Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE)

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Background and Objectives. Elderly patients with venous thromboembolism (VTE) have an increased rate of bleeding complications on therapeutic doses of anticoagulant therapy.

Design and Methods. Using data in RIETE, an international registry of consecutive patients with objectively confirmed, symptomatic acute VTE, we analyzed the clinical characteristics and outcome within 90 days of therapy of all enrolled patients aged ≥80 years old.

Results. Of the 13,011 patients with VTE enrolled in RIETE up tp September 2005, 2890 (22%) were aged ≥80 years old. During the study period 99 patients (3.4%) aged ≥80 years, and 212 aged <80 years (2.1%) had major bleeding events (odds ratio: 1.7; 95% CI: 1.3-2.1). Fatal bleeding occurred in 0.8% and 0.4%, respectively (odds ratio: 2.0; 95% CI: 1.2-3.4). The incidence of recurrent VTE was 2.1% and 2.8%. However, 3.7% of patients ≥80 years and 1.1% <80 years died of pulmonary embolism (PE) (odds ratio: 3.6; 95% CI: 2.7-4.7). On multivariate analysis, patients ≥80 years with symptomatic PE, heart failure, long-term therapy with low-molecular-weight heparin (LMWH) or a vena cava filter had an increased risk of recurrent VTE. Those with recent bleeding, abnormal renal function, use of corticosteroids or long-term therapy with LMWH had an increased risk of major bleeding.

Interpretation and Conclusions. In patients aged ≥80 years old the 3.4% incidence of major bleeding exceeded the 2.1% incidence of VTE recurrences. However, the 3.7% incidence of fatal PE outweighed the 0.8% of fatal bleeding. Thus, there seems to be more reason to be concerned about fatal PE than about bleeding in elderly patients with VTE.

Key words: venous thrombosis, pulmonary embolism, elderly, bleeding complications, mortality.

Haematologica 2006; 91:1046-1051

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The treatment of venous thromboembolism (VTE) in the elderly population presents certain unique problems related to aging, such as decreasing body weight, increasing renal insufficiency and numerous comorbid conditions, which complicate therapy. Current guidelines from the American College of Chest Physicians, based on evidence from clinical trials, recommend that all patients with VTE be treated initially with either low-molecular-weight heparin (LMWH), or unfractionated heparin (UFH) for at least 5 days and that this initial treatment be followed by long-term treatment with a vitamin K antagonist.[1] However, elderly patients are often excluded from clinical trials of anticoagulant treatment because of comorbid conditions, short life expectancy, long-term immobility, or contraindications to therapy[2-4] which means that treatment regimens based on the results from clinical trials might not be suitable for all elderly patients with VTE. Furthermore, an increasing body of evidence indicates that age is an independent risk factor for major bleeding.[5-10]

The *Registro Informatizado de la Enfermedad TromboEmbólica* (RIETE) was initiated in March 2001 to record current clinical management of VTE in Spanish hospitals and has now been expanded to include patients from other European countries.[11-16] It is an ongoing, multicenter, observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE. The aim of the present study was to analyze the clinical characteristics and 3-month clinical outcomes of all enrolled patients ≥80 years old in the registry, trying to identify which patients are at a higher risk of recurrent VTE or major bleeding.

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Design and Methods

Inclusion and exclusion criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests (contrast venography, ultrasonography or impedance plethysmography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography [CT] scan for suspected PE), are enrolled in RIETE. Patients are excluded if they are participating in a therapeutic clinical trial or if they are not available for the 3-month follow-up.

Clinical definitions

Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to the diagnosis of VTE. Surgical patients are defined as those who had undergone an operation in the 2 months prior to the diagnosis of VTE. Creatinine clearance on admission was estimated with the Cockcroft and Gault formula.[17] Fatal PE was defined as any death occurring shortly after the diagnosis of PE (either the initial episode or a recurrent PE), in the absence of an alternative cause of death. Bleeding complications were classified as *major* if they were overt and were associated with a decrease in the hemoglobin level of 2.0 g/dL or more, required a transfusion of 2 units of blood or more, or were retroperitoneal or intracranial.

