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Duration of anticoagulation after venous thromboembolism in real world clinical practice

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ABSTRACT

Introduction: Venous thromboembolism (VTE) carries a considerable risk of recurrence and anticoagulants should be administered for a minimum of three months. Since little is known about real life management of VTE, we aimed to describe current practice in the secondary prevention of VTE.
Materials and Methods: Using the database of an international, prospective registry on patients treated for VTE, RIETE, information was collected on risk factors for VTE and bleeding, anticoagulant treatment, and clinical outcomes during follow up. Multivariate analysis using logistic regression was performed to identify predictors of treatment duration.
Results: Of 6944 patients with a first episode of VTE 41.1% had unprovoked VTE, 31.8% had transient risk factors, 27.1% had cancer. After the exclusion of patients who died during the first year of observation, the rate of patients treated for >12 months was 55.1%, 41.9%, and 43.2%, respectively ($p < 0.001$). Pulmonary embolism at presentation, recurrence while on treatment, chronic heart failure and age >65 years were independently associated with treatment for >12 months. Body weight <75 kg, anemia, cancer, and the presence of transient risk factors were associated with treatment for 12 months or less. Major bleeding occurred more frequently than recurrent VTE in patients with VTE secondary to transient risk factors and cancer; fatal bleeding was more frequent than fatal recurrent PE in all subgroups.
Conclusions: We observed heterogeneous duration of anticoagulant treatment for the secondary prevention of VTE. A substantial proportion of patients, in particular those with VTE secondary to transient risk factors, may be exposed to a possibly unnecessary risk of bleeding.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) have a considerable long-term risk of recurrence [1,2]. The major determinant of this risk is the presence of identifiable major provoking factors at the time of the index event [3,4].

Based on evidence from clinical trials, the American College of Chest Physicians (ACCP) guidelines recommend 3 months of anticoagulant therapy in patients with venous thromboembolism (VTE) secondary to recent surgery or to a nonsurgical transient risk factor, and extended treatment duration in those with active cancer or unprovoked VTE [5]. However, little is known about patterns of management of VTE in real life, particularly after hospital discharge. Such information could identify amendable gaps in patient care.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Greece, Switzerland, Czech Republic and Macedonia), observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE. It started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the Registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and

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[1] A full list of the RIETE investigators is given in the appendix. Written permission has been obtained from all persons named in the acknowledgment.

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mortality, and risk factors for these outcomes. In the current analysis, we evaluated demographic and clinical characteristics of patients with VTE, trying to describe current practice in the secondary prevention of VTE and to identify determinants of duration of anticoagulant therapy.

Materials and Methods

Study Design

At each participating site, investigators of the RIETE registry enrolled consecutive patients with acute symptomatic VTE confirmed by objective testing including high probability ventilation-perfusion scan or positive spiral computerized tomography for PE, and positive compression ultrasonography for DVT. Treatment decisions were entirely left at the discretion of attending clinicians, and no therapeutic algorithms were provided. Patients enrolled in blinded randomized controlled trials on VTE treatment were excluded.

Investigators recorded data on a computer-based case report form and submitted the forms to a centralized coordinating center through a secure website. The RIETE coordinating center used multiple data quality control procedures to optimize data quality. In particular, data were regularly monitored to detect inconsistencies or errors, and queries requiring resolution by the local investigators were sent to each site. Furthermore, contract research organizations monitored data quality by comparing medical records with the submitted data during periodic visits to participating hospitals. All patients provided consent for participation in the registry in accordance with local ethics committee requirements. This Registry is supported by unrestricted educational grants from Sanofi Spain and Bayer Pharma AG.

The aim of the current study was to analyze actual treatment duration and factors associated with treatment duration in consecutive patients with a first episode of DVT of the lower limbs and/or PE enrolled in the RIETE registry. For this study, we involved only those centers where all study patients were regularly followed-up for at least 12 months. In all these centers, all patients underwent to follow-up clinical visits. The frequency of the visits was left to the discretion of the investigators at each center.

Patients were placed into subgroups according to the pathogenesis of VTE (unprovoked, secondary to cancer, secondary to a major transient risk factor). VTE was defined as unprovoked in the absence of cancer, surgery, leg trauma or fracture, medical immobilization, pregnancy, puerperium, or use of hormonal therapy.

