ERJ Express. **Published on September 1, 2011 as doi: 10.1183/09031936.00058811**

Word counts for the text: 2857/3000, and abstract: 195/200

Clinical presentation and outcome of venous thromboembolism in chronic obstructive pulmonary disease.

Laurent BERTOLETTI[1,2,3], laurent.bertoletti@gmail.com, MD;

Sara QUENET[1], sara.quenet@chu-st-etienne.fr, MS;

Patrick MISMETTI[1,2,3], patrick.mismetti@chu-st-etienne.fr, MD, PhD;

Luis HERNÁNDEZ[4], hernandez_lui@gva.es, MD PhD;

Juan José MARTÍN-VILLASCLARAS[5], jjvillas@gmail.com, MD;

Carlos TOLOSA[6], CTolosa@tauli.cat, MD. PhD;

Mariano VALDÉS[7], mvaldes@gencat.cat, MD ;

Manuel BARRÓN[8], mbarronm@riojasalud.es, MD ;

José A. TODOLÍ[9], jo.todolip@comv.es, MD. PhD;

Manuel MONREAL[10], mmonreal.germanstrias@gencat.cat, MD PhD and the RIETE Investigators *, riete@shmedical.es.

[1]Thrombosis Research Group, EA3065, Université de Saint-Etienne, Jean Monnet, F-42023, Saint-Etienne, France;

[2] Inserm, CIE3, F- 42055 Saint-Etienne, France;

[3] Service de Médecine Interne et Thérapeutique, Hôpital Nord, CHU de Saint-Etienne, Saint-Etienne, F-42055 France;

[4]Department of Pneumonology, Hospital General Universitario de Alicante, Alicante, Spain;

[5]Department of Pneumonology, Hospital General Universitario Carlos Haya, Málaga, Spain;

[6]Department of Internal Medicine. Corporación Sanitaria Parc Taulí. Sabadell. Barcelona. Spain

[7]Department of Internal Medicine. Hospital Viladecans. Viladencans. Barcelona. Spain

[8]Department of Pneumonology. Complejo Hospitalario San Millán y San Pedro. Logroño. La Rioja. Spain.

[9] Department of Internal Medicine. Hospital Universitario La Fe. Valencia, Spain.

[10]Department of Internal Medicine. Hospital Universitari Germans Trias i Pujol. Badalona, Barcelona, Spain;

***** A full list of RIETE investigators is given in the appendix

Corresponding author:

Laurent BERTOLETTI, M.D., laurent.bertoletti@gmail.com;

Tel : +33477120285, fax : +33477127820.

Postal address: Groupe de Recherche sur la Thrombose, EA3065, Université de Saint-Etienne, 42000 Saint-Etienne, France.

Short title: “COPD and VTE”

Abstract:

Background:

Chronic Obstructive Pulmonary Disease (COPD) is a moderate risk factor for venous thromboembolism (VTE), but neither the clinical presentation nor the outcome of VTE in COPD patients is well known.

Methods:

The clinical presentation of VTE, namely pulmonary embolism (PE) or deep venous thrombosis (DVT) and the outcome at 3 months (death, recurrent VTE or bleeding) were compared between 2984 COPD patients and 25936 non-COPD patients included in the RIETE registry. This ongoing international multicentre registry includes patients with proven symptomatic PE or DVT.

Results:

PE was the more frequent VTE presentation in COPD patients (1761, 59%). PE presentation was significantly more associated with COPD patients than with non-COPD patients (OR: 1.64 [1.49 – 1.80]). During the 3-month follow-up, mortality (10.8% vs 7.6%), minor bleeding (4.5% vs 2.3%) or first VTE recurrences as PE (1.5% vs 1.1%) were significantly higher in COPD patients than in non-COPD patients. PE was the first cause of death.

Conclusions:

COPD patients presented more frequently with PE than with DVT. It may explain the worse prognosis of COPD patients, with a higher risk of death, bleeding or VTE recurrences as PE compared with non-COPD patients. Further therapeutic options are needed.

Keywords:

Chronic obstructive pulmonary disease - deep venous thrombosis - prognosis - pulmonary embolism - venous thromboembolism.

