Arch Bronconeumol. 2009;**45(6)**:286-290

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

Chronic Obstructive Pulmonary Disease in Patients With Acute Symptomatic Pulmonary Embolism

Carolina Fernández,[a] David Jiménez,[a,*] Javier de Miguel,[b] David Martí,[c] Gema Díaz,[d] and Antonio Sueiro[a]

[a] *Servicio de Neumología, Hospital Ramón y Cajal, Madrid, Spain*
[b] *Servicio de Neumología, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[c] *Servicio de Cardiología, Hospital Ramón y Cajal, Madrid, Spain*
[d] *Servicio de Neumología, Hospital Puerta de Hierro, Madrid, Spain*

ARTICLE INFO

Article history:
Received August 26, 2008
Accepted October 22, 2008
Available online April 25, 2009

Keywords:
Pulmonary embolism
Chronic obstructive pulmonary disease (COPD)
Prognosis

ABSTRACT

Background: The diagnosis of pulmonary embolism (PE) is often complicated by the presence of chronic obstructive pulmonary disease (COPD). Some studies have suggested that patients with PE and concomitant COPD have a worse prognosis than patients without COPD.
Patients and Methods. Outpatients diagnosed with acute symptomatic PE at a university tertiary care hospital were prospectively included in the study. Clinical characteristics, time between onset of symptoms and diagnosis, and outcome were analyzed according to presence or absence of COPD. The primary endpoint was all-cause deaths at 3 months.
Results: Of 882 patients with a confirmed diagnosis of acute symptomatic PE, 8% (95% confidence interval [CI], 6%-9%) had COPD. Patients with COPD were significantly more likely to have a delay in diagnosis of more than 3 days and to have a low pretest probability of pulmonary embolism according to a standardized clinical score. The total number of deaths during 3 months of follow-up was 128 (14%; 95% CI, 12%-17%). Factors significantly associated with mortality from all causes were a history of cancer or immobilization, systolic blood pressure less than 100 mm Hg, and arterial oxyhemoglobin saturation less than 90%. COPD was significantly associated with PE-related death in the logistic regression analysis (relative risk, 2.2; 95% CI, 1.0-5.1).
Conclusions: Patients with COPD and PE more often have a lower pretest probability and a longer delay in diagnosis of PE. COPD is significantly associated with PE-related death in the 3 months following diagnosis.

Enfermedad pulmonar obstructiva crónica en pacientes con tromboembolia de pulmón aguda sintomática

Palabras clave:
Tromboembolia de pulmón
Enfermedad pulmonar obstructiva crónica (EPOC)
Pronóstico

RESUMEN

Introducción: El diagnóstico de tromboembolia de pulmón (TEP) es a menudo complicado en pacientes con enfermedad pulmonar obstructiva crónica (EPOC). Además, algunos estudios indican que la EPOC empeora el pronóstico de los pacientes con TEP.
Pacientes y métodos: Se incluyó prospectivamente en el estudio a todos los pacientes ambulatorios diagnosticados de TEP aguda sintomática en un hospital universitario terciario. Se compararon las características clínicas, el intervalo de tiempo desde el inicio de los síntomas hasta el diagnóstico y el pronóstico en función de la presencia o ausencia de EPOC. El criterio de evaluación principal fue la muerte por todas las causas a los 3 meses.

* Corresponding author.
E-mail address: djc_69_98@yahoo.com (D. Jiménez).

0300-2896/$ - see front matter

Resultados. Se incluyó a 882 pacientes con diagnóstico confirmado de TEP aguda sintomática. La prevalencia de EPOC fue de un 8% (intervalo confianza [IC] del 95%, 6-9%). En los pacientes con EPOC, fueron significativamente más frecuentes un retraso diagnóstico de la TEP superior a 3 días y una probabilidad clínica baja según una escala clínica estandarizada. Se produjo el fallecimiento de 128 pacientes (14%; IC del 95%, 12-17%) en los primeros 3 meses de seguimiento. Los antecedentes de cáncer y de inmovilización médica, las cifras de presión arterial sistólica menores de 100 mmHg y la saturación de oxígeno inferior al 90% se asociaron de forma significativa a la mortalidad por todas las causas. El antecedente de EPOC se asoció de forma significativa a la mortalidad por TEP en el análisis de regresión logística (riesgo relativo = 2,2; IC del 95%, 1,0-5,1).