Study Variables

The following baseline data were collected at the time of inclusion in the study: age; gender; body weight; VTE presentation (DVT or PE as the first presentation); presence of comorbid conditions including chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; concomitant medications, including antiplatelet drugs, statins, or steroids; presence of major provoking risk factors for VTE including active cancer (defined as newly diagnosed cancer, metastatic cancer or cancer undergoing treatment), recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ≥4 days 2 months prior to VTE), surgery (2 months prior to VTE), leg trauma or fracture, use of hormonal therapy, pregnancy or puerperium; laboratory results including full blood count and serum creatinine levels. Information on thrombophilia testing, when available, was also documented. Decision to test for thrombophilia was left to the discretion of attending physicians.

Therapeutic strategies were documented for both the treatment of the acute event and for the long-term secondary prevention. Information on the duration of secondary prevention of VTE was censored at >12 months. This cut-off was arbitrarily chosen since in real-life clinical practice treatment duration of secondary prevention usually exceeds the recommended cut-off of 3 months, and many patients are frequently left on treatment for a few additional months. The 1-year cut-off was therefore aimed to be sufficiently inclusive of all "definite" treatment durations.

During follow-up, investigators assessed the occurrence of symptomatic recurrent DVT (defined as a new non-compressible vein segment, or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography), recurrent symptomatic PE (defined as a new ventilation-perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography), or major bleeding (defined as fatal, retroperitoneal, spinal or intracranial, or requiring a transfusion of at least 2 units of blood). Information on mortality in the first 12 months after the index event was collected and assessed using medical record review, and proxy interviews when necessary. Information on the duration of secondary prevention of VTE was first estimated for the whole population and then after the exclusion of patients who died before day 365.

Statistical Analysis

Baseline characteristics are reported by means of descriptive statistics: continuous variables are expressed as mean plus or minus the standard deviation (SD) or as median with interquartile range when data did not have a normal distribution (according to the Wilk-Shapiro test); categorical data are given as counts and percentages. Baseline characteristics are compared between patients with unprovoked events and the other two patient subgroups, as well as the duration of anticoagulant treatment, using Mann Whitney test (for continuous variables)

Table 1
Clinical characteristics of patients, according to risk factors for VTE.

	Unprovoked	Transient risk factors	Cancer
Patients, N	2,851	2,209	1,884
Clinical characteristics,			
Mean age (years ± SD)	68 ± 16	62 ± 21‡	68 ± 13
Gender (male)	1,476 (52%)	837 (38%)‡	1,065 (57%)†
Body weight (mean kg ± SD)	77 ± 15	74 ± 16‡	72 ± 15‡
Initial VTE presentation,			
Pulmonary embolism	1,722 (60%)	1,279 (58%)	1,086 (58%)
Underlying diseases,			
Chronic heart failure	220 (7.72%)	196 (8.87%)	98 (5.20%)‡
Chronic lung disease	346 (12%)	213 (9.64%)†	230 (12%)
Recent major bleeding	24 (0.84%)	78 (3.53%)‡	50 (2.65%)‡
CrCl levels <60 mL/min	1,158 (41%)	804 (36%)†	807 (43%)
Anemia	617 (22%)	884 (40%)‡	1,118 (59%)‡
Risk factors for VTE,			
Recent surgery	-	539 (24%)‡	253 (13%)‡
Recent immobilization ≥4 days	-	1,282 (58%)‡	425 (23%)‡
Pregnancy or puerperium	-	101 (4.57%)‡	0
Estrogen use	-	285 (13%)‡	52 (2.76%)‡
Prolonged travel	-	114 (5.16%)‡	25 (1.33%)‡
Thrombophilia testing,			
Patients tested	1,003 (35%)	822 (37%)	205 (11%)‡
Factor V Leiden	103 (10%)	82 (9.98%)	12 (5.85%)
PT 20210 mutation	76 (7.58%)	89 (11%)*	20 (9.76%)
Antiphospholipid syndrome	86 (8.57%)	37 (4.50%)‡	15 (7.32%)
Protein C deficiency	20 (1.99%)	11 (1.34%)	4 (1.95%)
Protein S deficiency	32 (3.19%)	42 (5.11%)*	6 (2.93%)
Antithrombin deficiency	14 (1.40%)	3 (0.36%)*	2 (0.98%)
Concomitant medications,			
Antiplatelets (N = 6,709)	416 (15%)	403 (19%)‡	252 (14%)
Statins (N = 4,359)	445 (26%)	288 (20%)‡	271 (23%)
Corticosteroids (N = 6,700)	143 (5.20%)	154 (7.22%)†	287 (16%)‡

Differences between patients with transient risk factors or cancer and patients with unprovoked VTE: †p <0.01; ‡p <0.001.
Abbreviations: SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism.