

## TOPIC HIGHLIGHT

## Fragile Patients With Venous Thromboembolism, What did We Learn From RIETE

Eugenio Bucherini, Luis Manuel Hernández-Blasco, Carmen Fernández-Capitán, Alicia Lorenzo, Aurora Villalobos, Raimundo Tirado, Isabelle Mahé, Jana Hirmerova, Paolo Prandoni, Manuel Monreal, And the RIETE Investigators, A full list of the RIETE investigators is given in the appendix

Eugenio Bucherini, MD, Department of Vascular Medicine. Azienda U.S.L. Di Ravenna – O.C. Di Faenza. Ravenna. Italy

Luis Manuel Hernández-Blasco, Md. PhD, Department Of Pneumology, Hospital General Universitario De Alicante, Alicante, Spain

Carmen Fernández-Capitán, MD, PhD, Department Of Internal Medicine, Hospital Universitario La Paz, Madrid, Spain.

Alicia Lorenzo, MD, PhD, Department Of Internal Medicine, Hospital Universitario La Paz, Madrid, Spain.

Aurora Villalobos, MD, PhD, Department Of Internal Medicine. Hospital Regional Universitario De Málaga. Málaga. Spain.

Raimundo Tirado, MD, Department Of Internal Medicine, Hospital Infanta Margarita, Córdoba, Spain.

Isabelle Mahé, MD, PhD, Department Of Internal Medicine. Hôpital Louis Mourier. University Paris 7 (Aphp). Colombes. France.

Jana Hirmerova, MD, PhD, Department Of Internal Medicine, University Hospital Plzen, Plzen, Czech Republic

Paolo Prandoni, MD, PhD, Department Of Clinical Medicine, University Of Padua, Padua, Italy

Manuel Monreal, MD, PhD, Department Of Internal Medicine, Hospital De Badalona Germans Trias I Pujol, Universidad Católica De Murcia, Spain

Correspondence to: Manuel Monreal, Professor, MD, PhD, Servicio de Medicina Interna. Hospital Universitari Germans Trias i Pujol, 08916 Badalona (Barcelona), Spain.

Email: [mmonreal.germanstrias@gencat.cat](mailto:mmonreal.germanstrias@gencat.cat)

Telephone: +34 669675313

Received: April 9, 2015 Revised: May 7, 2015

Accepted: May 12, 2015

Published online: July 6, 2015

### ABSTRACT

In recent years, a number of new anticoagulants have been

developed for the treatment of venous thromboembolism (VTE), demonstrating significant reductions in major bleeding compared with standard therapy. Subgroup analyses showed favourable results for rivaroxaban in the so-called fragile patients (defined as those having creatinine clearance levels  $\leq 50$  mL/min, age  $\geq 75$  years or body weight  $\leq 50$  kg) compared with standard therapy. However, the prevalence of fragile patients with VTE in real life and their natural history during the course of anticoagulation has not been thoroughly investigated. We used the RIETE registry database to assess the proportion of fragile patients with VTE outside clinical trials, and their natural history during the course of anticoagulant therapy. We found that 43% of patients with VTE were fragile: 37% were aged  $\geq 75$  years, 4.0% weighed  $\leq 50$  kg, and 25% had CrCl levels  $\leq 50$  mL/min. During the course of anticoagulant therapy, the rate of major bleeding was over 2-fold higher in fragile- than in non-fragile patients: 6.6 (95% CI: 6.2-7.0) vs 2.3 (95% CI: 2.1-2.5) bleeds per 100 patient-years, and their recurrence rate was similar: 3.5 (95% CI: 3.2-3.8) vs 4.0 (95% CI: 3.7-4.2), respectively. Moreover, the rate of fatal bleeding was over 4-fold higher: 1.4 (95% CI: 1.2-1.6) vs 0.4 (95% CI: 0.3-0.5) deaths per 100 patient-years, and the rate of fatal PE was over 3-fold higher too: 2.5 (95% CI: 2.3-2.8) vs 0.7 (0.6-0.8), respectively.

© 2015 ACT. All rights reserved.