List of abbreviations:

COPD: chronic obstructive pulmonary disease

DVT: deep venous thrombosis

LMWH: Low Molecular Weight Heparin

PE: pulmonary embolism

VKA: Vitamin-K Antagonisms

VTE: venous thromboembolism

Acute pulmonary embolism (PE) and deep venous thrombosis (DVT) are manifestations of the overall disease known as venous thromboembolism (VTE). Epidemiological studies have demonstrated that DVT is the most frequent clinical presentation of VTE in general settings, with nearly two DVT for one PE[1, 2]. However, this clinical presentation may be influenced by certain risk factors. For example, total knee replacement surgery is a well-known predisposing factor for DVT[3]. Chronic Obstructive Pulmonary Disease (COPD) is a moderate predisposing factor for VTE, principally when associated with hospitalisation[3]. Post-hoc analyses of administrative healthcare databases using diagnostic codes[4-7] suggest that the increased risk of VTE in COPD patients may be manifested predominantly in the form of PE rather than DVT. An increased expression of VTE as PE in COPD patients may be problematic since the mortality of COPD patients with PE is particularly high[8, 9], and COPD has been integrated in prognostic rules as the “Simplified PESI”[10]. COPD has also been associated with inappropriate management in the case of suspected PE[11] and the evocation of PE may be challenging in COPD patients[12], because of the similarities in symptoms. The former consideration may apply particularly during COPD exacerbation[13-15], a situation in which undiagnosed PE was found in an autopsy study in up to 30% of COPD patients who died[16]. Finally, COPD have been associated with an increased risk of unsuspected fatal PE[17]. Confirming the increased rate of PE in COPD patients should prompt clinician to enhance PE suspicion in COPD patients at risk for VTE.

The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry is an ongoing, international (Spain, France, Italy, Israel, Switzerland, Germany), multi-centre, prospective registry of consecutive patients presenting with symptomatic acute venous thromboembolism (VTE). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes[18-20]. We then conducted this study with two goals: first, to check whether COPD patients really present more frequently with PE rather than DVT; second, to define the clinical characteristics and outcome of COPD patients with VTE, compared to patients with VTE

but without COPD. We were especially interested in determining if COPD influences a patient's risk of dying from PE or bleeding during treatment.

Materials and Methods

Registry design

The RIETE registry is an ongoing, international, multicentre, prospective cohort of consecutive patients with symptomatic, objectively confirmed, acute VTE (DVT, PE or both). Patients are managed according to the clinical practice of each participating hospital centre, and followed up for at least 3 months. There are only two exclusion criteria: a planned follow-up of less than 3 months and participation in a therapeutic clinical trial. For this analysis, only patients over 18 were considered.

At each participating centre, a registry coordinator controlled the quality of data collection (e.g. internal validity and coherence) and recorded the data from each patient on a computer-based case report form. Coordinators ensured that all consecutive patients with confirmed VTE were included in the registry. In addition, the database used for each analysis was controlled. The information was then transferred online, via a secure website, to the Study Coordinating Centre responsible for data management. Data quality was also monitored by members of contract research organisations, who compared the data on medical records with the data transferred online during periodic visits to the participating hospitals. All patients gave written consent to their participation in the registry, in accordance with the requirements of the ethics committee of each country. Death (and cause of death), bleeding and VTE recurrence during the follow-up were adjudicated by the RIETE registry coordinators.

Study outcomes

Baseline characteristics, thrombosis risk factors (including the presence of COPD) and clinical presentation of VTE (PE with or without DVT, DVT without any symptomatic PE) were recorded at baseline. In patients with acute respiratory symptoms suggesting PE, symptomatic

PE was confirmed if it was objectively documented (by positive helical computed tomography scan, high-probability ventilation–perfusion lung scan, positive pulmonary angiography, visualization of a thrombus in the right ventricle or in the right atrium on echocardiography, or intermediate-probability ventilation–perfusion lung scan associated with a diagnosis of DVT). DVT was diagnosed in the case of acute symptoms of DVT confirmed by compression ultrasound or contrast venography of the lower limbs. The following information was also collected: demographic data, symptoms on presentation, types and results of diagnostic methods, and risk factors for venous thromboembolism. Immobilised patients were defined as non-surgical patients who had been immobilised for ≥4 days during the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation within the 2 months prior to VTE. Patients were categorized as obese if their BMI was 30 kg/m^2 or above. The presence of COPD was assessed by the treating physician.