Conclusiones. Los pacientes con EPOC y TEP presentan con más frecuencia una probabilidad clínica baja y un mayor retraso en el diagnóstico de la TEP que los pacientes sin EPOC. La EPOC se asocia de manera significativa a mortalidad por TEP en los 3 meses posteriores al diagnóstico.

Introduction

Chronic obstructive pulmonary disease (COPD) is among the most prevalent in Western countries,[1,2] affecting 9% of the population over the age of 40 years and 20% of those aged over 65 years.[3] This disease is the fourth leading cause of death in Spain and puts a patient at higher risk of venous thromboembolic disease.[4] Beyond COPD itself, other risk factors, such as the presence of cancer, congestive heart failure, or immobilization, increase the risk of deep vein thrombosis or pulmonary embolism (PE) in these patients.[5] When COPD patients experience a thrombotic event, the signs and symptoms of the chronic respiratory condition may mask those of PE, complicating and delaying diagnosis.[6]

In a study of 15 531 patients discharged with a diagnosis of PE in Pennsylvania, all-cause mortality within 30 days of diagnosis was 3-fold higher in patients with a chronic respiratory disease.[7] In turn, PE has been shown to be an independent predictor of death and rehospitalization in patients with COPD.[8]

This study aimed to evaluate *a)* the impact of COPD on the diagnosis of PE in a series of consecutive patients with acute symptomatic PE, and *b)* the prognostic relevance of COPD in these patients.

Patients and Methods

Study Design

This prospective cohort study was carried out in a tertiary care hospital between January 2003 and December 2007. The hospital ethics committee approved the study, and written informed consent was obtained from each patient.

Patients and Inclusion Criteria

All patients diagnosed with acute symptomatic PE at the emergency department of Hospital Ramón y Cajal in Madrid were included consecutively. The only criteria for exclusion from analysis were participation in another study and lack of follow-up. PE was confirmed objectively. A diagnosis based on computed tomography (CT) angiography was made after demonstration of a partial intraluminal defect surrounded by contrast or evidence of complete occlusion of a pulmonary artery in 2 consecutive CT slices.[9] In cases of high pretest probability, the diagnosis was based on ventilation-perfusion scintigraphy according to the criteria of the PIOPED study[10] (at least 1 segmental perfusion defect or 2 subsegmental defects with normal ventilation). In cases of clinical suspicion of PE and inconclusive scan results, the diagnosis was based on the demonstration of a venous defect on compression ultrasound of the lower extremities as a sign of deep vein thrombosis.[11]

Interventions

Low molecular weight heparin (LMWH) therapy was administered every 12 hours for at least 5 days at weight-adjusted dosages. Between the first and third days of treatment, a vitamin K antagonist was also administered. The LMWH was discontinued when the international normalized ratio was stable and greater than 2.0 (checked according to the hospital's usual protocol).

Fibrinolytic therapy was given to patients with cardiogenic shock defined by a systolic blood pressure less than 100 mm Hg associated with clinical signs of tissue hypoperfusion. An inferior vena cava filter was inserted if anticoagulant therapy was contraindicated.

Definitions

Patients were considered to have COPD if they reported chronic respiratory symptoms and spirometry detected chronic airflow limitation (ratio of forced expiratory volume in 1 second to forced vital capacity <0.7).[12] All other patients were considered not to have COPD. Immobilization due to acute medical disease in the month before the diagnosis of PE was considered if the duration was at least 4 days. Patients were considered to have a history of cancer if there was an active tumor at the time of diagnosis of PE or if a tumor had been treated in the previous year. Recent hemorrhage was defined as clinically significant bleeding in the month prior to the diagnosis of PE.