Variables

The following parameters were recorded: patient's baseline characteristics, clinical status including risk factors for VTE and any coexisting or underlying conditions such as chronic heart or lung disease, recent bleeding complications, renal insufficiency, use of antiplatelet drugs, non-steroidal anti-inflammatory drugs or corticosteroids; the type, dose, and duration of treatment received upon VTE diagnosis; and the clinical outcome during the first 90 days of therapy.

Follow-up

All patients were followed-up for at least 3 months after hospital discharge. During each visit, any signs or symptoms suggesting recurrences of DVT or PE, or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical computed tomography scan, or pulmonary angiography.

Data collection

All patients provided oral consent to their participation in the registry, in accordance with the requirements of the ethics committee within each hospital. Data are recorded in a computer-based case report form by a RIETE registry co-ordinator at each participating hospital and submitted to a centralized co-ordinating center through a secure website. The co-ordinators also ensure that eligible patients are consecutively enrolled. Patient identities remain confidential because they are identified by a unique number assigned by the study co-ordinating center, which is responsible for all data management. Study outcomes are adjudicated by the attending physicians. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local co-ordinators. Data quality is also monitored by periodic visits to participating hospitals, by contract research organizations, who compare the medical records with the data in the web. A full data audit is performed at periodic intervals.

Statistical analysis

Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated using Confidence Interval Analysis software (version 2.0.0), and a p value less than 0.05 was considered to be statistically significant. The significance of a number of clinical variables on the risk of recurrent VTE or major bleeding complications was tested by a χ^2 test for categorical variables and by a t-test for numerical variables. Candidate variables were selected from clinical variables based on published literature and on expert opinion. A logistic regression model was used to examine the individual relationship between each variable and the risk of developing either VTE recurrences or major bleeding complications. Those variables identified by the univariate analyses as potential risk factors and achieving a significance level of <0.05 were considered for inclusion in a multivariate logistic regression analysis. A multivariate logistic regression analysis was conducted to determine the independent nature of the risk factors, while adjusting for other characteristics. Multivariate analysis was performed using the Statistical Package for Social Sciences (SPSS) program (version 12.5; SPSS Inc., Chicago, IL, USA).

Results

As of September 2005, 13011 patients with symptomatic, acute VTE had been consecutively enrolled at 124 participating centers. Of these, 2890 (22%) were ≥80 years of age. Patients ≥80 years old were more often female, more often weighed <65 kg, and more often had chronic lung disease, heart failure, creatinine clearance <60 mL/min or used antiplatelet drugs than did patients <80 years old (Table 1). Recent immobility for ≥4 days was more common, but they had cancer or recent surgery less often. Patients ≥80 years old were more often enrolled with symptomatic PE. Of the

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Table 1. Clinical characteristics, treatment details and clinical outcomes in patients ≥80 years and <80 years old.

