a temporary or reversible risk factor) from “unprovoked” events to guide therapeutic decision making regarding the duration of therapeutic anticoagulation based on the estimated risk of venous thromboembolism recurrence [19]. While single temporary predisposing factors such as hip or knee replacement are associated with a strong risk of venous thromboembolism by themselves, the contribution of comorbidities to the cumulative risk of venous thromboembolism becomes more relevant in patients with unprovoked events reflecting the

multicausal aetiology of the disease. In particular, the importance of infections and inflammatory diseases as risk factors for venous thromboembolism is increasingly being recognised [20] along with the advances in our knowledge of the complex interactions between inflammation and coagulation involving proinflammatory cytokines, chemokines, adhesion molecules, tissue factor expression, platelet, leucocyte and endothelial activation, microparticles and neutrophil extracellular traps [21]. COPD is characterised by an (local) inflammatory response by the lungs to inhaled substances, such as cigarette smoke and air pollutants. In addition, elevated levels of several circulating inflammatory markers indicate the presence of systemic inflammation which is discussed to contribute to systemic effects such as skeletal muscle dysfunction and cachexia, but also to the initiation and worsening of comorbidities, such as cardiovascular disease, diabetes mellitus and osteoporosis [2, 22]. Moreover, smoking itself (in the absence of COPD) has been shown to induce a low-grade systemic inflammatory response [23], to influence platelet-dependent arteriosclerosis and to interplay with plasmatic coagulation, and thus promotes venous thrombus formation [24]. Therefore, based on the concept of “inflammation-induced thrombosis”, it can be anticipated that COPD patients may have a higher incidence of both arterial and venous thrombotic events.

Indeed, in the present study by BØRVIK *et al.* [16], patients with COPD (any stage) had a higher overall venous thromboembolism incidence rate (5.0 per 1000 person-years, 78 events in 15446 person-years) compared with non-COPD patients (3.3 per 1000 person-years, 137 events in 41744 person-years). Consistently, in 35772 patients with COPD investigated using the General Practice Research Database in the UK, the risk of deep vein thrombosis (OR 1.35, 95% CI 0.97–1.89) and pulmonary embolism (OR 2.51, 95% CI 1.62–3.87) was increased if compared to randomly matched COPD-free comparison patients in a nested-case control analyses [25]. Similarly, in a retrospective cohort study including 11493 patients diagnosed with COPD in 1997–2000 in Canada, the risk for cardiovascular events such as pulmonary embolism (OR 5.46, 95% CI 4.25–7.02) was elevated compared with 1:1 age- and sex-matched controls [26]. A population-based cohort study using data retrieved from Taiwan’s National Health Insurance Research Database containing as many as 99% of Taiwanese healthcare data, observed an almost four-times higher incidence of pulmonary embolism in 355878 COPD patients (1.23 per 1000 person-years) compared with 355878 non-COPD patients (0.32 per 1000 person-years; HR 3.79, 95% CI 3.44–4.18) [27]. Of note, the relatively low overall annual incidence of pulmonary embolism reported in this study is consistent with recent findings indicating a lower venous thromboembolism incidence in Asian countries compared with Western populations [15]. The study by BØRVIK *et al.* [16] is in accordance with these data reporting a higher pulmonary embolism incidence rate in COPD patients (2.7 per 1000 person-years, 41 events in 15446 person-years) compared with non-COPD patients (1.6 per 1000 person-years, 68 events in 41744 person-years). Further evidence in line with these observations, although less pronounced, is provided by recent studies demonstrating a higher incidence of pulmonary embolism in patients with asthma: In 31356 asthma patients from Taiwan’s National Health Insurance Research Database, the incidence of pulmonary embolism was higher (0.10 per 1000 person-years) compared with 125157 individuals without asthma (0.03 per 1000 person-years; HR 3.24, 95% CI 1.74–6.01) [28, 29]. Additionally, the incidence of pulmonary embolism was higher in Dutch patients with severe asthma (0.93 per 1000 person-years) compared with mild-to-moderate asthma (0.33 per 1000 person-years) and a general population in Norway (0.18 per 1000 person-years) [30].

Despite the consistency of these data, however, the association between venous thromboembolism and COPD is more complex to prove than one might think. In fact, the results of the age- and sex-adjusted Cox-proportional hazard regression models aiming to describe the risk of venous thromboembolism during long-term follow-up in patients with COPD, shown in table 3 of Børvik *et al.* [16], appear to challenge the key message of the study “that patients with severe COPD may have an increased risk of secondary [venous thromboembolism]”. After stratifying COPD patients in different stages of disease severity and splitting venous thromboembolism events in the clinical presentation (deep vein thrombosis *versus* pulmonary embolism) and presence of provoking factors (provoked *versus* unprovoked venous thromboembolism), the authors found that COPD stage III/IV was associated with a 2-fold increased risk of secondary venous thromboembolism (defined as provoked or cancer-related venous thromboembolism) compared with subjects with normal spirometry findings (HR 2.05, 95% CI 1.02–4.10) while all other subgroup analyses failed to demonstrate a significant increase in the risk estimates (table 3 of BØRVIK *et al.* [16]). Furthermore, this finding was based on nine patients only (0.1% of the overall patient population) and unsurprisingly loses statistical significance after adjustment for age, sex, current smoking, body mass index and self-reported cardiovascular disease. The authors should be congratulated for their attempt to provide data demonstrating an increased risk for venous thromboembolism during the long-term course of COPD; however, given the statistical limitations, the presented analysis and the discussion of the study findings appear constrained and constricted, and further evidence is clearly needed to consolidate the thesis about the increased risk of venous thromboembolism in COPD patients.

In conclusion, evidence is accumulating that in COPD patients presenting with increasing dyspnoea, the differentiation of acute exacerbation from acute pulmonary embolism, which may be present in up to 29% of patients (table 1), is crucial to guide optimal management. In contrast, data regarding the incidence of venous thromboembolic events in COPD patients during the long-term course are still limited. The present study of Børvik *et al.* [16] adds to this knowledge by demonstrating a higher incidence rate of venous thromboembolism during a long-term observation period in individuals with COPD compared with persons without COPD included in a large population-based study in Norway. Although many systemic inflammatory diseases (such as inflammatory bowel diseases) and acute infections (such as pneumonia and urinary tract infections) have been identified to be associated with a thrombotic tendency and increased risk of venous thromboembolism [20], further studies are warranted to confirm and better understand the impact of systemic inflammation on the development and progression of cardiovascular comorbidities, and venous thromboembolism in particular, in COPD patients. Given the prognostic implications of cardiovascular events in COPD, further efforts should be taken to address the clinical relevant question on the need of prophylactic antiplatelet, anticoagulant and/or anti-inflammatory treatment in specific scenarios, and on the duration of anticoagulation after an episode of “inflammation-induced venous thromboembolism”.

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