The pretest probability of PE was determined a priori in accordance with the modified Wells scale.[13]

Episodes Analyzed

The primary endpoint was all-cause deaths during the 3 months after diagnosis. The secondary outcome measure was PE-related deaths during the same period. The cause of death was determined by consensus between 2 researchers (D.J. and D.M.) without regard to the clinical characteristics of the patients.

Statistical Analysis

Continuous variables, which are expressed as means (SD), were compared using *t* tests for paired and unpaired data. Categorical variables, which are expressed as percentages, were compared with the χ^2 test or the Fisher exact test as necessary. Variables that were significantly different between patients with and without COPD were introduced into a multivariate logistic regression model. Statistical significance was set at a value of *P* less than .05. Kaplan-Meier survival curves were used to analyze the time patients survived PE (no PE-related death) during the follow-up period. The curves for the groups with and without COPD were compared using the log-

rank test. The SPSS software package, version 14.0 was used for statistical analysis.

Results

Between January 2003 and December 2007, 937 patients were diagnosed with acute symptomatic PE in the emergency department of Hospital Ramón y Cajal. Thirty-six (4%) were excluded because they were enrolled in other studies of venous thromboembolic disease and 19 (2%) were lost to follow-up. Thus, the population analyzed comprised 882 patients (94%) with a diagnosis of acute symptomatic PE.

One hundred twenty-eight patients (14%; 95% confidence interval [CI], 12%-17%) died during the 3 months following diagnosis. Forty-seven deaths were PE-related. Other causes of death were cancer (37), infection (18), hemorrhage (6), unknown causes (5), COPD (4), heart failure (3), and miscellaneous (8).

Table 1
Characteristics of the 882 Patients

	COPD (n = 67)	No COPD (n = 815)	*P*
Clinical characteristics			
Age >65 years	59 (88%)	535 (66%)	< .001
Sex, male	59 (88%)	336 (41%)	< .001
Risk factors for VTD			
Cancer	10 (15%)	205 (25%)	.06
Surgery	4 (6%)	85 (10%)	.243
Immobilization ≥4 days	21 (31%)	144 (18%)	.006
History of VTD	10 (15%)	84(10%)	.24
Recent hemorrhage[a]	6 (9%)	36 (4%)	.094
Comorbidity			
Heart failure	8 (12%)	52 (6%)	.082
Clinical characteristics			
Diagnostic delay >3 d	39 (58%)	356 (44%)	.022
Low pretest probability[b]	42 (63%)	152 (19%)	< .001
Syncope	3 (4%)	123 (15%)	.017
Dyspnea	61 (91%)	575 (71%)	< .001
Chest pain	22 (33%)	372 (46%)	.042
SaO_2 < 90%	37 (55%)	190 (23%)	< .001
HR >100 beats/min	16 (24%)	194 (24%)	.961
Treatment			
Insertion of an IVC filter	0 (0%)	16 (2%)	.246
Thrombolysis	1 (1%)	19 (2%)	.655

Abbreviations: HR, heart rate; IVC, inferior vena cava; VTD, venous thromboembolic disease; SaO_2, arterial oxyhemoglobin saturation.
[a] In the last month.
[b] Modified Wells scale[13].

Sixty-seven patients (8%; 95% CI, 6%-9%) had been previously diagnosed with COPD. The characteristics of patients with and without COPD are shown in Table 1. Patients with COPD were significantly older and the majority were men. The COPD group also had more patients with a history of immobilization, congestive heart failure, or hemorrhage in the month before the diagnosis of PE. Fewer COPD patients had a history of cancer, although the between-group difference was not significant. At the time of diagnosis, more COPD patients had dyspnea and respiratory failure. Syncope and chest pain, however, were less frequent. The pretest probability (Wells score) was low for a larger proportion of COPD patients and more time had passed before they were diagnosed. No between-group differences were observed for frequency of insertion of a vena cava filter or need for thrombolytic therapy.