Information on treatment and outcome (i.e. occurrence of death, major bleeding, minor bleeding or another objectively confirmed VTE event) was also recorded at day 7 and during the 3-month follow-up period. If the patient died, death was considered to be due to PE if this diagnosis had been documented at autopsy, or if the patient died shortly after objectively confirmed symptomatic PE, and in the absence of any alternative diagnosis. Bleeding complications were classified as “major” if they were overt and required a transfusion of 2 or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal. Other types of bleeding were classified as “minor”. Each recurrent VTE event was objectively confirmed using the same criteria as for the index VTE event. Every event was adjudicated by the RIETE registry coordinators.

Data analysis

Qualitative data were reported as numbers and percentages. Quantitative data were reported as median values with the first quartile (Q1) and third quartile (Q3). A logistic regression model

was used to examine the individual relationship between each variable and the presence of COPD.

The selection of variables was based on the literature and on expert opinion. Any variable achieving a p value of less than 0.15 on univariate analysis was included in a multivariate logistic regression analysis. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated. Some COPD patients may experience a high rate of exacerbation leading to non-surgical immobilisation[21], a type of immobilisation not applicable to non-COPD patients, by definition. We therefore considered two immobilisation variables: one being “all-cause immobilisation”, the other being “immobilisation excluding immobilisation for COPD exacerbation”. The cumulative rates of death, VTE, and bleeding were estimated by the Kaplan-Meyer method and compared between COPD and non-COPD patients by the log-rank test. P values were considered statistically significant at a level of 0.05 or less. Data were processed and analysed using SAS-Windows™ software (version 9.13).

Results

Between March 2001 and October 2009, a total of 28,920 consecutive adult patients with objectively confirmed acute VTE were included in the RIETE registry. Of these, 2984 (10.3%) were diagnosed as having COPD.

Clinical characteristics and VTE presentation in COPD and non-COPD patients

In univariate analyses (Table 1), COPD was significantly associated with male gender, with a sex ratio of 2 men for 1 woman in the group of COPD patients. COPD patients were also significantly older, half of them being above 75 years old. Obesity was associated to a slightly greater extent with COPD. Regarding thrombosis risk factors, no difference in VTE history was found between COPD and non-COPD patients. COPD exacerbation was the main reason for immobilisation, accounting for about one-third of the immobilisation causes in COPD patients,

followed by acute infection. Taken together, exacerbation and infection prompted 50% of non-surgical immobilisations among COPD patients.

Regarding VTE presentation, PE (with or without DVT) was the most frequent initial clinical presentation of VTE in COPD patients (1761/2984, 59%). In the univariate analysis, COPD patients presented with PE more frequently than non-COPD patients.

In the multivariate analysis (Table 1), male gender, age over 75 and obesity remained positively associated with COPD, whereas surgery, cancer and immobilisation for non-surgical reasons (excluding COPD exacerbations) were more weakly associated with COPD. COPD remained associated with a higher risk of PE presentation than in non-COPD patients (OR: 1.64 [1.49 – 1.80])

Therapeutic strategies

Regarding initial VTE treatment, COPD patients received less often Thrombolytics (1%) or Inferior vena cava filter (1.6%) than non-COPD patients (1.5%, 2.3%, respectively). During the 3-month follow-up, COPD patients were more frequently treated with VKA (76%) than non-COPD patients (73%), and inversely less treated with LMWH (24% versus 28% for non-COPD patients).

Early and 3-month clinical outcomes

At day 7 (table III), the overall mortality was significantly higher in COPD patients (2.6%) than in non-COPD patients (1.7%) (p log-rank=0.001). PE was the cause of death in the vast majority of COPD patients (52 of the 78 deaths). There were slightly more VTE recurrences in COPD patients (0.6%) than in non-COPD patients (0.4%) but the difference was not statistically significant (p log-rank=0.09). There were more VTE recurrences as PE in COPD patients (0.6%) than in non-COPD patients (0.3%) (p=0.02). There was no statistically significant difference between the groups with regard to the cumulative incidence of major bleeding at day 7 (0.8%

versus 0.8%, p log-rank=0.76), but COPD patients had a higher 7-day cumulative incidence of minor bleeding (1.6% versus 0.6%, p log-rank<0.0001).