**Key words:** Venous thromboembolism; Real life; Registry; Anticoagulant therapy and outcome

Bucherini E, Hernández-Blasco LM, Fernández-Capitán C, Lorenzo A, Villalobos A, Tirado R, Mahé I, Hirmerova J, Prandoni P, Monreal M. Fragile Patients With Venous Thromboembolism, What did We Learn From RIETE. *International Journal of Hematology Research* 2015; 1(2): 35-39 Available from: URL: <http://www.ghrnet.org/index.php/ijhr/article/view/1153>

## INTRODUCTION

The benefits of anticoagulant therapy in patients with acute venous thromboembolism (VTE) are well established. In recent years, a number of direct oral anticoagulants (DOACs) have been developed for the treatment of VTE, demonstrating non-inferiority compared with standard therapy, and most showed significant reductions in major bleeding<sup>[1-5]</sup>. Hence, direct factor Xa inhibitors apixaban and rivaroxaban, and direct thrombin inhibitor dabigatran etexilate have been approved for use in the European Union for the treatment of patients with deep vein thrombosis (DVT) or pulmonary embolism (PE), and for prevention of recurrent DVT and PE. Another direct factor Xa inhibitor, edoxaban, is currently being evaluated by the regulatory agencies in Europe for both indications.

In a systematic review of registration-track trials of the DOACs in the treatment of VTE, we reported a potential benefit of the new compounds in terms of major bleeding rate and corresponding case-fatality rate (CFR) in comparison with standard therapy, and a similar CFR of recurrent VTE<sup>[6,7]</sup>. The use of DOACs was associated with a lower rate of major bleeding and critical bleeding (including intracranial bleeding) and a trend towards a lower CFR of bleeding compared with standard therapy. In sensitivity analyses, these results were consistent under different assumptions, thus supporting the robustness of the data.

Subgroup analyses from these randomized clinical trials have delivered further promising results. For example, data from the EINSTEIN DVT and PE trials showed favourable results for rivaroxaban in the so-called fragile patients (defined as those having creatinine clearance levels  $\leq 50$  mL/min, age  $\geq 75$  years or body weight  $\leq 50$  kg) compared with standard therapy, where the rate of VTE recurrences was 2.7% and 3.8%, respectively (hazard ratio [HR]: 0.68; 95% CI 0.39-1.18) and the rate of major bleeding was 1.3% and 4.5%, respectively (HR: 0.27; 95% CI 0.13-0.54)<sup>[8]</sup>. Thus, fragile patients with VTE might be ideal candidates for long-term therapy with rivaroxaban since their bleeding rate with rivaroxaban was much lower than the rate in those receiving standard therapy. However, the prevalence of fragile patients with VTE outside clinical trials and their natural history during the course of anticoagulant therapy has not been thoroughly investigated. This article will review available information on the natural history of VTE in fragile- and non-fragile patients outside clinical trials.

## VTE PATIENTS IN REAL WORLD

A large proportion of VTE patients were not recruited into randomized clinical trials involving DOACs owing to the presence of a number of exclusion criteria, e.g. renal insufficiency, high bleeding risk, concomitant therapies, pregnancy, recent thrombolytic therapy or recent trauma/major surgery<sup>[9]</sup>. Hence, clinical information is limited in patient subgroups, e.g. fragile patients or patients with renal impairment or cancer, who may be at higher risk of bleeding and/or VTE.

The Registro Informatizado de Enfermedad TromboEmbólica (RIETE Registry) is an ongoing, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Belgium, Czech Republic, Republic of Macedonia, Greece, Canada, United States, Brazil, Venezuela, Argentina and Ecuador), prospective registry of consecutive patients with acute VTE designed to gather and analyze data on treatment patterns and outcomes in patients with acute VTE<sup>[10-13]</sup>. 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. It is aimed to improve the treatment of VTE through a better understanding of patient demographics, management, and in-hospital and post-discharge outcomes.

In contrast to randomized controlled trials, there was no imposed experimental intervention in RIETE: the management was determined solely by physicians. Thus, it provides data on patients with VTE outside clinical trials with an unselected patient population. It can, therefore, help to identify practices for providing treatment to patients, and factors associated with better or worse patient outcomes. Data from RIETE are hypothesis-generating and provide feedback from real-world clinical situations which may be of help when designing new randomized clinical studies. Patients were managed according to the clinical practice of each participating hospital (i.e., there is no standardization of treatment). The drug, dose and duration of anticoagulant therapy were recorded. During each visit, any signs or symptoms suggesting VTE recurrences, bleeding complications, and any other adverse events were noted. After initial diagnosis, patients were followed-up for at least 3 months.

