

Baseline Analysis on the Outcome of Patients with Deep Vein Thrombosis (DVT) Before the Global Impact of New Oral Anticoagulants in Italy: Data from RIETE Registry

Pierpaolo Di Micco^{1*}, Adriana Visonà², Gianluca Di Micco³, Anna Guida⁴, David Jimenez⁵, Paolo Prandoni⁶, Iolanda Enea⁷, Alferio Niglio⁸, Laurent Bertoletti⁹ and Manuel Monreal¹⁰

¹Emergency Room, Fatebenefratelli Hospital of Naples, Italy

²Department of Angiology, Castelfranco Veneto, Italy

³Division of Cardiology, Fatebenefratelli Hospital of Naples, Italy

⁴Dipartimento Area Critica AOU S. Giovanni e Ruggi, Salerno, Italy

⁵Department of Pneumology, Hospital Universitario Ramon y Cajal, Madrid, Spain

⁶Clinica Medica, University of Padua, Italy

⁷Emergency Medicine, Ospedale Civile di Caserta, Italy

⁸Internal Medicine, Second University of Naples, Italy

⁹Thrombosis Research Group, EA3065, University Saint-Etienne, Jean Monnet, Saint-Etienne F-42023, France

¹⁰Servicio de Medicina Interna, Hospital Universitari Germans Trias y Pujol, Badalona, Spain

*Corresponding author: Pierpaolo Di Micco, Emergency Room, Fatebenefratelli Hospital of Naples, Italy, Tel: 393398 078146; E-mail: pdimicco@libero.it

Rec date: October 09, 2014, Acc date: November 19, 2014, Pub date: November 21, 2014

Copyright: © 2014 Di Micco P et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: In patients with venous thromboembolism (VTE), assessment of the risk of recurrent VTE and major bleeding may help to guide intensity and duration of anticoagulant therapy.

Methods: We used the Registro Informatizado de Enfermedad Tromboembólica (RIETE) to identify predictors of poor adherence to guidelines in patients with- and without cancer, and to assess the rate and severity of VTE recurrences and major bleeding during the course of anticoagulation in Italian patients with deep vein thrombosis (DVT).

Results: A total of 3541 patients with objectively diagnosed VTE were enrolled in Italy, of whom 1832 (52%) initially presented DVT. Of these, 409 (22%) patients had already known cancer at baseline. In all, 32% of patients with cancer and 74% of those without cancer received long-term therapy with vitamin K antagonists, 55% and 19% respectively received long-term therapy with low-molecular-weight heparin, and 11% and 5.3% respectively received long-term therapy with Fondaparinux. During the 3-month study period, DVT patients with cancer experienced an increased rate of DVT recurrences (odds ratio: 3.1; 95% CI: 1.2-8.2), major bleeding episodes (odds ratio: 4.3; 95% CI: 2.2-8.4), all-cause death (odds ratio: 11; 95% CI: 6.7-19), and fatal bleeding (odds ratio: 11; 95% CI: 1.1-101), compared with those without cancer. Interestingly, the rate of major bleeding events outweighed the rate of VTE recurrences, both in patients with cancer (19 major bleeds vs. 4 PE recurrences and 8 DVT recurrences) and in those without cancer (16 major bleeds vs. 5 PE recurrences and 9 DVT recurrences).

Conclusions: In real life, adherence of VTE therapy to guidelines is poor. During the course of anticoagulation, the rate of major bleeding events exceeded the rate of VTE recurrences.

Keywords: Deep vein thrombosis; RIETE; Venous thromboembolism; Low-molecular-weight heparin; New oral anticoagulants

Background

Acute venous thromboembolism (VTE) is a commonly diagnosed condition with significant morbidity and mortality [1]. Current guidelines from the American College of Chest Physicians (ACCP), based on the results of randomized clinical trials, recommend patients with VTE to be treated with unfractionated heparin, low-molecular-weight heparin (LMWH) or fondaparinux, followed by long-term anticoagulation, which is usually accomplished with vitamin K antagonists (VKA)[2,3]. As for the duration of anticoagulant therapy, current guidelines recommend that patients with unprovoked VTE be

treated for at least 3 months, and then to prolong therapy in patients at low or moderate risk for bleeding [4,5]. In patients with active cancer, guidelines recommend to continue therapy as far as the cancer is active [5]. For patients with transient risk factors for VTE, they recommend to discontinue therapy after the third month. However, since a number of patients are often excluded from randomized trials of anticoagulant therapy because of co-morbid conditions, short life expectancy, pregnancy, or contraindications to therapy, treatment regimens based on the results from randomized clinical trials may not be generalizable to all patients with VTE.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, Greece, Canada and Ecuador), 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 mortality, and risk factors for these outcomes [6-9].

Since the prescription of the new oral anticoagulants (NOACs) for acute and long-term therapy of VTE in Italy is ongoing since 2013, the aim of the current study was to use the RIETE data from Italian patients to assess the outcome (recurrent VTE, major bleeding and death) during the course of anticoagulation with classical anticoagulants (i.e. LMWH and VKA), so as to compare these data with those obtained with novel oral anticoagulants afterwards.