At 3 months (table IV), the cumulative incidence of mortality was significantly higher in VTE patients with COPD (10.8%) than in VTE patients without COPD (7.6%) (p log-rank <0.0001) (Fig 1). The main cause of death was PE (2.3%), followed by respiratory insufficiency, disseminated cancer (both 1.6%) and infection (1.2%). Global rate of VTE recurrence was similar between COPD and non-COPD patients (table IV). However, the incidence of VTE recurrences as PE during the 3-month follow-up was significantly higher in COPD patients than in non-COPD patients (1.5% versus 1.1%, p log-rank=0.04), whereas the incidence of VTE recurrences as DVT was significantly lower (0.7% versus 1.1%, p log-rank=0.05). There was no statistically significant difference between the groups with regard to the cumulative incidence of major bleeding at 3 months (2.7% versus 2.2%, p log-rank=0.16), but COPD patients had a higher 3-month cumulative incidence of minor bleeding (4.5% versus 2.3%, p log-rank<0.0001).

Discussion

These data, obtained from a multicentre clinical registry of consecutive patients with confirmed symptomatic VTE provide important information about the clinical characteristics of COPD patients presenting with acute symptomatic VTE. We confirm that COPD patients with acute symptomatic VTE present more frequently with PE than with DVT (59% vs 41%), with a 60% increase in the risk of presenting with PE rather than DVT compared to non-COPD patients with VTE. COPD patients also have a poorer 3-month prognosis than non-COPD patients, with higher rates of death, VTE recurrences as PE and minor bleeding.

Main results

The predominance of males and older patients in the COPD group is easily understood as the prevalence of COPD increases with age, and as the expected sex ratio in COPD patients

above 65 years is 2 men for 1 woman[22]. Obesity was found to be slightly more prevalent in COPD patients than in non-COPD patients with VTE, with a median BMI of 27 kg/m^2 and a BMI above 30 kg/m^2 in 30% of COPD patients with VTE. Obesity is a well-known risk factor for VTE[23]. Of note, the prevalence of obesity in our COPD patients with VTE was two-fold higher than that observed in a large primary care population of European patients with COPD[24]. The lower rate of surgery in COPD patients is easily explained by the fragility of these patients, for whom conservative options may generally be preferred.

We confirmed the results of post-hoc analyses of administrative healthcare data[4-7], finding an increased presentation of VTE as PE in COPD patients. It is possible that PE was more frequently searched for (and found) in COPD patients. By definition, COPD patients present respiratory symptoms, which can enhance the suspicion of PE. However, the chronicity and variability of symptoms, as well as the frequent exacerbations, may conversely decrease the suspicion of PE in some COPD patients. Hence, Fernandez et al[25] found that COPD patients diagnosed with PE were more likely to experience a longer delay before diagnosis than non-COPD patients. Pineda et al[17] found that COPD was associated with a higher risk of unsuspected fatal PE. We therefore cannot rule out a possible underdiagnosis of PE in COPD patients, but this would rather strengthen our results.

Concerning outcome during the 3-month follow-up, the higher mortality in the COPD group is in accordance with previous studies, in which COPD was associated with a poorer prognosis[26]. This difference is already present at day 7, mainly because of PE-related death. Interestingly, more aggressive treatment as thrombolytics or Inferior Vena Cava Filter (IVCF) have been less frequently used in COPD patients with VTE.

We did not find any statistically significant difference in the risk of major bleeding between COPD and no-COPD patients, although such a difference has been evoked in smaller studies[27]. The higher rate of minor bleeding may be explained by the co-prescription of drugs like steroids or antiplatelets, which may increase the bleeding risk in COPD patients. Moreover,

COPD patients were older than non-COPD patients, and this may also account for the differences.

Main limitations

Our study has several limitations. Some are due to the RIETE registry design. By definition, all patients included presented symptomatic and objectively confirmed VTE. However, they were diagnosed according to the clinical practice of each participating hospital centre. Therefore, we cannot exclude the possibility that some patients classified as having DVT in fact had asymptomatic and/or undiagnosed PE. This clinical classification is nevertheless frequently employed, even in randomised controlled therapeutic trials. Our results therefore cannot be extended to COPD patients with undiagnosed PE. PE may also have been underestimated in COPD patients presenting with signs of DVT and acute respiratory symptoms, as respiratory symptoms are spontaneously attributed to COPD without any screening for PE. Undiagnosed recurrent PE may explain part the high rate of mortality due to PE.