Table 2 shows the variables that were associated with all-cause death in the 3 months after diagnosis in the bivariate analysis. After adjusting for predictors identified in the bivariate analysis, the variables that remained significantly associated with all-cause mortality were a history of cancer and immobilization for medical reasons, low blood pressure, and oxyhemoglobin saturation less than 90%. Variables associated with PE-related death during follow-up are shown in Table 3. A history of COPD was significantly associated with PE-related death in the logistic regression analysis.

At the end of the follow-up period, survival rates were 88% and 95% in the groups with and without COPD, respectively (log rank test, *P*=.02; Figure).

Discussion

We analyzed the prognostic relevance of COPD in a series of consecutively enrolled patients with a confirmed diagnosis of acute symptomatic PE. Two main findings have emerged from the study. The first is that PE is less often suspected in COPD patients and diagnosis is delayed in this group. The second is that patients with COPD who develop PE are at higher risk of dying in the first 3 months after diagnosis than are patients without COPD.

The prevalence of COPD in our series of 882 patients was 8%, a finding similar to reports of rates between 8% and 9% for other cohorts.[14-17] Although the prevalence of chronic respiratory disease was 18% in a study by Aujesky et al,[7] those authors took all chronic respiratory disorders into account, while we considered only diagnoses of COPD confirmed by lung function testing. This would account for the difference in prevalence rates observed.

Patients with a history of COPD were classified on a standard clinical scale[13] as having a low pretest probability of PE more often

Table 2
Predictors of All-Cause Death at 3 Months

			Univariate		Multivariate	
	Dead (n=128)	Living (n=754)	RR (95% CI)	*P*	RR (95% CI)	*P*
Patient characteristics						
Age >65 years	93 (73%)	501 (66%)	1.3 (0.9-2.0)	.17	–	
Sex, male	67 (52%)	328 (43%)	1.4 (1.0-2.1)	.06	1.3 (0.9-1.9)	.18
Risk factors for VTD						
Cancer	65 (51%)	150 (20%)	4.1 (2.8-6.1)	< .001	4.6 (3.0-6.9)	< .001
Immobilization ≥4 days	35 (27%)	130 (17%)	1.8 (1.2-2.8)	.007	2.4 (1.5-3.8)	< .001
Comorbidity						
COPD	10 (8%)	57 (8%)	1.0 (0.5-2.1)	.92	–	
Heart failure	13 (10%)	47 (6%)	1.7 (0.9-3.2)	.10	–	
Presenting symptoms						
Dyspnea	100 (78%)	536 (71%)	1.4 (0.9-2.3)	.92	–	
Chest pain	48 (37%)	346 (46%)	0.7 (0.5-1.0)	.07	0.9 (0.6-1.3)	.50
SaO_2 < 90%	65 (51%)	296 (39%)	1.6 (1.1-2.3)	.01	1.5 (1.0-2.2)	.05
HR >110 beats/min	32 (25%)	145 (19%)	1.4 (0.9-2.2)	.13	–	
SBP < 100 mm Hg	20 (16%)	59 (8%)	2.2 (1.3-3.8)	.004	1.9 (1.0-3.3)	.04

Abbreviations: CI, confidence interval; HR, heart rate; RR, relative risk (hazard ratio); SaO_2, arterial oxyhemoglobin saturation; SBP, systolic blood pressure; VTD, venous thromboembolic disease.