Methods

Inclusion criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan or ventilation-perfusion lung scintigraphy for PE), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

	Cancer	No cancer	Odds ratio (95% CI)
Patients, N	409	1,423	
Clinical characteristics,			
Age (mean years ± SD)	66 ± 14	60 ± 19‡	
Gender (males)	74 (57%)	558 (53%)	1.19 (0.82-1.72)
Body weight (mean kg ± SD)	72 ± 14	76 ± 16†	
Underlying diseases,			
Chronic heart failure	10 (7.8%)	48 (4.6%)	1.75 (0.86-3.56)
Chronic lung disease	5 (3.9%)	48 (4.6%)	0.84 (0.33-2.15)
Recent major bleeding	3 (2.3%)	6 (0.57%)	4.14 (1.02-16.8)
Abnormal creatinine levels	18 (15%)	83 (9.8%)	1.67 (0.96-2.90)
Other drugs,			
NSAIDs (N=445)	2 (1.6%)	15 (1.5%)	1.06 (0.24-4.70)
Steroids (N=447)	8 (6.5%)	48 (4.9%)	1.35 (0.62-2.92)
Aspirin (N=449)	18 (14%)	110 (11%)	1.35 (0.79-2.32)

Table 1: Clinical characteristics of Italian patients with DVT presentation enrolled in the RIETE registry. Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; CI,

confidence intervals. Differences between subgroups: p <0.05; †p <0.01; ‡p <0.001

Physicians participating in the RIETE registry ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study design

For this study, only patients recruited in Italian centers were considered. Aim of the present study was to analyze actual treatments used for DVT in Italy and clinical features associated with treatment duration in consecutive patients enrolled in the RIETE registry, followed-up for at least 3 months. Subjects were divided in two subgroups (cancer and non-cancer), other thrombotic risk factors were also recorded (i.e. 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 (i.e. DVT as the first presentation); presence of comorbid conditions including chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; concomitant medications use, including antiplatelet drugs, statins, or steroids; presence of major risk factors for VTE including active cancer (defined as newly diagnosed cancer, metastatic cancer or cancer undergoing treatment), 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 tests 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.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). Patients were followed-up in the outpatient clinic (or telephone interviews in patients who could not show up for a clinic visit). During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

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.

	Total	Cancer	No cancer	Odds ratio
				(95% CI)
Patients, N	1,832	409	1,423	
Long term treatment,				
Unfractionated heparin	3 (0.16%)	3 (0.73%)	0*	-
Low-molecular-weight heparin	492 (27%)	224 (55%)	268 (19%)‡	5.2 (4.1-6.6)
Fondaparinux	120 (7%)	45 (11%)	75 (5.3%)‡	2.2 (1.5-3.3)
Vitamin antagonists K	1,179 (64%)	129 (32%)	1,050 (74%)‡	0.16 (0.13-0.21)

Table 2: Long term treatments used in Italian patients with DVT enrolled in RIETE, Abbreviations: CI, confidence intervals. Differences between subgroups: *p <0.05; †p <0.01; ‡p <0.001

	Total	Cancer	No cancer	Odds ratio
				(95% CI)
Patients, N	1,832	409	1,423	
During anticoagulation,				
Recurrent PE	9 (0.49%)	4 (0.98%)	5 (0.35%)	2.8 (0.75-10)
Recurrent DVT	17 (0.93%)	8 (2.0%)	9 (0.63%)*	3.1 (1.2-8.2)
Major bleeding	35 (1.91%)	19 (4.6%)	16 (1.1%)‡	4.3 (2.2-8.4)
Overall death	77 (4%)	57 (14%)	20 (1.4%)‡	11 (6.7-19)
Fatal PE	3 (0.16%)	1 (0.24%)	2 (0.14%)	1.7 (0.16-19)

Table 3: Ninety-day outcome during the course of anticoagulant therapy in Italian patients with DVT enrolled in RIETE, Abbreviations: DVT- Deep vein thrombosis; PE- Pulmonary embolism; CI, Confidence intervals. Differences between subgroups: *p <0.05; †p <0.01; ‡p <0.001

Results

A total of 3541 patients with objectively diagnosed VTE were enrolled in Italy, of whom 1832 (52%) initially presented DVT. Of these, 409 (22%) patients had already known cancer at baseline (with or without additional risk factors). DVT patients with cancer were significantly older, weighed less, and more likely had recent major bleeding than those without cancer (Table 1).

As to the therapeutic strategies, 32% of patients with cancer and 74% of those without cancer received VKA therapy (Table 2). Additionally, 55% of patients with cancer and 19% of those without cancer received long-term therapy with LMWH. Interestingly, 11% of patients with cancer and 5.3% of those without cancer received long-term therapy with Fondaparinux.