Second, results of lung function tests were not available for all our COPD patients. Diagnosis of COPD was based solely on the clinical information available to the investigator. Patients may therefore have been misclassified as COPD or non-COPD. This lack of lung function tests is unfortunately shared by many studies on this topic[28-31]. For example, data on lung function were available for only 28% of the patients included in a recent study[29] of acute exacerbation of COPD. However, the prevalence of COPD in the RIETE registry is similar to that in general settings[32] as in the above-mentioned study. Moreover, COPD is usually underdiagnosed[32], so if there was any misclassification, this would rather be underdiagnosis (i.e. classification of undiagnosed COPD patients as non-COPD patients) than overdiagnosis. Furthermore, we could not subdivide COPD patients according to different stages of severity.

Clinical Impact, unanswered questions and future research

The clinical characteristics of COPD patients with VTE shown by our study may partly explain the difference between studies searching for PE during COPD exacerbation. The patients included in the study of Rutschmann et al[33] were more similar to ours, in terms of age and sex ratio, than those included in the studies of Tillie-Leblond et al[34] and Gunen et al[35]. Similarly, the rates of past VTE (25%) or active cancer (43%) were much higher in the study of Tillie-Leblond et al[34] than in our VTE series. Selection bias may explain these differences, resulting in contradictory results.

Our results may also be viewed in a physiological perspective. Recent studies established that COPD may induce an additional specific pro-thrombotic biological situation, particularly during acute exacerbation of COPD[36, 37]. It is worth noting that only one-third of immobilised COPD patients with VTE received thrombosis prophylaxis during immobilisation. Efforts to improve thromboprophylaxis use are therefore needed. Elsewhere, links between obesity, adipokines and the abnormal inflammatory response seen in COPD are currently debated[38] and the potential effect of these interactions on pro-thrombotic states in COPD patients deserves further research. Moreover, the pulmonary arteries of COPD patients are characterised by endothelial cell dysfunction[39] and the hypothetical COPD-related pro-thrombotic status may predominate with regard to the pulmonary vascular bed, leading to *in-situ* thrombosis

Finally, more aggressive VTE treatments, such as thrombolytics or placement of a vena cava filter, have been proposed for COPD patients, particularly those presenting DVT[30], but we found them to be less frequently used in our COPD patients. IVCF might protect the reduced pulmonary vascular bed of COPD patients from PE, which constitutes the main presentation of VTE in COPD patients according to our results, without any increase in the bleeding risk. However, if we consider that PE may sometimes be an *in situ* thrombosis rather than an embolic complication of a DVT, placement of a vena cava filter might not be appropriate in the former case.

Conclusion

Our study is the largest clinical study to date focusing on clinical presentation and outcome of VTE in COPD patients. We confirmed that PE is more frequently diagnosed in COPD patients, and that such patients have a poorer prognosis than non-COPD patients, with higher rates of mortality and minor bleeding. Treatment with higher efficiency on recurrence risk but with no increase in bleeding risk deserves further evaluation.

APPENDIX

Role of individual authors

- LB designed the study
- LB, PM, LH, JJMV, CT, MV, MB, MM and the RIETE members included patients
- SQ and LB performed the statistical analyses
- LB, SQ, and PM drafted the manuscript
- All authors read and approved the manuscript

Coordinator of the RIETE Registry:	Dr. Manuel Monreal (Spain)
RIETE Steering Committee Members:	Dr. Hervè Decousus (France)
	Dr. Paolo Prandoni (Italy)
	Dr. Benjamin Brenner (Israel)
RIETE National Coordinators:	Dr. Raquel Barba (Spain)
	Dr. Pierpaolo Di Micco (Italy)
	Dr. Laurent Bertoletti (France)
	Dr. Manolis Papadakis (Greece)
	Dr. Marijan Bosevski (R.Macedonia)
	Dr. Henri Bounameaux (Switzerland)
RIETE Registry Coordinating Center:	S & H Medical Science Service

