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ORIGINAL ARTICLE

Clinical characteristics of italian patients with venous thromboembolism enrolled in the RIETE Registry

Caratteristiche cliniche dei pazienti italiani iscritti nel Registro RIETE

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Immobility.

Summary
Introduction: The clinical characteristics, treatment strategies and outcome of patients with venous thromboembolism (VTE) may vary from country to country.
Materials and methods: The RIETE (Registro Informatizado su la Enfermedad TromboEmbolica) is an ongoing, prospective registry of consecutive patients with acute, objectively confirmed, symptomatic VTE. Our aim was to assess the influence of surgery and immobility for non-surgical reasons on 3-month outcomes of all Italian patients registered in the RIETE.
Results: Through July 2008, 21,397 patients with acute VTE were registered in the RIETE. Of these, 896 (4.2%) were Italian, and 360 (40%) presented with pulmonary embolism (PE). Overall, 137 (15%) developed VTE after surgery; 156 (17%) developed VTE after $\geq$4 days of immobility, and 603 (67%) developed VTE in the absence of surgery or immobility. Most patients (83%) received initial therapy with low-molecular-weight heparin; 15% received unfractionated heparin. For long-term therapy, 63% of patients received vitamin K antagonists. The incidence of fatal PE

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during the first 3 months of therapy was 1.5% for patients with postoperative VTE, 7.7% for who developed VTE after immobility, and 1.2% for the remaining patients. The incidence of fatal bleeding among these patients was 1.5%, 1.9% and 0.3%, respectively. Of the 137 patients with postoperative VTE, 61% had received VTE prophylaxis. Of the 156 patients with recent immobility, 24% had received VTE prophylaxis.

Conclusions: VTE arising after a period of immobility was associated with the highest rates of fatal PE and fatal bleeding during the first 3 months of therapy. The use of thromboprophylaxis in this population should be improved.

Introduction

A previous Spanish study of patients with acute venous thromboembolism (VTE) showed large differences in outcome (incidence of major bleeding, fatal PE, and fatal bleeding) between surgical patients and immobilized acutely ill medical patients [1]. However, the clinical characteristics, treatment strategies and outcome of patients with VTE may vary from country to country. Until now, these data have not been confirmed in Italian patients. A better knowledge of the influence of the different risk factors on outcome in patients with VTE would be useful to guide new strategies for early diagnosis, prophylaxis and/or therapy.

The RIETE Registry is an ongoing, international (including Spain, France, Italy, Israel, Germany, Republic of Macedonia, Switzerland, and Brazil), multicenter, prospective registry of consecutive patients presenting with symptomatic, acute VTE confirmed by objective tests. It was designed to gather and analyze data about treatment patterns and outcomes in patients with symptomatic, objectively confirmed, acute VTE [2]. 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 [3,4]. In this analysis, we assessed the influence of predisposing factors for VTE (i.e., recent surgery or immobility) on the incidence of fatal PE and fatal bleeding during the first 3 months of anticoagulant therapy in all Italian patients enrolled in the registry.

Materials and methods

Patient Entry Criteria

Participating hospitals enrolled all patients who meet predefined eligibility criteria. Patients were included if they had symptomatic, acute deep-vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (i.e., contrast venography, ultrasonography or impedance plethysmography for suspected DVT; pulmonary angiography, lung scintigraphy or helical computed tomography scan for suspected PE) [5,6]. Patients were excluded if they were participating in a therapeutic clinical trial blinded to medication, or if they would not be available for a 3-month follow-up. All patients provided informed consent for their participation in the study, according to the requirements of each hospital's ethics committee. Data quality was monitored and documented, and a full data audit was performed at periodic intervals.

The RIETE enrolled more than 35,000 patients with VTE between 2001 and February 2011. The registry enrolls patients from several (predominantly European) countries, particularly Spain, Italy and France. We analyzed data from Italy from January 2006 to July 2008. Italy was the first country after Spain to join the registry; it joined in 2006 and had enrolled 896 patients by July 2008.