## VTE PATIENTS WEIGHING <50 KG

The influence of extreme body weight on the natural history of VTE during the course of anticoagulant therapy had not been consistently studied. As of August 2004, 8845 patients with acute VTE were enrolled from 94 participating centres<sup>[14]</sup>. Of these, 169 (1.9%) weighed  $<50$  kg, 8382 (95%) weighed 50-100 kg and 294 (3.3%) weighed  $>100$  kg. Patients weighing  $<50$  kg received higher doses of low-molecular-weight heparin (LMWH) than those weighing 50-100 kg ( $208 \pm 51$  vs  $181 \pm 36$  IU/kg/day) and had a higher rate of bleeding complications during the first 15 days of therapy: five patients (3.0%) had major bleeding and nine patients (5.3%) had minor bleeding, compared with 1.3% and 2.6%, respectively in patients weighing 50-100 kg (odds ratio [OR]: 2.2; 95% CI 1.2-4.0). They also had a higher mortality (7.7% vs 3.0%; OR: 2.7; 95% CI: 1.5-4.7). The use of high doses of LMWH ( $>200$  IU/kg/day) in over 50% of patients weighing  $<50$  kg may have contributed to this significant increase in the bleeding rate.

In another study, we examined the association between body mass index (BMI) and mortality during the first 3 months of therapy<sup>[15]</sup>. As of March 2006, there were 10,114 patients enrolled in RIETE. Of these, 153 (1.5%) were underweight (BMI  $<18.5$ ), 2,882 (28%) normal weight (BMI: 18.5-24.9), 4,327 (43%) overweight (BMI: 25.0-30.0) and 2,752 (27%) were obese (BMI:  $>30.0$ ). Underweight patients were significantly younger and more likely had cancer, immobilization or renal insufficiency compared with those with normal weight. During the first 3 months of therapy, their rates of major bleeding were 7.2% vs 2.7%, fatal bleeding were 2.0% vs 0.6% and all-cause death were 28% vs 12%, respectively. On multivariate analysis, the relative risk for death after adjusting for confounding variables including age, cancer or renal insufficiency in patients with underweight was: 2.1 (95% CI: 1.5-2.7) compared with patients with normal weight.

## RENAL INSUFFICIENCY

Patients with renal insufficiency are often excluded from clinical trials of anticoagulant therapy, which means that treatment regimens based on the results from clinical trials may not be suitable for these patients. Moreover, the influence of renal insufficiency on the risk

of bleeding complications, a factor which can lead to physicians withholding anticoagulant therapy, is not clear. Of 10526 patients enrolled in 2005, 88% had creatinine clearance (CrCl) levels >60 mL/min, 6.7% had 30-60 mL/min, and 5.6% had CrCl <30 mL/min<sup>[15]</sup>. Patients with CrCl levels <30 mL/min were more often female and significantly older than patients with CrCl >60 mL/min. They more likely had recent immobility or chronic heart failure, and less likely had recent surgery. Most patients in all 3 subgroups were initially treated with LMWH, but those with CrCl levels <30 mL/min more likely received unfractionated heparin (UFH) (8.8%) than those with CrCl levels >60 mL/min (6.1%). The rate of fatal PE during the first 15 days was 1.0%, 2.6%, and 6.6%, respectively. Major bleeding appeared in 1.0%, 4.0% and 5.4%, respectively. Fatal bleeding occurred in 0.2%, 0.3%, and 1.2%, respectively. Thus, patients with severe renal insufficiency had an increased rate of both fatal PE and fatal bleeding, but the risk of fatal PE far exceeded that of fatal bleeding. In fact, the rate of fatal PE was over 5-fold higher than that of fatal bleeding in all three groups, but patients with CrCl levels <30 mL/min had a 6-7 times greater mortality due to PE or bleeding than those with normal function.