Members of the RIETE Group

SPAIN: Alcalde M, Arcelus JI, Arcos MP, Barba R, Barrón M, Blanco-Molina A, Bosco J, Cámara T, Calvo M, Casado I, Casas JM, Cisneros E, Chaves E, Conget F, Delgado C, del Toro J, Durán M, Falgá C, Fernández-Capitán C, Ferreiro M, Font C, Gabriel F, Gallego P, García-Bragado F, Guil M, Guillém N, Gutiérrez J, Hermosa MJ, Hernández L, Hernández-

Huerta D, Hernández-Toboso F, Jaras MJ, Jiménez D, Jiménez S, Jiménez-Gil M, Lecumberri R, Lobo JL, López-Jiménez L, Lorenzo A, Luque JM, Madridano O, Maestre A, , Manzano V, Marchena PJ, Martín-Villasclaras JJ, Monreal M, Monte R, Morales M, Muñoz S, Nauffal MD, Nieto JA, Ogea JL, Oribe M, Otero R, Pedrajas JM, Rabuñal R, Riera-Mestre A, Rodríguez-Dávila MA, Román M, Román P, Román-Bernal B, Rosa V, Rubio S, Ruíz J, Ruiz-Gamietea A, Ruiz-Giménez N, Sahuquillo JC, Samperiz A, Sánchez R, Sánchez Muñoz-Torrero JF, Soler S, Soto MJ, Tiberio G, Tolodí JA, Tolosa C, Torres MI, Trujillo J, Uresandi F, Valdés M, Valdés V, Valle R, Vidal G, Villalta J. Zorrilla V. **FRANCE :** Bertoletti L, Bura-Riviere A, Debourdeau P, Mahe I, Rivron-Guillot K, **GREECE:** Papadakis, M. **ISRAEL**: Brenner B, Zeltser D **ITALY:** Barillari A, Barillari G, Ciammaichella M, Di Micco P, Dalla Valle F, Duce R, Maida R , Pasca S, Piovella C, Poggio R, Prandoni P, Quintavalla R, Rocci A, Schenone A, Tiraferri E, Tonello D, Visonà A, Zalunardo B. **REPUBLIC OF MACEDONIA:** Bosevski M. **SWITZERLAND:** Bounameaux H, Righini M.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Silvy LAPORTE (St-Etienne, France) and Pr Arnaud PERRIER (Geneva, Switzerland) for their intellectual input and critical revisions, and all RIETE members for including patients. We thank Paula Harry of MediBridge (Vélizy, France) for her revision of the English text, supported by the University Hospital of Saint-Etienne. We express our gratitude to Sanofi-Aventis Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Schering Pharma for supporting this Registry. Bayer Schering Pharma's support was limited to the part of RIETE outside Spain, which accounts for a 13,39% of the total patients included in the RIETE Registry. We also thank the Registry Coordinating Center, S & H Medical Science Service, for their quality control, logistic and administrative support. Laurent BERTOLETTI thanks the "Collège des Enseignants de Pneumologie" who provided a research grant.

Tables and Figure legends

Table I

*Age in years, median (Q1-Q3); Q1 and Q3: first and third quartiles; †Prolonged immobilisation (≥ 4 days) for any non-surgical reason; BMI: body-mass index; CI: confidence interval; ns: result not statistically significant on multivariate analysis.

Table III

*: Only the first recurrent event is presented.

$^{\mu}$: including initial fatal PE and fatal PE during the follow-up.

Table IV

*: Only the first recurrent event is presented.

$^{\mu}$: including initial fatal PE and fatal PE during the follow-up.