Study Parameters and Endpoints

The following parameters were recorded when the qualifying episode of DVT was diagnosed: the patient's sex, age, and body weight; the presence of coexisting conditions, such as chronic heart or lung disease; recent ($<$30 days prior to VTE) major bleeding; the presence of risk factors for DVT, including active cancer (defined as newly diagnosed cancer or cancer that is being treated, i.e., via surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments), recent immobilization (i.e., nonsurgical patients who were confined to bed with bathroom privileges for $\geq$4 days in the 2 months prior to VTE diagnosis), surgery (i.e., patients who had undergone an operation in the 2 months prior to VTE); extent of the DVT (distal DVT was DVT confined to the infrapopliteal veins); and laboratory data.

Study endpoints were clinically recognized risk factors, prophylaxis and VTE outcomes (i.e., VTE recurrences, major and minor bleeding complications, and death). Bleeding complications were classified as major or minor according to the criteria established by Doyle et al. Bleeding was classified as "major" if it was overt and led to a transfusion of 2 U of blood or more, if it was fatal, or if it was retroperitoneal or intracranial. Bleeding was defined as minor if it was clinically relevant but did not meet the other criteria for major bleeding.

Use of the RIETE Study Database

Although it is not intended to influence the routine management of patients participating in the registry, collated data from the RIETE are available on the registry's website (www.riete.org) for use by participating physicians and others in the field. An underlying or coexisting medical condition can be selected from a drop-down list to display data from the RIETE database, including the treatments,

doses and outcomes of patients with similar clinical profiles. Users can thus compare different therapies and decide which is the most appropriate for their patient, based on previous real-world outcomes.

Data Management and Confidentiality

S & H Medical Science Service is the coordinating center for the registry and assumes responsibility for all data management activities. Data for each patient are entered on a standard case report form and submitted to the coordinating center via a secure website. Patient, physician and hospital data confidentiality is protected prior to data submission by assigning a unique study number to each patient at enrollment and by deleting or coding all other information that could identify a person or institution. Confidential electronic data are further protected by passwords, and all paper copies of data and reports are stored in a secure facility.

Results

General data

Through July 2008, 21,397 patients with acute VTE were enrolled in the RIETE, and 896 (4.2%) were Italian. Of these Italian patients, 423 (47%) were males, and mean age was 64 ± 11 years. Three hundred sixty patients (40%) initially presented with PE; 65 (7.3%) presented with arm DVT, and 351 (39%) presented with proximal lower-limb DVT. Overall, 156 patients (17%) developed the VTE after ≥4 days of immobility, 137 (15%) after surgery. Two hundred fifty-three patients (28%) had active cancer, and 337 (38%) had an unprovoked VTE (Table 1).

Surgery

One hundred thirty-seven patients suffered VTE after surgical procedures: 47% of these were males with a mean age of

Table 1 Clinical characteristics and outcomes of Italian patients enrolled in RIETE, according to their risk factors for VTE.

