

# Can Home Prophylaxis for Venous Thromboembolism Reduce Mortality Rates in Patients With Chronic Obstructive Pulmonary Disease?

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**OBJECTIVE:** The incidence of venous thromboembolism (VTE) in patients with chronic obstructive pulmonary disease (COPD) ranges from 20% to 60% in different studies and the mortality rates are higher for patients with both conditions. Heparin prophylaxis is therefore usually prescribed for COPD patients who are hospitalized for exacerbation. Once their situation becomes stable, however, they are discharged to home without prophylaxis even though the low level of physical activity their disease allows continues to put them at risk for VTE.

The aim of this study was to test the efficacy of home heparin prophylaxis on reducing the incidence of VTE and on the overall mortality rate in patients with severe COPD.

**PATIENTS AND METHODS:** We conducted a prospective, randomized controlled trial of 87 patients with severe COPD who required home oxygen therapy ( $\geq 18$  h/d) and whose physical activity was highly restricted. A total of 44 patients received low molecular weight heparin (3500 IU/d of bempiparin) subcutaneously for 6 months. The outcome measures were incidence of VTE and mortality at 3 and 6 months.

**RESULTS:** Four patients (9.1%) died in the heparin group and 9 (20.4%) died in the control group; the difference was not statistically significant ( $P=.23$ ). VTE without pulmonary embolism developed in 1 patient (2%) in each group. Slight bleeding complications appeared in 9 patients (20.4%) in the heparin group and 1 patient (2.3%) in the control group, a difference that was statistically significant ( $P=.015$ ).

**CONCLUSIONS:** Home prophylaxis with heparin does not reduce the incidence of VTE or overall mortality in patients with severe COPD.

**Key words:** COPD. Pulmonary embolism. Deep vein thrombosis. Venous thromboembolism prophylaxis.

¿Puede reducir la mortalidad de los pacientes con EPOC la profilaxis domiciliar de la enfermedad tromboembólica venosa?

**OBJETIVO:** La incidencia de enfermedad tromboembólica venosa (ETV) en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) oscila entre el 20 y el 60% según las series, y la mortalidad por ETV es superior en estos enfermos. Por ello suele prescribirse profilaxis con heparina a los pacientes con EPOC hospitalizados por una agudización. Sin embargo, una vez que se estabiliza su situación, se les remite a su domicilio sin dicha profilaxis, a pesar de que la escasa actividad física que les permite su enfermedad sigue constituyendo un factor de riesgo para la aparición de ETV. El objetivo de este estudio ha sido analizar si la profilaxis domiciliar con heparina reduce la aparición de ETV y la mortalidad global en los enfermos con EPOC evolucionada.

**PACIENTES Y MÉTODOS:** Se ha realizado un ensayo clínico prospectivo aleatorizado con 87 pacientes afectados de EPOC grave que precisaban oxigenoterapia domiciliar (18 h o más al día), con una alta limitación de la actividad física. Un total de 44 sujetos recibió heparina de bajo peso molecular (HBPM; 3.500 U/día de bempiparina) por vía subcutánea durante 6 meses. Las variables estudiadas fueron la incidencia de ETV y la mortalidad a los 3 y 6 meses.

**RESULTADOS:** Durante el estudio fallecieron 4 pacientes del grupo que recibió HBPM (9,1%) y 9 del grupo control (20,4%); las diferencias entre ambos grupos no fueron estadísticamente significativas ( $p = 0,23$ ). Presentó trombosis venosa profunda sin embolia pulmonar un paciente de cada grupo (2%). Aparecieron complicaciones hemorrágicas leves en 9 pacientes del grupo con HBPM (20,4%), frente a una en el grupo control (2,3%), diferencia que fue estadísticamente significativa ( $p = 0,015$ ).

**CONCLUSIONES:** La profilaxis domiciliar con heparina no reduce la aparición de ETV ni la mortalidad global en los pacientes con EPOC avanzada.

**Palabras clave:** EPOC. Embolia pulmonar. Trombosis venosa profunda. Profilaxis de la tromboembolia venosa.

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## Introduction

The efficacy of heparin therapy to prevent venous thromboembolism—specifically deep vein thrombosis (DVT) with or without pulmonary embolism—is currently

unquestioned in view of the reduction of up to 50% in the rate of pulmonary embolism in hospitalized surgical patients receiving prophylaxis.<sup>1</sup> Reports of series of patients treated on medical wards, however, give a picture that is less clear. In a nonrandomized controlled trial enrolling emergency patients admitted with medical problems, Halkin et al<sup>2</sup> found that the mortality rate attributable to pulmonary embolism was lower (by around 31%) in the group receiving prophylaxis than in the control group, regardless of underlying disease. Two other large studies (2472 and 19 751 patients, respectively) showed that although the incidence of DVT was not lower with prophylaxis, deaths from pulmonary embolism were fewer.<sup>3,4</sup>

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent conditions treated on medical wards and the associated mortality rate is high at around 33 deaths per 100 000 inhabitants per year in Spain; the rate is higher for advanced stages of disease in patients over 75 years of age (176/100 000 inhabitants/year).<sup>5</sup> Furthermore, mortality seems to rise if DVT, with or without pulmonary embolism, develops in these patients.<sup>6,7</sup> Among other reasons for the rise might be the difficulty of diagnosing thrombosis, given that it can be masked by COPD.<sup>8-12</sup>

The incidence of DVT is high in patients with COPD regardless of disease severity. It ranges from 20% to 60% in different patient series<sup>13</sup> and is diagnosed in 11% of COPD patients admitted to the intensive care unit.<sup>14</sup> Advanced COPD, for example, especially when associated with heart failure or other vascular disease, seems to be a risk factor for developing DVT with or without pulmonary embolism.<sup>15</sup>

Patients who are hospitalized for COPD exacerbation are generally prescribed low molecular weight heparin (LMWH), which is administered in hospital as a preventive measure and withdrawn at discharge. The physical activity of patients in advanced stages of COPD is very restricted, particularly if they also suffer heart failure or another vascular disease (such as ischemic heart disease or sequelae of cerebrovascular accident) or if they require home oxygen therapy 24 hours a day. Forced immobility continues to be a risk factor for development of DVT in these patients after discharge.

The lack of studies in this clinical setting led us to design the present study to assess whether long-term home prophylaxis with LMWH would reduce the incidence of DVT and overall mortality in patients with severe COPD.

## Patients and Methods

### Study Population

This randomized controlled trial enrolled patients with severe COPD, according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD),<sup>7</sup> who required home oxygen therapy for 18 hours per day or longer. The patients were recruited in hospital, where they had been admitted for exacerbation of their respiratory disease. They were enrolled when discharged in stable condition according

to the GOLD criteria.<sup>7</sup> Signed informed consent was obtained after the study had been approved by the ethics committee of Hospital Universitario La Fe in Valencia.

The sample size needed was calculated and randomization was in blocks of a size sufficient to ensure the sequence would be hidden.

It was difficult to predict mortality for the type of patient enrolled based on the literature published at the time the present study was designed. In a recent study by Almagro et al<sup>5</sup> in a series of COPD patients similar to those of our study population, mortality rates of 13.4% and 22% were reported at 6 and 12 months, respectively. A more detailed analysis of that data showed that the mortality rate was higher for patients with severe COPD who required home oxygen therapy. Therefore, we assumed that the mortality rate would be near 20% for patients with severe COPD undergoing home oxygen therapy in our study. Assuming a 20% risk of death for the control subjects and accepting an alpha risk of 5% and a power of 80%, it was calculated that 86 patients would be needed to detect a change in relative risk of death of 0.25.

Patients excluded were those receiving anticoagulant therapy for DVT or who had a history of allergy to heparin, thrombopenia due to heparin, severe intracranial or peritoneal bleeding requiring transfusion or causing a fall of 3 points on hematocrit levels in the past month, hemorrhagic cerebrovascular accident in the past month, presence of signs or symptoms of DVT, contraindications for heparin therapy, neoplasm or other restrictive diseases, or any life-threatening disease.

### Outcome Measures

A physical examination and medical history, including patient characteristics and concurrent diseases, were performed on all patients. A blood work-up included a basic hemostasis study. Other tests were arterial blood gases at rest breathing room air, electrocardiography and Doppler ultrasound of the lower extremities to detect the presence of previous DVT.

The patients were randomly assigned to 2 groups; the treatment group received LMWH prophylaxis for DVT (3500 U/d of subcutaneous bemparin)<sup>16,17</sup> for 6 months. That dose was considered to be indicated because these patients had 2 accumulated risk factors for DVT: severe COPD and consequent restriction of activity. The correct administration of the drug was periodically evaluated during a visit to the hospital clinic.