During the 3-month study period, DVT patients with cancer experienced an increased rate of DVT recurrences, major bleeding episodes, all-cause death and fatal bleeding (Table 3). Interestingly however, the rate of major bleeding events outweighed the rate of VTE recurrences, both in patients with cancer (19 major bleeds vs. 4 PE recurrences and 8 DVT recurrences) and in those without cancer (16 major bleeds vs. 5 PE recurrences and 9 DVT recurrences).

Discussion

The objective of our study was to obtain clinical practice-based data from the RIETE registry on the management of symptomatic DVT. Our analysis provides useful information on clinical features of patients, management of DVT, and degree of adherence to DVT management guidelines. In our experience, obtained from a large series of Italian patients with acute DVT in the RIETE registry, only in two in every 3 patients with DVT adherence to ACCP recommendations [5] was good. Among DVT patients with cancer, only 55% received long-term therapy with LMWH, as recommended by the current guidelines [5,10]. Interestingly, an unexpected 11% of cancer patients (and 5.3% of those without cancer) received long-term therapy with Fondaparinux, in the absence of clinical trials comparing its efficacy and safety with standard therapy. Among DVT patients without cancer, only 74% received long-term therapy with VKAs, as recommended [5,11,12]. The reasons for this poor adherence warrant further investigation [10-12].

Our data also confirm that the 3-month outcome in patients with cancer is much worse (in terms of VTE recurrences, bleeding complications and mortality) than in those without cancer. But our most interesting finding was that the rate of major bleeding complications during the course of anticoagulation exceeded the rate of VTE recurrences, both in patients with cancer and in those without cancer. Moreover, the rate of fatal bleeding exceeded the rate of fatal PE in patients with cancer, but not in those without cancer.

The increased rate of bleeding complications seems to be related to the global complexity of the cancer patients that may also influence daily difficulties to have a good INR range if VKAs are chosen, while it is not expected for LMWH. The difficulties to manage INR in cancer patients on long term therapy with VKAs is one of the most important risk factors for bleeding, due to the frequent co-administration of other drugs (chemotherapy, antibiotics, NSAIDs or other analgesics), and invasive procedures. Moreover, the complexity of management of cancer patients with increased risk for both thrombotic and bleeding events concomitantly may explain the increased bleeding rate while taking anticoagulants for VTE during cancer.

Current guidelines on antithrombotic therapy provide a critical review of the literature related to the management of patients with VTE and lay the scientific groundwork for the standard of care, based largely on data from randomized controlled clinical trials. However, a number of VTE patients are often excluded from randomized clinical trials. Thus, there is scarce evidence on what would be the best therapeutic approach for these patients. The RIETE Registry was designed to gather and analyze data on treatment patterns and

outcomes in patients with acute VTE. In contrast to randomized controlled trials, there is no imposed experimental intervention: management is determined solely by physicians. Thus, it provides data on patients with VTE in a real-world situation with an unselected patient population. Data from RIETE are hypothesis-generating and provide feedback from real-world clinical situations. Strengths of the current analysis include that a large number of consecutive unselected patients were enrolled, and that the diagnosis of DVT both at baseline and during recurrences was objectively confirmed.

In conclusion, Italian patients enrolled in RIETE for acute DVT with cancer seem to present an increased haemorrhagic risk, in particular if treated with oral anticoagulants as VKAs. VKAs in fact seem to have increased bleeding risk compared to heparinoids in both groups (oncological and non-oncological patients).

References

1. Monreal M, Kakkar AK, Caprini JA, Barba R, Uresandi F, et al. (2004) RIETE Investigators. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. *J Thromb Haemost* 2: 1892-1898.
2. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, et al. (1999) Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 159: 445-453.
3. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, et al. (2007) The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. *Haematologica* 92: 199-205.
4. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, et al. (2000) Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 18: 3078-3083.
5. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, et al. (2012) American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141: e419S-494S.
6. Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, et al. (2008) Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* 117: 1711-1716.
7. Monreal M, Falgá C, Valdés M, Suárez C, Gabriel F, et al. (2006) Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE Registry. *J Thromb Haemost* 4: 1950-1956.
8. Trujillo-Santos J, Herrera S, Page MA, Soto MJ, Raventós A, et al. (2006) Predicting adverse outcome in outpatients with acute deep vein thrombosis: findings from the RIETE Registry. *J Vasc Surg* 44:789-793.
9. López-Jiménez L, Montero M, González-Fajardo JA, Arcelus JI, Suárez C, et al. (2006) RIETE Investigators. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). *Haematologica* 91: 1046-1051.
10. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, et al. (2014) Optimal Duration of Low Molecular Weight Heparin for the Treatment of Cancer-Related Deep Vein Thrombosis: The Cancer-DACUS Study. *J Clin Oncol* 32: 3607-3612.
11. Prandoni P (2014) Treatment of patients with acute deep vein thrombosis and/or pulmonary embolism: efficacy and safety of non-VKA oral anticoagulants in selected populations. *Thromb Res* 134: 227-233.
12. Vo T, Vazquez S, Rondina MT (2014) Current state of anticoagulants to treat deep venous thrombosis. *Curr Cardiol Rep* 16: 463.