	Age ≥80 yrs. n=2890	*Age <80 yrs. n=10121*	*Odds ratio (95 % CI)*	*p value*
Clinical characteristics				
Gender (males)	1022 (35%)	5464 (54%)	0.5 (0.4-0.5)	<0.001
Body weight <65 kg	1206 (42%)	2237 (22%)	2.5 (2.3-2.8)	<0.001
Inpatients	837 (29%)	3049 (30%)	1.0 (0.9-1.1)	0.446
Underlying conditions and co-medications				
Chronic lung disease	394 (14%)	1068 (11%)	1.3 (1.2-1.5)	<0.001
Chronic heart failure	392 (14%)	386 (3.8%)	4.0 (3.4-4.6)	<0.001
Creatinine clearance <60 mL/min	772 (27%)	934 (9.2%)	3.6 (3.2-4.0)	<0.001
NSAID intake	141 (4.9%)	590 (5.8%)	0.8 (0.7-1.0)	0.056
Antiplatelet drugs	525 (18%)	845 (8.3%)	2.4 (2.2-2.7)	<0.001
Corticosteroid intake	210 (7.3%)	726 (7.2%)	1.0 (0.9-1.2)	0.864
Recent major bleeding	74 (2.6%)	258 (2.5%)	1.0 (0.8-1.3)	0.973
Risk factors for VTE				
Cancer	510 (18%)	2134 (21%)	0.8 (0.7-0.9)	<0.001
Surgery	231 (8.0%)	1481 (15%)	0.5 (0.4-0.6)	<0.001
Immobility ≥4 days	1022 (35%)	2208 (22%)	2.0 (1.8-2.1)	<0.001
Previous VTE	431 (15%)	1651 (16%)	0.9 (0.8-1.0)	0.070
VTE characteristics				
Distal DVT	217 (7.5%)	1355 (13%)	0.5 (0.5-0.6)	<0.001
Symptomatic PE	1518 (52%)	4283 (42%)	1.5 (1.4-1.6)	<0.001
Patients with PE				
Arterial PO_2 <60 mmHg	677 (53%)	1343 (40%)	1.8 (1.5-2.0)	<0.001
Treatment				
Initial therapy, LMWH	2690 (93%)	9080 (90%)	1.6 (1.3-1.8)	<0.001
Mean LMWH doses (IU/kg/d)	183±38	179±37	–	<0.001
Initial therapy, UFH	181 (6.3%)	884 (8.8%)	0.7 (0.6-0.8)	<0.001
Initial therapy, thrombolytics	8 (0.3%)	114 (1.1%)	0.2 (0.1-0.5)	<0.001
Inferior vena cava filter	37 (1.3%)	218 (2.2%)	0.6 (0.4-0.8)	0.003
Long-term therapy, LMWH†	903 (34%)	2401 (25%)	1.6 (1.4-1.7)	<0.001
Mean LMWH doses (IU/kg/d)	157±55	142±47	–	<0.001
Long-term therapy, AVK†	1768 (66%)	7306 (75%)	0.6 (0.6-0.7)	<0.001
3-month clinical outcomes				
Fatal PE	106 (3.7%)	107 (1.1%)	3.6 (2.7-4.7)	<0.001
Fatal initial PE	83 (2.9%)	69 (0.7%)	4.3 (3.1-5.9)	<0.001
Fatal recurrent PE	23 (0.8%)	38 (0.4%)	2.1 (1.3-3.6)	0.004
Recurrent VTE	62 (2.1%)	285 (2.8%)	0.8 (0.6-0.99)	0.048
Fatal bleeding	24 (0.8%)	42 (0.4%)	2.0 (1.2-3.3)	0.006
Major bleeding	99 (3.4%)	212 (2.1%)	1.7 (1.3-2.1)	<0.001
Overall death	396 (14%)	675 (6.7%)	2.2 (1.9-2.5)	<0.001

†*Some patients died during initial therapy and therefore did not receive long-term treatment. NSAID: non-steroidal anti-inflammatory drugs; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; AVK: antivitamin K drugs; CI: confidence intervals.*

Table 2. Univariate analysis of variables associated with recurrent VTE within 3 months in patients aged ≥80 years.

	Recurrent VTE n=62	No recurrences n=2828	Odds ratio (95% CI)	*p* value
Clinical characteristics				
Gender (males)	24 (39%)	998 (35%)	1.2 (0.7-1.9)	0.577
Body weight <65 kg	27 (44%)	1179 (42%)	1.1 (0.6-1.8)	0.771
Inpatients	24 (39%)	763 (28%)	1.7 (1.0-2.8)	0.050
Underlying conditions and co-medications				
Chronic lung disease	11 (18%)	383 (14%)	1.4 (0.7-2.7)	0.341
Chronic heart failure	18 (29%)	374 (13%)	2.7 (1.5-4.7)	<0.001
Creatinine clearance <60 mL/min	20 (32%)	752 (27%)	1.3 (0.8-2.3)	0.318
NSAID intake	1 (1.6%)	140 (5.0%)	0.3 (0.04-2.3)	0.228
Antiplatelet drugs	17 (27%)	508 (18%)	1.7 (0.98-3.0)	0.056
Corticosteroids intake	6 (9.7%)	204 (7.2%)	1.4 (0.6-3.2)	0.460
Recent major bleeding	4 (6.5%)	70 (2.5%)	2.7 (1.0-7.7)	0.050
Risk factors for VTE				
Cancer	12 (19%)	498 (18%)	1.1 (0.6-2.1)	0.721
Surgery	10 (16%)	221 (7.8%)	2.3 (1.1-4.5)	0.017
Immobility ≥4 days	19 (31%)	1003 (36%)	0.8 (0.5-1.4)	0.432
Previous VTE	11 (18%)	420 (15%)	1.2 (0.6-2.4)	0.527
VTE characteristics				
Symptomatic PE	45 (73%)	1473 (52%)	2.4 (1.4-4.3)	0.001
Initial therapy				
LMWH	53 (86%)	2637 (93%)	0.4 (0.2-0.9)	0.013
Mean LMWH doses (IU/kg/d)	182±45	183±38	–	0.794
UFH	9 (14%)	172 (6.1%)	2.6 (1.3-5.4)	0.007
Thrombolytics	0 (0%)	8 (0.3%)	–	0.675
Inferior vena cava filter	4 (6.5%)	33 (1.2%)	5.8 (2.0-17)	<0.001
Long-term therapy				
AVK	24 (44%)	1750 (66%)	0.4 (0.2-0.7)	0.001
LMWH	28 (51%)	886 (33%)	2.1 (1.2-3.5)	0.007
Mean LMWH doses (IU/kg/d)	165±46	153±55	–	0.272
LMWH dose <150 IU/kg/day	10 (35%)	387 (44%)	0.7 (0.3-1.5)	0.328