	All	Surgery	Immobility ≥4 days	Neither
Patients, N	***896***	***137***	***156***	***603***
Clinical characteristics				
Gender (male)	423 (47%)	64 (47%)	56 (36%)	303 (50%)
Age (years ± SD)	64 ± 11	60 ± 20	74 ± 16	63 ± 18
Body weight (kg ± SD)	73 ± 14	72 ± 16	71 ± 12	75 ± 15
Height (cm ± SD)	167 ± 11	166 ± 12	164 ± 12	167 ± 11
Outpatient	405 (46%)	46 (34%)	46 (30%)	313 (53%)
Underlying conditions				
Chronic lung disease	59 (6.6%)	11 (8.0%)	19 (12%)	29 (4.8%)
Chronic heart failure	48 (5.4%)	4 (2.9%)	21 (14%)	23 (3.8%)
CrCl <30 mL/min	41 (4.7%)	4 (3.0%)	13 (8.6%)	24 (4.1%)
Risk factors				
Cancer	253 (28%)	43 (31%)	35 (22%)	175 (29%)
Prior VTE	135 (15%)	13 (9.5%)	13 (8.3%)	109 (18%)
VTE characteristics				
Clinically overt PE	360 (40%)	67 (49%)	77 (49%)	216 (36%)
If only DVT signs:				
Proximal DVT	351 (76%)	47 (78%)	59 (82%)	245 (75%)
Upper extremity DVT	65 (12%)	8 (11%)	6 (7.6%)	51 (13%)
Treatment				
Initial therapy, UFH	130 (15%)	26 (19%)	24 (15%)	80 (13%)
Initial therapy, LMWH	741 (83%)	108 (79%)	131 (84%)	502 (83%)
Mean LMWH doses (IU/kg)	187 ± 43	192 ± 43	186 ± 44	186 ± 43
Long-term, AVK drugs	566 (63%)	80 (58%)	81 (52%)	405 (67%)
Long-term, LMWH	299 (33%)	52 (38%)	69 (44%)	178 (30%)
Inferior vena cava filter	35 (3.9%)	8 (5.8%)	5 (3.2%)	22 (3.6%)
3-month outcome				
Major bleeding	19 (2.1%)	6 (4.4%)	6 (3.8%)	7 (1.2%)
Fatal bleeding	7 (0.8%)	2 (1.5%)	3 (1.9%)	2 (0.3%)
Recurrent DVT	2 (0.2%)	1 (0.7%)	0	1 (0.2%)
Recurrent PE	10 (1.1%)	1 (0.7%)	2 (1.3%)	7 (1.2%)
Fatal PE	21 (2.3%)	2 (1.5%)	12 (7.7%)	7 (1.2%)
Overall death	77 (8.6%)	13 (9.5%)	27 (17%)	37 (6.1%)

Abbreviations: VTE, venous thromboembolism; SD, standard deviation; CrCl, creatinine clearance; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; AVK, anti-vitamin K drugs; OR, odds ratio; CI, confidence intervals.

Table 2 Surgical patients with subsequent VTE and their prophylaxis.

Type of surgery	Patients, N	Mean age (years±SD)	Prophylaxis (yes)	Prophylaxis LMWH	Duration (days±SD)
All	137	60±20	(%)	(%)	30±58
Major orthopedic	24 (18%)	73±17	24(100%)	22 (100%)	46±94
Other orthopedic	14 (10%)	47±18	12 (86%)	11 (100%)	49±69
Cancer	15 (11%)	69±11	9 (60%)	9 (100%)	17±10
Abdominopelvic	28 (20%)	54±20	14 (50%)	10 (83%)	19±11
Genitourinary	19 (14%)	57±21	10 (53%)	9 (100%)	14±9.2
Neurosurgery	9 (6.6%)	58±15	2 (22%)	2 (100%)	12±2.8
Vascular	5 (3.6%)	63±15	3 (60%)	3 (100%)	23±12
Other	23 (17%)	60±22	10 (44%)	6 (67%)	18±9.7

60 ± 20 years (Table 2). Of these, 49% initially presented with PE, and only 61% of them VTE prophylaxis with LMWH was prescribed for 94% of the patients, frequently for an extended period (i.e., 30 ± 58 days). The surgical procedures most frequently involved were orthopedic (18% had major orthopedic surgery, and 10% had some other orthopedic procedure), followed by abdominopelvic surgery (20% for abdominal procedures and 14% for genitourinary interventions). The rate of VTE after neurosurgery and vascular surgery was relatively low (6.6% and 3.6%, respectively). VTE after oncological surgery was reported in 11% of cases. All other surgical procedures accounted for nearly 17% of VTE cases.