Patient follow-up consisted of a visit with the physician, a blood work-up, and Doppler ultrasound of the lower limbs 3 and 6 months after discharge. A telephone number was provided for reporting possible complications. If significant signs of DVT were evident on the follow-up ultrasound study, angiography and computed tomography were performed to confirm the findings and treatment was withdrawn. Treatment was also withdrawn from those developing severe side effects (severe internal bleeding or low platelet levels) and even those with mild side effects (subcutaneous hematomas). Patients in the control group received the same follow-up studies at the same intervals.

### Statistical Analysis

Statistical analysis was carried out with the program SPSS, version 10.0 for Windows XP (Chicago, IL, USA). The outcome measures studied were overall mortality at 3 and 6

months and incidence of DVT. An intention-to-treat analysis of the relative risk of DVT and mortality was carried out. Results of bivariable analyses were considered significant when *P* was less than .05.

A forward stepwise logistic regression model based on the maximum likelihood ratio test was used to assess the effect on mortality of the individual variables: treatment, presence of heart failure, duration of oxygen therapy, baseline PaCO<sub>2</sub>, and restricted activity.

## Results

### Study Population

A total of 87 patients were enrolled: 44 in the bemiparin treatment group and 43 in the control group. The groups were similar in age, sex, COPD severity, restrictions on activity, and duration of oxygen therapy and flow levels, as shown in Table 1. The mean (SD) age of patients was 72 (7.6) years; 75 were men and 12 were women. Forty-nine patients (56.3% of the total number) also had heart failure. The difference in rates of heart failure between the 2 groups (Table 1) was not statistically significant (*P*=.18).

Nor were there between-group differences in arterial pH values, hematocrit, or platelet counts recorded to describe the sample at baseline or to monitor the results of prophylaxis. While the median PaO<sub>2</sub> at baseline was similar in both groups, nonsignificant differences (*P*=.18) in median PaCO<sub>2</sub> were observed at baseline between the 2 groups.

### Mortality, DVT, and Complications

Four patients (9.1%) in the bemiparin treatment group and 9 patients (20.9%) in the control group died during the study (Table 2). The difference in mortality was not significant (*P*=.23), even after analysis by degree of restriction of mobility. Similarly, analysis by presence or absence of heart failure showed no differences: 5 deaths occurred among the 49 (10.21%) with heart failure and 5 among the 38 (13.41%) without heart failure (*P*=.27).

Only age was an independent risk factor for mortality (Table 3) according to the regression model.

One patient (2.3%) in each group developed DVT without pulmonary embolism (Table 3). Hemorrhagic complications (mild bleeding or hematoma) developed in 9 patients (20.4%) in the bemiparin group and in 1 (2.3%) in the control group, a difference that was statistically significant (*P*=.015). Treatment was withdrawn from 2 patients (4.6%) in the bemiparin group due to thrombopenia (<80 000 platelets/μL), even though the difference between the 2 groups for this variable was not significant (*P*=.49).

## Discussion

There is disagreement about the efficacy of heparin in preventing DVT in nonsurgical hospitalized patients.

TABLE 1  
Patient Characteristics, Comorbidity, and Baseline Status of Patients Enrolled in the Trial\*

	Bemiparin	Control	Total
No. of patients	44	43	87
Mean (SD) age, years	71.4 (7.1)	72.5 (8.1)	71.9 (7.6)
Sex, M/F	39/5	36/7	75/12
Comorbidity			
Heart failure	24 (54.5%)	49 (56.2%)	25 (56.8%)
Duration of oxygen therapy			
18 h/day	22 (50%)	17 (39.5%)	39 (44.8%)
24 h/day	22 (50%)	26 (60.5%)	48 (55.2%)
Oxygen flow rate			
1.5 L/min	4	4	8
2.0 L/min	24	23	47
2.5 L/min	1	0	1
Other rates	15	16	31
Mobility			
Moderately restricted	16 (36.3%)	13 (30.2%)	29 (33.3%)
Very restricted	28 (63.6%)	28 (65.1%)	56 (64.3%)
Complete rest	0	2 (4.6%)	2 (2.3%)

\*M indicates males; F, females.

TABLE 2  
Incidence of DVT and Mortality: Between-Group Comparisons\*

	Bemiparin	Control	Total
No. of patients	44	43	87
DVT			
(with/without PE)	1 (2%)	1 (2%)	2 (2%)
Deaths	4 (9.1%)	9 (20.9%)	13 (14.9%)

\*DVT indicates deep vein thrombosis; PE, pulmonary embolism.