In another study, we assessed the 3-month outcome in VTE patients with CrCl levels <30 mL/min<sup>[16]</sup>. In March 2007, 1037 of 18251 (5.7%) patients enrolled in RIETE had CrCl levels <30 mL/min at baseline. During the 3-month study period, these patients had an increased incidence of fatal bleeding, fatal PE, and overall death compared to those with CrCl levels >30 mL/min. Of 579 patients initially presenting with PE, 52 (9.0%) died of the initial PE event, 13 (2.2%) died of recurrent PE and 9 (1.6%) died of bleeding. During the first 15 days of therapy their 10% incidence of fatal PE was 10-fold higher than their 1.0% of fatal bleeding. From day 16 to 90, their 1.0% rate of fatal PE was non-significantly higher than their 0.5% rate of fatal bleeding. However, of 458 patients with CrCl levels <30 mL/min initially presenting with DVT alone, 14 (3.1%) had fatal bleeding and only one patient (0.2%) died of PE. These findings revealed the existence of major differences in outcome of VTE patients with severe renal insufficiency, according to their initial VTE presentation. In those initially presenting with PE, the rate of fatal PE was 7-fold higher than the rate of fatal bleeding, while in those initially presenting with DVT the rate of fatal bleeding was 10-fold higher than the rate of fatal PE.

Finally, in a third study, we evaluated the 15-day outcome in 38531 patients and used propensity score matching to compare patients treated with UFH with those treated with LMWH in 3 groups stratified by CrCl levels at baseline: >60 mL/min, 30 to 60 mL/min, or <30 mL/min<sup>[17]</sup>. Propensity score-matched groups showed an increased 15-day mortality for UFH compared with LMWH [4.5% vs 2.4% ( $p<0.001$ ), 5.4% vs 5.8% ( $p=NS$ ) and 15% vs 8.1% ( $p=0.02$ )], an increased rate of fatal PE [2.8% vs 1.2% ( $p<0.001$ ) 3.2% vs 2.5% ( $p=NS$ ), and 5.7% vs 2.4% ( $p<0.02$ )], and a similar rate of fatal bleeding (0.3% vs 0.3%, 0.7% vs 0.7%, and 0.5% vs 0.0%). Multivariate analysis confirmed

that patients treated with UFH were at increased risk for all-cause death (OR: 1.8; 95% CI, 1.3-2.4) and fatal PE (OR: 2.3; 95% CI, 1.5-3.6) compared with those receiving LMWH.

## ELDERLY PEOPLE

Some patients with VTE are often excluded from randomized clinical trials of anticoagulant treatment because of existing conditions (such as renal insufficiency, short life expectancy, long-term immobility, or because of contraindications to therapy). These conditions occur more often in elderly patients. Moreover, the influence of advanced age on the risk of bleeding, a factor which can lead to physicians withholding anticoagulant therapy, is not clear. Up to September 2005, 2,890 (22%) of 13,011 patients in RIETE were aged  $\geq 80$  years<sup>[19]</sup>. Most patients in both subgroups (93% and 90%, respectively) were initially treated with LMWH. As for long-term therapy, 34% of patients aged  $\geq 80$  years, and 25% of those <80 years received LMWH.

During the first 3 months of anticoagulant therapy, 106 patients (3.7%) aged  $\geq 80$  years and 107 (1.1%) aged <80 years (1.1%) died of PE (OR: 3.6; 95% CI: 2.7-4.7). Eighty-three patients aged  $\geq 80$  years (2.9%) died of their initial PE 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  $\geq 80$  years old. Moreover, in patients aged  $\geq 80$  years the 3.4% rate of major bleeding exceeded the 2.1% rate of VTE recurrences. However, the 3.7% rate of fatal PE clearly outweighed the 0.8% rate of fatal bleeding.

In another study, we used the RIETE Registry data to assess the risk of fatal PE and fatal bleeding in 16,199 patients with lower limb DVT (without symptomatic PE at the time of inclusion) during the three months after diagnosis, with patients categorized according to age<sup>[20]</sup>. During the first 3 months of anticoagulant therapy, there were 31 fatal PE events (0.19%) and 83 fatal bleeds (0.51%). During the first 7 days of therapy, the rate of fatal PE was similar to the rate of fatal bleeding (12 vs 14 deaths, respectively; OR: 0.86; 95% CI: 0.39-1.87). However, from Day 8 to Day 90 the rate of fatal bleeding was greater than the rate of fatal PE (69 vs 19 deaths; OR: 3.64; 95% CI: 2.22-6.20). The higher frequency of fatal bleeding compared to fatal PE from Day 8 to Day 90 appeared to be confined to patients aged  $\geq 60$  years. On multivariate analysis, the patient's age was independently associated with an increased risk for death from bleeding during the first 3 months: every 10 years the odds ratio increased by 1.37 (95% CI: 1.12-1.67).

## FRAGILE PATIENTS AND BLEEDING

Up to February 2015, there were 54,939 patients with acute VTE in RIETE. Of these, 20,558 (37%) were aged  $\geq 75$  years, 2,194 (4.0%) weighed  $\leq 50$  kg, 13,736 (25%) had CrCl levels  $\leq 50$  mL/min, and 23,866 (43%) were fragile (Table 1)<sup>[21]</sup>. During the course

**Table 1** Clinical characteristics and rate of major bleeding events during the course of anticoagulant therapy in several subgroups of patients with acute venous thromboembolism.

	N	Major bleeding	Fatal bleeding	VTE recurrences	Fatal PE
Age $\geq 75$ years	20,558	6.4 (6.0-6.8)‡	1.4 (1.2-1.6)‡	3.2 (2.9-3.5)‡	2.4 (2.2-2.7)‡
Body weight $\leq 50$ kg	2,194	9.1 (7.5-11)‡	2.7 (1.8-3.7)‡	5.1 (3.9-6.6)	4.4 (3.3-5.8)‡
CrCl levels $\leq 50$ mL/min	13,736	8.1 (7.5-8.7)‡	1.8 (1.5-2.1)‡	3.9 (3.5-4.3)	3.6 (3.2-4.0)‡
Any of the above (Fragile)	23,866	6.6 (6.2-7.0)‡	1.4 (1.2-1.6)‡	3.5 (3.2-3.8)*	2.5 (2.3-2.8)‡
None of the above (Ref.)	31,073	2.3 (2.1-2.5)	0.4 (0.3-0.5)	4.0 (3.7-4.2)	0.7 (0.6-0.8)

Comparisons between different rates and those in non-fragile patients: \* $p<0.05$ ; † $p<0.01$ ; ‡ $p<0.001$ . Rates are expressed as number of events per 100 patient-years. VTE: venous thromboembolism; PE: pulmonary embolism; CrCl: creatinine clearance levels.

of anticoagulant therapy, the rate of major bleeding was over 2-fold higher in fragile- than in non-fragile patients: 6.6 (95% CI: 6.2-7.0) vs 2.3 (95% CI: 2.1-2.5) bleeds per 100 patient-years, and their recurrence rate was similar: 3.5 (95% CI: 3.2-3.8) vs 4.0 (95% CI: 3.7-4.2), respectively. Moreover, the rate of fatal bleeding was over 4-fold higher: 1.4 (95% CI: 1.2-1.6) vs. 0.4 (95% CI: 0.3-0.5) deaths per 100 patient-years, and the rate of fatal PE was over 3-fold higher too: 2.5 (95% CI: 2.3-2.8) vs 0.7 (0.6-0.8), respectively.

## DISCUSSION

In real world practice, over 40% of patients with acute symptomatic VTE were fragile (i.e., weighed  $\leq 50$  kg, had CrCl levels  $\leq 50$  mL/min or were aged  $\geq 75$  years). During the course of anticoagulant therapy they had an over 2-fold higher rate of major bleeding complications than non-fragile patients. Since rivaroxaban seemed to be (in post-hoc analyses) equally effective and safer than standard therapy in this patient population, our data may help to identify the ideal candidates for long-term therapy with this new compound.

Certainly, RIETE has a number of limitations. First, patients are not treated with a standardized anticoagulant regimen; treatment varies with local practice, and is likely to be influenced by a physician's assessment of a patient's risk of bleeding. Second, to fulfil the definition of fatal PE in RIETE, patients must first experience an objectively confirmed PE event, followed by death within 10 days. Thus, all sudden unexplained deaths that are usually considered as "likely" fatal recurrent PE are not considered, and the rate of fatal PE may have been underestimated, especially after hospital discharge. Third, RIETE is an ongoing observational registry (and not a randomized controlled trial), and the data are hypothesis-generating. Thus, we should be extremely cautious before suggesting changes in treatment strategies based on uncontrolled registry data. Finally, there is no external adjudication of the events, which are merely reported by the authors. Strengths of the registry include that a large number of consecutive unselected patients were enrolled, and a large number of variables were considered.

### Coordinator of the RIETE Registry:

Dr. Manuel Monreal (Spain)

### RIETE Steering Committee Members:

Dr. Hervé Decousus (France)

Dr. Paolo Prandoni (Italy)

Dr. Benjamin Brenner (Israel)

### RIETE National Coordinators:

Dr. Raquel Barba (Spain)

Dr. Pierpaolo Di Micco (Italy)

Dr. Laurent Bertoletti (France)

Dr. Sebastian Schellong (Germany)

Dr. Inna Tzoran (Israel)

Dr. Abilio Reis (Portugal)

Dr. Marijan Bosevski (R.Macedonia)

Dr. Henri Bounameaux (Switzerland)

Dr. Radovan Malý (Czech Republic)

Dr. Philip Wells (Canada)

Dr. Manolis Papadakis (Greece)

### RIETE Registry Coordinating Center:

S & H Medical Science Service

## APPENDIX

**Members of the RIETE Group:** SPAIN: Adarraga MD, Arcelus JI, Auguet T, Ballaz A, Barba R, Barrón M, Barrón-Andrés B,

Bascuñana J, Blanco-Molina A, Casado I, Castejón-Pina N, de Miguel J, del Molino F, del Toro J, Díaz JA, Espuis M, Falgá C, Fernández-Capitán C, Font L, Gallego P, García-Bragado F, Gómez V, González J, Grau E, Guijarro R, Guirado L, Gutiérrez J, Hernández-Blasco L, Hernández-Huerta S, Jara-Palomares L, Jaras MJ, Jiménez D, Lacruz B, Lecumberri R, Lobo JL, López-Jiménez L, López-Reyes R, López-Sáez JB, Lorente MA, Lorenzo A, Madridano O, Maestre A, Marchena PJ, Martín-Antorán JM, Martín-Martos F, Monreal M, Morales MV, Nauffal D, Nieto JA, Núñez MJ, Ochoa-Urizar FP, Otero R, Pagán B, Pedrajas JM, Pérez G, Peris ML, Pons I, Porras JA, Riera-Mestre A, Rivas A, Rodríguez-Dávila MA, Rosa V, Ruiz-Giménez N, Sampéris A, Sánchez R, Sanz O, Soler S, Suriñach JM, Tiberio G, Tirado R, Tolosa C, Trujillo-Santos J, Uresandi F, Valero B, Valle R, Vela J, Vidal G, Villalobos A, Villalta J, BELGIUM: Vanassche T, Verhamme P, CANADA: Wells P, CZECH REPUBLIC: Hirmerova J, Malý R, ECUADOR: Salgado E, FRANCE: Bertoletti L, Bura-Riviere A, Farge-Bancel D, Hij A, Mahé I, Merah A, Moustafa F, GERMANY: Schellong S, GREECE: Babalis D, Papadakis M, Tzinieris I, ISRAEL: Braester A, Brenner B, Tzoran I, ITALY: Apollonio A, Barillari G, Bucherini E, Ciammaichella M, Di Micco P, D'Onofrio P, Ferrazzi P, Lodigiani C, Maida R, Mastroiacovo D, Pace F, Pesavento R, Pinelli M, Piovello C, Prandoni P, Rota L, Tiraferri E, Tonello D, Tufano A, Visonà A, Zalunardo B, LATVIA: Belovs A, Skride A, PORTUGAL: Pipa S, Ribeiro JL, Sousa MS, REPUBLIC OF MACEDONIA: Bosevski M, SWITZERLAND: Alatri A, Bounameaux H, Calanca L, Mazzolai L.

## ACKNOWLEDGEMENTS

We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for a 22.2% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S & H Medical Science Service, for their quality control data, logistic and administrative support and Prof. Salvador Ortiz, Universidad Autónoma de Madrid and Statistical advisor at S&H Medical Science Service for the statistical analyses in this manuscript.

## CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

## REFERENCES

- Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361: 2342-2352.
- Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; 369: 799-808.
- EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499-2510.
- EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366: 1287-1297.
- Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwacho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban

- versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; 369: 1406-1415.
6. Gomez-Outes A, Lecumberri R, Suarez-Gea ML, Terleira-Fernandez AI, Monreal M, Vargas-Castrillo E. Case-fatality rates of recurrent thrombo-embolism and bleeding in patients receiving direct oral anticoagulants for the initial and extended treatment of venous thromboembolism: a systematic review. *J Cardiovasc Pharmacol Ther* 2015 (in press).
  7. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg* 2014; 48: 565-575.
  8. Prins MH, Lensing AW, Bauersachs R, van BB, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; 11- 21.
  9. Tzoran I, Brenner B, Papadakis M, Di Micco P, Monreal M. VTE Registry. What can be learned from RIETE? *Rambam Maimonides Med J*. 2014 Oct 29; 5: e0037. doi: 10.5041/RMMJ.10171.
  10. Nieto JA, Bruscas MJ, Ruiz-Ribo D, Trujillo-Santos J, Valle R, Ruiz-Gimenez N, Monreal M. Acute venous thromboembolism in patients with recent major bleeding. The influence of the site of bleeding and the time elapsed on outcome. *J Thromb Haemost* 2006; 4: 2367-2372.
  11. Monreal M, Falga C, Valdes M, Suarez C, Gabriel F, Tolosa C, Montes J. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost* 2006; 4: 1950-1956.
  12. Trujillo-Santos J, Nieto JA, Tiberio G, Piccioli A, Di MP, Prandoni P, Monreal M. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; 100: 435-439.
  13. Muriel A, Jimenez D, Aujesky D, Bertoletti L, Decousus H, Laporte S, Mismetti P, Munoz FJ, Yusen R, Monreal M. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J Am Coll Cardiol* 2014; 63: 1675-1683.
  14. Barba R, Marco J, Martin-Alvarez H, Rondon P, Fernandez-Capitan C, Garcia-Bragado F, Monreal M. The influence of extreme body weight on clinical outcome of patients with venous thromboembolism: findings from a prospective registry (RIETE). *J Thromb Haemost* 2005; 3: 856-862.
  15. Barba R, Zapatero A, Losa JE, Valdes V, Todoli JA, Di MP, Monreal M. Body mass index and mortality in patients with acute venous thrombo-embolism: findings from the RIETE registry. *J Thromb Haemost* 2008; 6: 595-600.
  16. Monreal M, Falga C, Valle R, Barba R, Bosco J, Beato JL, Maestre A. Venous thromboembolism in patients with renal insufficiency: findings from the RIETE Registry. *Am J Med* 2006; 119: 1073-1079.
  17. Falgá C, Capdevila JA, Soler S, Rabuñal R, Sánchez Muñoz-Torrero JF, Gallego P, Monreal M. Clinical outcome of patients with venous thrombo-embolism and renal insufficiency. Findings from the RIETE registry. *Thromb Haemost* 2007; 98: 771-776.
  18. Trujillo-Santos J, Schellong S, Falga C, Zorrilla V, Gallego P, Barron M, Monreal M. Low-molecular-weight or unfractionated heparin in venous thromboembolism: the influence of renal function. *Am J Med* 2013; 126: 425-434.
  19. Lopez-Jimenez L, Montero M, Gonzalez-Fajardo JA, Arcelus JL, Suarez C, Lobo JL, Monreal M. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). *Haematologica* 2006; 91: 1046-1051.
  20. Muñoz-Torrero JF, Bounameaux H, Pedrajas JM, Lorenzo A, Rubio S, Kearon C, Hernandez L, Monreal M. Effects of age on the risk of dying from pulmonary embolism or bleeding during treatment of deep vein thrombosis. *J Vasc Surg* 2011; 54 (6 Suppl): 26S-32S.
  21. [www.riete.org](http://www.riete.org). Accessed on March 06,2015.
- Peer reviewer:** Stavros K. Kakkos, MD, PhD, RVT, Department of Vascular Surgery, University of Patras Medical School, Patras, 26504, Greece.