Table 3
Predictors of Death Due to Pulmonary Embolism Within 3 Months

			Univariate		Multivariate	
	Dead (n=51)	Living (n=830)	RR (95% CI)	*P*	RR (95% CI)	*P*
Patient characteristics						
Age >65 years	40	554	1.8 (0.9–3.6)	.08	–	
Sex, male	22	373	0.9 (0.5–1.6)	.81	–	
Risk factors for VTD						
Cancer	20	195	2.1 (1.2–3.8)	.01	2.7 (1.4–5.1)	.002
Immobilization ≥4 days	22	143	3.6 (2.0–6.5)	< .001	3.8 (2.0–7.2)	< .001
Comorbidity						
COPD	8	59	2.4 (1.1–5.4)	.02	2.2 (1.0–5.1)	.05
Heart failure	5	55	1.5 (0.6–4.0)	.38	–	
Presenting symptoms						
Dyspnea	40	596	1.4 (0.7–2.8)	.30	–	
Chest pain	18	376	0.6 (0.4–1.2)	.16	–	
SaO_2 <90%	31	330	2.3 (1.3–4.2)	.003	1.9 (1.1–3.5)	.03
HR >110 beats/min	15	162	1.7 (0.9–3.2)	.09	–	
SBP <100 mm Hg	13	66	4.0 (2.0–7.8)	< .001	3.3 (1.6–6.8)	.001

Abbreviations: CI, confidence interval; HR, heart rate; RR, relative risk (hazard ratio); SaO_2, arterial oxyhemoglobin saturation; SBP, systolic blood pressure; VTD, venous thromboembolic disease.

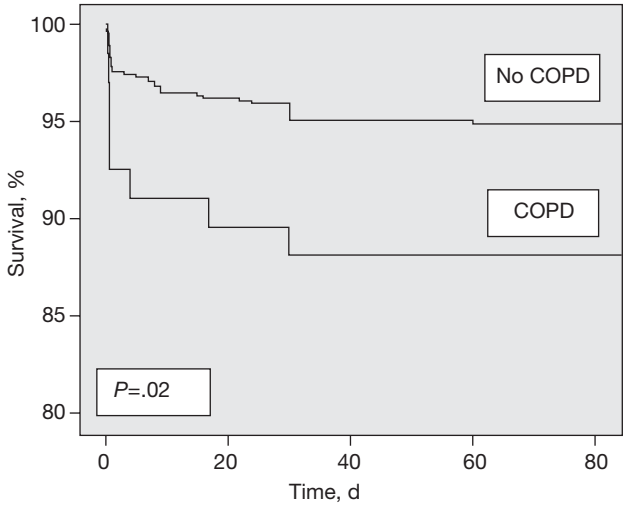

Figure. Survival curves according to the presence or absence of chronic obstructive pulmonary disease (COPD).

than those who did not have COPD. This observation was also reported for a cohort of 4444 consecutively enrolled patients in the RIETE registry.[18] Breathlessness in patients with both COPD and PE may be erroneously attributed to chronic respiratory disease. Furthermore, both dyspnea and right heart failure are not infrequent manifestations in patients with COPD.[19] The patients with COPD in our series were diagnosed later than those without COPD. Although a recent study did not find any predictor of delayed diagnosis of PE,[20] the guidelines of the American College of Chest Surgeons recommend early diagnosis of this condition.[21]

Although the all-cause mortality rate was not different for patients with COPD, the rate of PE-related death after adjustment for confounders was significantly higher in this group. Massive PE is the result of the interaction between the size of the embolus and the patient's cardiopulmonary reserve.[22] Our results confirm that patients with COPD are less able to tolerate a thrombotic event, possibly because of compromised cardiopulmonary reserve.

We believe our findings have important practical implications. First, stratifying patients with acute symptomatic PE into prognostic classes identifies those at lower risk of all-cause death (and who can be discharged early or treated as outpatients).[23] Stratification also identifies patients at high risk of PE-related death (who require stricter monitoring and should be considered for thrombolytic therapy).[24] Patients with acute symptomatic PE who have a history of COPD can be classed in a subgroup with a worse prognosis and alternatives to conventional anticoagulant therapy should be considered for them. Second, steps to prevent venous thromboembolic disease become particularly important for patients with COPD. One study assessed the efficacy of the LMWH bemiparin for primary thromboprophylaxis in these patients,[25] but the results were inconclusive.[26] Further, rigorously designed studies are required to assess the impact of thromboprophylaxis in this scenario.