TABLE 3  
Contribution of Age to Risk of Death for Patients Enrolled in the Trial

	Variables	
	Age	Constant
B	0.125	-11.198
Significance	0.016	0.005
Exp. (B)	1.134	0.000
Confidence interval	1.024-1.255	-

While some authors have not found prophylaxis to be effective in preventing death due to pulmonary embolism in these patients, others have reported reductions in the incidence of DVT ranging from 40% to 60% in bedridden patients, of nearly 55% in patients with hemiplegia after cerebrovascular accident, of 25% in patients after myocardial infarction, and of 15% in patients with other medical diseases.<sup>3,18</sup> Therefore, consensus guidelines for the prevention of DVT establish that heparin prophylaxis is indicated in hospitalized nonsurgical patients at high or moderate risk of thromboembolism,<sup>19-24</sup> although the utility of such therapy in the home environment is unknown.

The risk of DVT with or without pulmonary embolism in patients with COPD is high, probably because of restricted physical activity, and is particularly high in those in advanced stages of disease, those who also have heart failure, and/or who require home oxygen therapy more than 18 hours a day. Likewise, patients with exacerbated COPD are at increased risk of DVT, especially if they require invasive mechanical ventilation.<sup>25</sup>

We are unaware of any study evaluating the efficacy of heparin in the long-term prevention of DVT in patients with advanced COPD and highly restricted physical activity. In our study, only 2 patients (2%) with severe COPD, one receiving bemiparin and the other in the control group, developed DVT without pulmonary embolism, whereas most patients did not, in spite of their advanced stage of COPD.

DVT is responsible for a high rate of mortality and is considered the most common cause of preventable hospital deaths<sup>26</sup>; around 10% are due to pulmonary embolism and 75% of those are in nonsurgical patients.<sup>27</sup>

It is also known that mortality due to these entities is very high in the context of COPD: it is estimated to be around 160 and 60 cases per 100 000 inhabitants for DVT and pulmonary embolism, respectively.<sup>28</sup> The best way to demonstrate the efficacy of heparin prophylaxis is a reduction in mortality and it is considered that, independently of cost, treatment is able to prevent a great many such deaths every year.<sup>29</sup> We aimed to assess the effect of treatment to prevent DVT on overall mortality in patients with COPD, hypothesizing that overall mortality would fall if the deaths caused by DVT decreased. However, although mortality was higher in the group that did not receive prophylaxis, the difference was too small to attribute to the incidence of DVT and was probably due to the COPD itself. As no other studies have been done in similar settings, we can not compare our results with others'.

These results do not allow us to conclude that LMWH prophylaxis increases survival in advanced COPD. Furthermore, our findings differ from those of other studies<sup>8,30,31</sup> in that we found that preventive treatment with LMWH, the presence of heart disease, duration of oxygen therapy, baseline PaCO<sub>2</sub>, and restricted mobility did not influence mortality in these patients. Our findings confirm what is known about the age-related increase in mortality in patients with COPD.<sup>7</sup>

Our study also found a high prevalence of all types of bleeding (most cases being mild) in the group that received bemiparin. That adverse effect made it necessary to withdraw LMWH treatment from patients who were affected. These data differ from those obtained in other studies of heparin prophylaxis on medical wards. In those studies, the incidence of hemorrhagic complications was similar in the treatment and control groups.<sup>32,33</sup>

Based on our results, we can say that long term preventive therapy to protect against DVT gives rise to frequent, though mild, bleeding.

The main contributions of this study are *a)* it is the first to assess long term efficacy of domiciliary heparin prophylaxis for DVT in patients with advanced stage COPD, *b)* we provide information on the prevalence of DVT in patients with COPD in Spain and on mortality in patients with severe COPD who are using home oxygen therapy, and *c)* we analyze the incidence of hemorrhagic complications arising from long term use of heparin. The main limitation is the relatively small patient sample size and we therefore think it would be useful to carry out similar, larger studies to confirm our findings.

We conclude that patients with advanced stage COPD whose physical activity is highly restricted do not seem to be at increased risk of DVT. We can also state that preventing DVT does not seem to affect mortality in this type of COPD patient and, therefore, the bleeding arising from long term use of prophylactic heparin would weigh against using it in such patients in the absence of vascular comorbidity.

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