Figure 1

Kaplan-Meier Curve of 3-month overall mortality in COPD and non-COPD patients

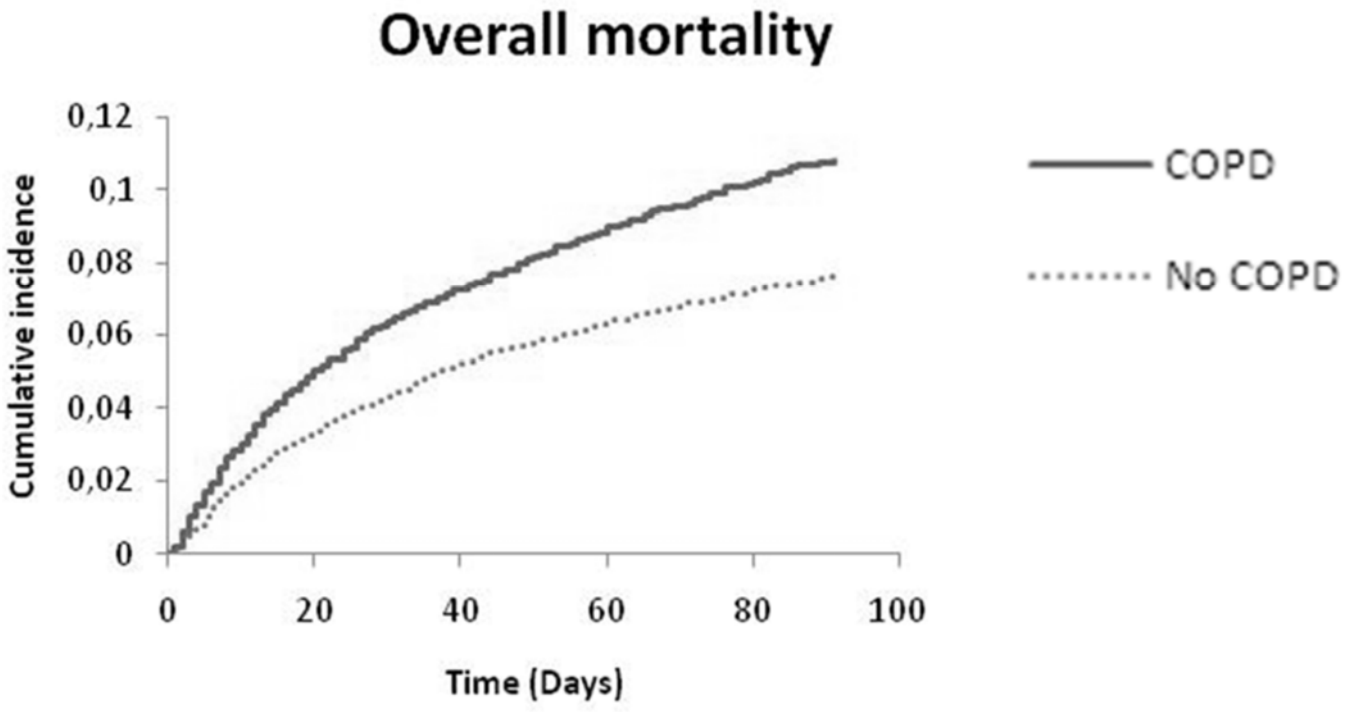

Table I. Patient characteristics at baseline, thrombosis risk factors and index VTE event for COPD *versus* non-COPD patients with VTE (univariate and multivariate analyses)

Characteristics	COPD (N=2984)	No COPD (N=25,936)	Univariate analysis COPD *versus* no COPD	Multivariate analysis COPD *versus* no COPD
	n/N (%)	n/N (%)	Odds ratio [95% CI]	Odds ratio [95% CI]
Men	2005 (67.2)	12216 (47.1)	2.30 [2.12 – 2.49]	2.72 [2.46 – 3.01]
Obesity (BMI ≥ 30 kg/m^2)	596/2022 (29.5)	4697/17385 (27.0)	1.13 [1.02 – 1.25]	1.31 [1.18 – 1.45]
Age (years)[*]	75 (68-80)	70 (55 - 78)	-	-
Age ≥ 75 years	1503 (50.4)	9519 (36.7)	1.75 [1.62 – 1.89]	2.08 [1.89 – 2.29]
Thrombosis risk factors				
Personal history of VTE	488 (16.4)	4033 (15.5)	1.06 [0.96 – 1.18]	Ns
Cancer	600 (20.1)	5534 (21.3)	0.93 [0.84 – 1.02]	0.88 [0.79 – 0.99]
Surgery within the last 2 months	239 (8.0)	3321 (12.8)	0.59 [0.52 –0.68]	0.67 [0.57 – 0.80]
Immobilisation[†]	968 (32.4)	6303 (24.3)		
COPD exacerbation	308 (32)	NA		
Trauma without surgery	88 (9)	1290 (21)		
Acute infection	208 (21)	843 (13)		
Mental disorders	57 (6)	958 (15)		
Neoplasia	39 (4)	425 (7)		
Neurological disorders	66 (7)	815 (13)		
Cardiac disorders	39 (4)	313 (5)		
Others	163 (17)	1659 (26)		
Thromboprophylaxis	306 (32)	1492 (23.7)		
Immobilisation (excluding that for COPD exacerbation)	660 (22.1)	6303 (24.3)	0.88 [0.81 – 0.97]	0.89 [0.80 – 1.00]
Index VTE event				
Symptomatic PE	1761 (59.0)	12314 (47.4)	1.59 [1.47 – 1.72]	1.64 [1.49 – 1.80]

Table II. Therapeutic strategies.

