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

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


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.
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\[1-5\]. 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\[6,7\]. 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 ≤50 mL/min, age ≥75 years or body weight ≤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 0.49-0.94)\[8\]. 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\[9\]. 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 TromboEmbolica (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\[10-13\]. 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 inhospital 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\[14\]. 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±51 vs 181±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\[15\]. 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.

RENAI 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[19]. 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 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[19]. 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 0.5% rate of fatal bleeding. However, of 458 patients with CrCl levels <30 mL/min initially presenting with VTE 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 VTE 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[18]. 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 0.5%). 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 ≥80 years[16]. Most patients in both subgroups (93% and 90%, respectively) were initially treated with LMWH. As for long-term therapy, 34% of patients aged ≥80 years, and 25% of those <80 years received LMWH.

During the first 3 months of anticoagulant therapy, 106 patients (3.7%) aged ≥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 ≥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 ≥80 years old. Moreover, in patients aged ≥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[19]. 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 ≥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 ≥75 years, 2,194 (4.0%) weighed ≤50 kg, 13,736 (25%) had CrCl levels ≤50 mL/ min, and 23,866 (43%) were fragile (Table 1)[20]. During the course

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and rate of major bleeding events during the course of anticoagulant therapy in several subgroups of patients with acute venous thromboembolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Major bleeding</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>20,588</td>
</tr>
<tr>
<td>Body weight ≤50 kg</td>
<td>2,194</td>
</tr>
<tr>
<td>CrCl levels ≤30 mL/min</td>
<td>13,736</td>
</tr>
<tr>
<td>Any of the above (Frail)</td>
<td>23,866</td>
</tr>
</tbody>
</table>

Comparisons between different rates and those in non-frail 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 fulfill 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.

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**APPENDIX**


**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.

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