NSAID: non-steroidal anti-inflammatory drugs; VTE: venous thromboembolism; PE, pulmonary embolism; LMW: low-molecular-weight heparin; UFH, unfractionated heparin; CI, confidence intervals.

patients with symptomatic PE, those aged ≥80 years more commonly had severe hypoxemia. Among patients with symptomatic DVT, those ≥80 years old were diagnosed with distal DVT less often. Most patients in both groups were initially treated with LMWH. As for long-term therapy, 34% of patients aged ≥80 years, and 25% of those <80 years received LMWH. Mean daily doses of LMWH were slightly higher in the elderly, for both initial and long-term therapy (Table 1).

During the 90-day study period 106 patients (3.7%) aged ≥80 years and 107 <80 years (1.1%) died of PE (OR: 3.6; 95% CI: 2.7-4.7), as shown in Table 1. Eighty-three patients aged ≥80 years (2.9%) died of their initial PE episode and 23 (0.8%) died of recurrent PE. Fatal bleeding occurred in 0.8% and 0.4%, respectively (OR: 2.0; 95% CI: 1.2-3.4). In other words, 50% of all patients with fatal PE and 36% of those with fatal bleeding were aged ≥80 years old.

VTE recurrences

Sixty-two patients aged ≥80 years (2.1%) had VTE recurrences during the study period: 40 had recurrent PE (fatal in 23), 22 had DVT. On univariate analysis, initial diagnosis of PE, chronic heart failure, recent surgery, initial therapy with unfractionated heparin, insertion of an inferior vena cava filter and long-term therapy with LMWH were associated with an increased risk of recurrences (Table 2). Multivariate analysis confirmed that only PE diagnosis at baseline, chronic heart failure, inferior vena cava filter and long-term therapy with LMWH were independently associated with an increased risk of recurrences (Table 3).

Major bleeding complications

Ninety-nine patients aged ≥80 years (3.4%) had major bleeding complications (gastrointestinal 37, intracerebral 15, other 47): 39 patients bled during the first week,

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Table 3. Multivariate logistic regression analysis of variables associated with VTE recurrences.

Variables	*Odds ratio (95% CI)*	*p value*
Inpatients	1.5 (0.8-2.7)	0.166
Chronic heart failure	3.0 (1.6-5.4)	<0.001
Recent major bleeding	1.5 (0.4-5.4)	0.545
Surgery	1.8 (0.8-3.9)	0.165
Symptomatic PE	2.9 (1.5-5.5)	0.001
Initial therapy, LMWH	0.5 (0.2-1.2)	0.141
Inferior vena cava filter	4.9 (1.5-16)	0.009
Long-term therapy, LMWH	2.5 (1.5-4.5)	0.001

VTE: venous thromboembolism; PE: pulmonary embolism; LMWH: low-molecular weight heparin; CI: confidence intervals.