Immobility and medical illness

Immobility ≥4 days for nonsurgical procedures was reported in 156 patents (Table 3). Thirty-six percent were male, and their mean age was 74 ± 16 years. Of these, 49% initially presented with PE. Both acute and chronic medical illnesses induced immobility. Among the acute causes of immobility, 5.0% of patients experienced ischemic events (1.8% ischemic heart disease and 3.2% ischemic stroke), 5.8% experienced heart failure and 5.1% experienced acute infection. The chronic medical illness associated with immobility included mainly minor trauma (i.e., injuries that did not require surgery), 17%; arthropathy, 10%; COPD, 5.1%; leg paralysis, 1.3%; cancer, 6.4%; mental disorders, 24%.

VTE prophylaxis was provided for 24% of immobilized patients, mainly with LMWH, with 32 ± 47 days of prophylaxis. Immobilized patients were kept mainly at home (93% of cases), but a small number of cases stayed in hospitals (3.2%) or long-term facilities (3.8%).

Treatment

Most patients (83%) received initial therapy with low-molecular-weight heparin (LMWH) or fondaparinux, and 15% received unfractionated heparin. Less than 2% underwent thrombolysis or received other drugs as initial therapy. Long-term treatment for VTE was performed with LMWH in 15% of cases and with AVK drugs in 80% of cases; in less than 5% of cases, other drugs were chosen. Vena cava filter placement was performed in 3.9% of cases.

Of the 137 patients with postoperative VTE, 61% had received VTE prophylaxis. Of the 156 patients with recent immobility, 24% had received VTE prophylaxis.

Outcomes

The incidence of fatal PE during the first 3 months of therapy was 1.5% for patients with postoperative VTE, 7.7% for those who had been immobilized, and 1.2% for patients with unprovoked VTE. The incidence of fatal bleeding was 1.5%, 1.9% and 0.3%, respectively. Of the 137 patients with postoperative

Table 3 Reason for immobility and type of prophylaxis in Italian patients with VTE.

Reason for immobility	Patients, N	Mean age years±SD)	Place of immobility (hospital)	Prophylaxis (yes)	Prophylaxis with LMWH	Duration (days±SD)
All	156	74±16	23 (15%)	38 (24%)	22 (60%)	3.2±1.1
Trauma with no surgery	26 (17%)	67±19	2 (7.7%)	13 (50%)	11 (85%)	3.2±1.0
Mental disorders	31 (20%)	81±13	2 (6.5%)	3 (9.7%)	1 (33%)	3.6±1.3
Acute infection	8 (5.1%)	71±21	2 (25%)	2 (25%)	1 (50%)	2.3±0.5
Arthropathy	16 (10%)	79±13	1 (6.3%)	1 (6.3%)	0 (0%)	3.7±1.1
Leg paralysis	2 (1.3%)	70±2.8	0 (0%)	0 (0%)	-	4.0±1.4
Cancer	10 (6.4%)	67±16	1 (10%)	3 (30%)	2 (67%)	2.9±1.2
Chronic lung disease	8 (5.1%)	76±6.1	2 (25%)	1 (13%)	1 (100%)	2.9±1.0
Acute stroke	5 (3.2%)	76±10	2 (40%)	1 (20%)	1 (100%)	3.2±1.1
Heart failure	9 (5.8%)	83±9.0	1 (11%)	4 (44%)	1 (25%)	3.2±0.8
Ischemic heart disease	3 (1.9%)	72±2.1	3 (100%)	3 (100%)	0 (0%)	2.7±0.6
Other	38 (24%)	69±16	7 (18%)	7 (18%)	4 (67%)	3.1±1.1

VTE, 61% had received VTE prophylaxis. Of the 156 patients with recent immobility, 24% had received VTE prophylaxis.

Discussion

The data presented in this analysis confirm the existence of significant differences in outcomes (fatal PE, fatal bleeding, and overall death) between surgical patients and immobilized patients treated for acute VTE. Furthermore, a substantial underuse of thromboprophylaxis was found in patients with immobility $\geq$4 days who eventually developed VTE compared with surgical patients who eventually developed VTE. To our knowledge, this is the first report on the influence of surgery or immobility in Italian patients with VTE. As of July 2008, Italy had enrolled 896 patients in the registry. The literature includes information concerning VTE in Italy from other registries, but their data are different and focused on other topics, as discussed below.