	COPD	No COPD	p- value
Patients, N	**2984**	**25936**	
Initial therapy,			
LMWH	**2773 (93%)**	**24197 (93%)**	**0.45**
Unfractionated heparin	**254 (8.5%)**	**2168 (8.4%)**	**0.77**
Thrombolytics	**30 (1.0%)**	**375 (1.5%)**	**0.053**
Inferior vena cava filter	**48 (1.6%)**	**607 (2.3%)**	**0.011**
Long term therapy,			
LMWH	**722 (24%)**	**7152 (28%)**	**<0.001**
Vitamin K antagonists	**2273 (76%)**	**19047 (73%)**	**0.001**

Table III. 7-day outcome.

	COPD	No COPD	p- value
Patients, N	**2984**	**25936**	
7-day outcome,			
Recurrent VTE*	**18 (0.6%)**	**103 (0.4%)**	**0.09**
Recurrent VTE as DVT*	**1 (0.03%)**	**24 (0.1%)**	***0.30***
Recurrent VTE as PE*	**17 (0.6%)**	**79 (0.3%)**	***0.02***
Bleeding			
Major bleeding	**25 (0.8%)**	**205 (0.8%)**	**0.76**
Minor bleeding	**46 (1.6%)**	**159 (0.6)**	**<0.0001**
Overall death	**78 (2.6%)**	**438 (1.7%)**	**0.001**
Causes of death:			
Pulmonary embolism[µ]	**52 (1.7%)**	**245 (1.0%)**	
Bleeding	**4 (0.1%)**	**29 (0.1%)**	
Disseminated cancer	**1 (0.03%)**	**45 (0.2%)**	
Sudden, unexpected	**0**	**3 (0.01%)**	
Respiratory insufficiency	**7 (0.2%)**	**18 (0.1%)**	
Heart failure	**2 (0.1%)**	**12 (0.05%)**	
Infection	**6 (0.2%)**	**30 (0.1%)**	
Myocardial infarction	**0**	**2 (0.01%)**	
Ischemic stroke	**0**	**3 (0.01%)**	
Other	**6 (0.2%)**	**51 (0.2%)**	

Table IV. 90-day outcome.

	COPD	No COPD	p- value
Patients, N	**2984**	**25936**	
90-day outcome,			
Recurrent VTE*	**63 (2.2%)**	**547 (2.2%)**	**0.89**
Recurrent VTE as DVT*	**20 (0.7%)**	**280 (1.1%)**	**0.05**
Recurrent VTE as PE*	**43 (1.5%)**	**267 (1.1%)**	**0.04**
Bleeding			
Major bleeding	**76 (2.7%)**	**564 (2.2%)**	**0.16**
Minor bleeding	**127(4.5%)**	**567 (2.3%)**	**<0.001**
Overall death	**322 (10.8%)**	**1970 (7.6%)**	**<0.001**
Causes of death:			
Pulmonary embolism[µ]	**69 (2.3%)**	**373 (1.4%)**	
Bleeding	**19 (0.6%)**	**153 (0.6%)**	
Disseminated cancer	**48 (1.6%)**	**574 (2.2%)**	
Sudden, unexpected	**6 (0.2%)**	**25 (0.1%)**	
Respiratory insufficiency	**47 (1.6%)**	**96 (0.4%)**	
Heart failure	**11 (0.4%)**	**61 (0.2%)**	
Infection	**36 (1.2%)**	**182 (0.7%)**	
Myocardial infarction	**2 (0.1%)**	**9 (0.03%)**	
Ischemic stroke	**2 (0.1%)**	**19 (0.07%)**	
Other	**80 (2.7%)**	**478 (1.8%)**	

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