60 bled from day 8-90. Of these 99 patients, 24 died: 7 during the first week, 17 after discharge. On univariate analysis, creatinine clearance <60 mL/min, use of corticosteroids, recent bleeding, immobility for ≥4 days, and long-term therapy with LMWH were associated with an increased incidence of major bleeding (Table 4). Multivariate analysis confirmed that only recent bleeding, CrCl <60 mL/min, use of corticosteroids, and long-term therapy with LMWH were independently associated with an increased risk for major bleeding (Table 5).

Discussion

A number of studies have shown that elderly patients with VTE have a higher incidence of bleeding complications on therapeutic doses of anticoagulant therapy.[5-8] The findings in this analysis, obtained from a large prospective series of consecutive patients in the RIETE registry, confirm these data: the 3.4% incidence of major bleeding complications in patients ≥80 years clearly exceeded the 2.1% rate of recurrent VTE. However, these data may be misleading since the 3.7% incidence of fatal PE (either the initial episode or recurrent PE) clearly outweighed the 0.8% incidence of fatal bleeding. Indeed, while the rate of fatal PE was 2.5 times higher than the rate of fatal bleeding in patients aged <80 years, the ratio was 4.4 times higher in those aged ≥80 years. This increased mortality should be attributed to the more severe presentation of PE and the more frequent occurrence of co-existing underlying conditions.

As for long-term therapy, we found that elderly patients receiving LMWH had a higher incidence of both major bleeding and VTE recurrences compared to those receiving coumarin. Secondary prevention of VTE with vitamin K antagonists is often problematic in the very elderly.[18-20] Achieving the target International Normalized Ratio is especially problematic because of a high background risk of drug interactions, malnutrition, dehydration, and difficulties with periodic monitoring of the prothrombin time. Thus, in clinical practice many physicians may be reluctant to use long-term warfarin therapy in the very elderly, as shown in our series. Several trials have compared LMWH with oral anticoagulants in this setting.[21-26] Although these trials did not focus primarily on elderly patients, they found no difference in the rate of VTE recurrences between recipients of the two different types of drugs, but demonstrated a non-significant trend towards increased bleeding in

Table 4. Univariate analysis of variables associated with major bleeding within 3 months in patients aged ≥80 years.

	Major bleeding n=99	*No major bleeding n=2791*	*Odds ratio (95 % CI)*	*p value*
Clinical characteristics				
Gender (males)	35 (35%)	987 (35%)	1.0 (0.7-1.5)	0.998
Body weight <65 kg	47 (47%)	1159 (42%)	1.3 (0.9-1.9)	0.239
Inpatients	29 (30%)	758 (28%)	1.1 (0.7-1.7)	0.625
Underlying conditions and co-medications				
Chronic lung disease	15 (15%)	379 (14%)	1.1 (0.6-2.0)	0.654
Chronic heart failure	12 (12%)	380 (14%)	0.9 (0.5-1.6)	0.670
Creatinine clearance <60 mL/min	40 (40%)	732 (26%)	1.9 (1.3-2.9)	0.002
NSAID intake	5 (5.1%)	136 (4.9%)	1.0 (0.4-2.6)	0.936
Antiplatelet drugs	20 (20%)	505 (18%)	1.1 (0.7-1.9)	0.593
Corticosteroids	15 (15%)	195 (7.0%)	2.4 (1.3-4.2)	0.002
Recent major bleeding	10 (10%)	64 (2.3%)	4.9 (2.4-9.6)	<0.001
Risk factors for VTE				
Cancer	23 (23%)	487 (17%)	1.4 (0.9-2.3)	0.138
Surgery	9 (9.1%)	222 (8.0%)	1.2 (0.6-2.3)	0.682
Immobility ≥4 days	47 (47%)	975 (35%)	1.7 (1.1-2.5)	0.010
Previous VTE	14 (14%)	417 (15%)	0.9 (0.5-1.7)	0.826
VTE characteristics				
Symptomatic PE	54 (54%)	1646 (53%)	1.1 (0.7-1.6)	0.682
Initial therapy				
LMWH	92 (93%)	2598 (93%)	0.9 (0.4-2.1)	0.889
Mean LMWH doses (IU/kg/d)	186 ±40	183 ± 38	–	0.532
UFH	6 (6.1%)	175 (6.3%)	1.0 (0.4-2.2)	0.928
Thrombolytics	1 (1.0%)	7 (0.3%)	4.0 (0.5-33)	0.158
Inferior vena cava filter*	2 (2.0%)	23 (0.8%)	2.5 (0.6-11)	0.207
Long-term therapy				
Antivitamin K drugs	40 (48%)	1734 (66%)	0.5 (0.3-0.7)	0.001
LMWH	41 (49%)	873 (33%)	2.0 (1.3-3.0)	0.002
Mean LMWH doses (IU/kg/d)	156 ± 61	154±55	–	0.804
LMWH dose <150 IU/kg/day	18 (42%)	379 (43%)	0.9 (0.5-1.7)	0.841