The mean age of the Italian patients enrolled in the RIETE was lower than that reported in the MASTER registry, which also enrolled patients affected by VTE [7]. Moreover, a high incidence of upper limb DVT has been recorded in the RIETE as compared with a previous Italian report by Balbarini et al. [8]. This difference might be related to better surveillance of central venous lines in the upper extremities, especially for oncology patients. One in every three (61%) surgical patients with VTE received VTE prophylaxis (94% with LMWH). These data are similar to those reported in a previous study by Ricci et al. [9]. However the duration of thromboprophylaxis for surgical patients in the RIETE was more prolonged (30$\pm$58 days), particularly when compared to the data on oncological surgery available from the ARISTOS registry [10].

Different data may be found for nonsurgical immobility. Only one in every 4 medical patients with immobility $>$4 days received VTE prophylaxis (with LMWH in 61% of patients). This rate of thromboprophylaxis is very low and differs from the data for Italian medical patients reported in another study, although only inpatients were evaluated in that study [11]. Again, in this clinical setting, the duration of thromboprophylaxis was rather long (32$\pm$47 days); however, it may actually be too short given that many medical illnesses (such as end-stage neoplasia, dementia, trauma without surgery, and leg paralysis) often induce prolonged bedrest. In the studied population, prophylaxis was provided for 35% of inpatients and 41% of immobilized patients in long-term care centers, but only 19% of patients treated at home. The evaluation of the duration and discontinuation of thromboprophylaxis in this area should be better evaluated given this patient population's higher risk for recurrences or bleeding complications. The high proportion of patients with dementia (20%) in our series confirms that many patients were immobilized for long periods. Consequently, prolonged thromboprophylaxis in immobilized patients with chronic medical illness should be considered in further studies, particularly because the current literature does not offer other data from Italy.

The initial therapy of patients with VTE frequently includes the use of unfractioned heparin (15%), although LMWH use remains considerable (83%). Other treatments, particularly thrombolysis, are reserved for a reduced number of cases. Long—term VTE treatment with LMWH occurred in an unexpectedly high number of our cases (33%) compared with the data from WODIT and ISCOAT [12,13], while oral anticoagulation with anti-vitamin K drugs was used in 63% of our patients. Other drugs accounted for less than 4% of patients, and a vena cava filter was inserted in nearly 4% of patients.

Regarding outcomes after the first three months of follow up, we recorded a 2.1% incidence of major bleeding events (fatal bleeding: 0.8%). These data differ from those reported in ISCOAT [13], although that study recorded a cumulative bleeding incidence for patients receiving ongoing oral anticoagulation for either recent VTE or atrial fibrillation. There was also was a 1.3% rate of VTE recurrences. This is similar to the rate reported in the PROLONG study, in which a 4.4% rate of recurrent VTE was reported in patients with increased d-dimer levels after an episode of VTE and the discontinuation of oral anticoagulants [14]. However, these data are different from those reported in the WODIT study and in another study by Prandoni et al. [15]. Finally, 8.6% of Italian patients died in our series (2.3% from fatal PE); these data are quite similar to those reported in a series by Giuntini et al. [16] and different from those reported by Prandoni et al. [15].

In conclusion, our data from a prospective series of consecutively enrolled patients indicate that immobilized patients with VTE are less likely to receive VTE prophylaxis than surgical patients. Because medical patients with VTE had a worse outcome (mostly due to a more severe presentation of VTE, coexisting underlying conditions, or associated therapies), a higher rate of VTE prophylaxis is warranted. Further studies should focus on this topic, particularly on the prescription of pharmacological prophylaxis and the type and duration of drugs used to reduce the VTE incidence in this clinical area.

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Conflict of interest statement

The authors have no conflict of interest.

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Appendix A. Italian Members of the RIETE Group

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, Rota L, Schenone A, Tiraferri E, Tonello D, Visonà A.

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