Our study has certain limitations. First, our subjects came from a register of patients with a diagnosis of PE. It is therefore possible that we have not controlled for certain variables that might influence the findings. Second, we cannot evaluate the impact of anticoagulant therapy (regarding either the dosage or quality of anticoagulation) on the course of disease for these patients. Third, we were unable to assess whether there might be a relation between COPD severity (as determined by forced expiratory volume in the first second) and the prognosis of patients with acute symptomatic PE.

In conclusion, PE often goes unnoticed in patients with COPD. PE-related mortality is significantly higher in these patients, meaning that optimal thromboprophylaxis should be provided.

References

1. National Heart, Lung, and Blood Institute. Morbidity and mortality chartbook on cardiovascular, lung and blood diseases. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, National Institutes of Health. Available from: http://www.nhlbi.nih.gov/resources/docs/cht-book.htm
2. López AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J. 2006;27:397-412.
3. Sobradillo V, Miratvilles M, Jiménez CA, Gabriel R, Viejo JL, Masa JF, et al. Estudio IBERPOC en España: prevalencia de síntomas respiratorios habituales y de limitación crónica al flujo aéreo. Arch Bronconeumol. 1999;35:159-66.
4. Shetty R, Seddighzadeh A, Piazza G, Goldhaber SZ. Chronic obstructive pulmonary disease and deep vein thrombosis: a prevalent combination. J Thromb Thrombolysis. 2008;26:35-40.
5. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest. 2005; 128:2099-107.
6. Lesser BA, Leeper KV Jr, Stein PD, Saltzman HA, Chen J, Thompson BT, et al. The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease. Chest. 1992;102:17-2.
7. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172:1041-6.
8. Carson JL, Terrin ML, Duff A, Kelley MA. Pulmonary embolism and mortality in patients with COPD. Chest. 1996;110:1212-9.

9. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold-technique-comparison with pulmonary angiography. Radiology. 1992;185:381-7.
10. PIOPED investigators. Value of ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of the pulmonary embolism diagnosis (PIOPED). JAMA. 1990;263:2753-9.
11. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med. 1998;129:1044-9.
12. Global strategy for diagnosis, management and prevention for COPD-Update 2007. Available from: http://www.goldcopd.org
13. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-20.
14. Perrier A, Howarth N, Didier D, Loubeyre P, Unger PF, Moerloose P, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med. 2001;135:88-97.
15. Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med. 2004;116:291-9.
16. Perrier A, Roy PM, Sánchez O, Le Gal G, Meyer G, Gourdier AL, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352:1760-8.
17. Roy PM, Meyer G, Vielle B, le Gall C, Verschuren F, Carpentier F, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. Ann Intern Med. 2006;144:157-64.
18. Monreal M, Sánchez Muñoz-Torero JF, Naraine VS. Pulmonary embolism in patients with chronic obstructive pulmonary disease or congestive heart failure. Am J Med. 2006;119:851-8.
19. Álvarez Sala JL, Cimas E, Masa JF, Miravitlles M, Molina J, Naberan K, et al. Recomendaciones para la atención al paciente con enfermedad pulmonar obstructiva crónica. Arch Bronconeumol. 2001;37:269-78.
20. Jiménez D, Sueiro A, Díaz G, Escobar C, García-Rull S, Picher J, et al. Prognostic significance of delays in diagnosis of pulmonary embolism. Thromb Res. 2007;121: 153-8.
21. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:401S-28S.
22. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002;121:877-905.
23. Uresandi F, Otero R, Cayuela A, Cabezudo MA, Jiménez D, Laserna E, et al. A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism. Arch Bronconeumol. 2007;43:617-22.
24. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315.
25. Modesto-Alapont M, Nauffal-Manzur D, Ansótegui-Barrera E, Menéndez-Villanueva R, Ballesta A, Touza R, et al. ¿Puede reducir la mortalidad de los pacientes con EPOC la profilaxis domiciliaria de la enfermedad tromboembólica venosa? Arch Bronconeumol. 2006;42:130-4.
26. Rocha E, Jiménez D. Can home prophylaxis for venous thromboembolism reduce mortality rates in patients with chronic obstructive pulmonary disease? Arch Bronconeumol. 2007;43:523-4.