*NSAID: nonsteroidal anti-inflammatory drugs; VTE: venous thromboembolism; PE: pulmonary embolism; AVK: LMWH: low-molecular-weight heparin; CI: confidence intervals. *only patients in whom a vena cava filter was inserted before a bleeding complication are considered in this table.*

Table 5. Multivariate logistic regression analysis of variables associated with major bleeding.

Variables	*Odds (95 % CI)*	*ratio p value*
Creatinine clearance <60 mg/dL	1.8 (1.2-2.9)	0.010
Corticosteroids	2.6 (1.4-4.8)	0.002
Recent major bleeding	3.4 (1.5-8.0)	0.004
Immobility ≥4 days	1.4 (0.9-2.2)	0.168
Long-term therapy, LMWH	1.7 (1.1-2.7)	0.017

LMWH: low-molecular-weight heparin; CI: confidence intervals.

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patients treated with oral anticoagulants.[27] Our findings do not support this. The higher incidence of VTE recurrences and bleeding complications in patients ≥80 years old treated with long-term LMWH in our series may be partially attributed to selection bias: the fact that a patient receives long-term LMWH treatment is usually indicative of some underlying condition (i.e., cancer, other severe illness) that has interfered with the switch to vitamin K antagonists.

The RIETE registry provides data on the treatment of VTE in a real-world situation with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, provide insights into the natural history of VTE in very elderly patients. It can also help to identify practices for providing treatment to patients, and factors associated with better or worse patient outcomes.

However, as the basis for observational studies, RIETE is not designed to answer questions regarding the relative efficacy and safety of different modalities of therapy. Data from the registry are hypothesis-generating and provide feedback from real-world clinical situations which is invaluable when designing new randomized clinical studies.

In conclusion, data from this large series of patients indicate that the incidence of fatal PE in VTE patients aged ≥80 years far outweighs the incidence of fatal bleeding. Thus, there seems to be more reason to be concerned about fatal PE than about bleeding in elderly patients with VTE.

Appendix

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MM is the Coordinator of the RIETE Registry. He and the rest of the authors recruited patients in the data base, discussed the aims of the manuscript, and read and approved the final manuscript. All authors contributed to the research presented in this manuscript and had full access to all data and hold final responsibility for the decision to submit this manuscript for publication. The RIETE registry is an independent registry, partially supported by Sanofi-Aventis in Spain and Red Respira from the Instituto Carlos III (RedRespira-ISCiii-RTIC-03/11). Sanofi-Aventis has no right to access to the database, and there is no payment per patient recruitment. Manuel Monreal acted as a member of the Steering Committee of the EXCLAIM clinical trial and the IMPROVE Registry, both sponsored by Sanofi-Aventis. The other authors declare that they have no potential conflicts of interest. We express our gratitude to Sanofi-Aventis for supporting this Registry with an unrestricted educational grant and the Registry Coordinating Center, S&H Medical Science Service, for their logistic and administrative support. The project was partially supported by Red Respira from the Instituto Carlos III. (RedRespira-ISCiii-RTIC-03/11). We would like to thank Salvador Ortiz, Prof. Universidad Autónoma de Madrid and Statistical Advisor S & H Medical Science Service for the statistical analysis of the data presented in this paper. Manuscript received March 8, 2006. Accepted June 14, 2006.

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