Rivaroxaban for the treatment of venous thromboembolism in real life

A single-center prospective study

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Abstract
The clinical profile, evolution and complications of treatment with rivaroxaban in a cohort of patients presenting with venous thromboembolism (VTE) were analyzed in an observational, non-interventional and prospective study.

A total of 111 patients were included in the study. Clinical data were collected from the medical history of the patients and recorded in a specific database.

Mean age was 63.8±17.4 years, 53.2% of patients were men, 55.9% had at least another concomitant condition, and 40.9% at least 1 VTE risk factor. 54.1% of patients presented with deep venous thrombosis, 32.4% with pulmonary embolism and 13.5% with both conditions simultaneously. The 61% of patients were admitted to hospital and mean hospital length-of-stay was 8.8±9.9 days. After a mean follow-up 530±464 days (median follow-up of 405 days), 3.9% of patients died and VTE recurrence occurred in 2.9% of patients. While receiving rivaroxaban, a first bleeding complication occurred in 8.1%; all events were minor bleeding.

Our study supports the current literature data and confirms the similar results of real-life VTE patients with those enrolled in the rivaroxaban pivotal clinical trials. Rivaroxaban may facilitate outpatient treatment and might be considered as a first-line therapy for the management of VTE patients.

Abbreviations: CT = computed tomography, DOACs = direct oral anticoagulants, DVT = deep venous thrombosis, IQR = interquartile range, PE = pulmonary embolism, SD = standard deviation, VKA = vitamin K antagonists, VTE = venous thromboembolism.

Keywords: anticoagulation, deep venous thrombosis, direct oral anticoagulants, pulmonary embolism, rivaroxaban, venous thromboembolism

1. Introduction
Venous thromboembolism (VTE), that include deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major health care problem. Although the exact incidence of VTE is unknown, the estimated annual incidence rates of VTE among people of European ancestry range from 104 to 183 per 100,000 person-years\textsuperscript{[1,2]} In addition, VTE is the third cause of vascular death after myocardial infarction and stroke.\textsuperscript{[3,4]} Moreover, the risk of recurrence among survivors is approximately 10% per patient during the first year after the event and the costs associated with VTE are considerable.\textsuperscript{[3,5-7]}

The treatment of choice for VTE is anticoagulation.\textsuperscript{[6]} Traditionally, standard therapy comprised low-molecular-weight heparin (LMWH) followed by vitamin K antagonists (VKA).\textsuperscript{[8,9]} However, the introduction of direct oral anticoagulants (DOACs) in clinical practice may have changed this pattern,\textsuperscript{[9]} due to the advantages of DOACs over VKA.\textsuperscript{[10-11]}

Rivaroxaban is a once-daily direct factor Xa inhibitor indicated for the management of VTE.\textsuperscript{[12]} In the EINSTEIN-DVT study, rivaroxaban was as effective and safe as standard therapy for acute treatment of symptomatic DVT.\textsuperscript{[13]} In the continued-treatment study, compared with placebo, rivaroxaban 20mg once daily was superior in terms of efficacy, without a significant increase in the risk of major bleeding.\textsuperscript{[13]} In the EINSTEIN-PE study that included patients with acute symptomatic PE with or without DVT, rivaroxaban was noninferior to standard therapy (enoxaparin followed by VKA) with regard to the risk of symptomatic recurrent VTE. However, treatment with rivaroxaban was associated with a lesser risk of major bleeding.\textsuperscript{[14]} In the pooled analysis of both studies, rivaroxaban had a similar efficacy than standard therapy, but importantly, with a lesser risk of major bleeding.\textsuperscript{[15]} Besides, lower doses of rivaroxaban have shown efficacy in the prevention of VTE in the extended phase (beyond the first 3–6 months).\textsuperscript{[16]}

The strict inclusion/exclusion criteria of clinical trials may limit the external validity of these studies.\textsuperscript{[17]} In this context, observational studies may provide relevant information and may
help to establish the effectiveness and safety of a drug in routine practice. To date, only a small number of studies, many of them with a retrospective design, analyzing the use of rivaroxaban in VTE patients in clinical practice have been published and more information is warranted.[18–27]

The objective of this study was to analyze the clinical profile, evolution, and complications of treatment with rivaroxaban in a cohort of patients presented with VTE.

2. Methods
This was an observational, non-interventional and prospective study. All patients with a diagnosis of VTE treated with rivaroxaban and admitted in the VTE unit of the Internal Medicine department of University Hospital Gregorio Marañon between January 2014 and September 2017 were consecutively included. The local Clinical Research Ethics Committee of the hospital approved this study. Informed consent was obtained from patients prior to the inclusion in the study.

Clinical data were collected from the medical history of the patients and recorded in a specific database. Biodemographic data, cardiovascular risk factors, cardiovascular disease, other concomitant conditions, type of VTE (DVT, PE or both) and VTE risk factors were recorded. In addition, dose and duration of treatment with rivaroxaban were also collected. Diagnosis of VTE was established with venous doppler ultrasound or computed tomography (CT) for DVT and CT contrast angiography or ventilation/perfusion scintigraphy for PE. Patients follow-up was performed in the VTE clinic.

Data about hospitalizations, VTE recurrence, bleeding (severity and origin) and mortality during the follow-up were analyzed. The risk of bleeding was calculated according to the RIETE (0 points: low risk; 1 to 4 points: intermediate risk; > 4 points: high risk) and the HAS-BLED scores (0 points: low risk; 1 to 2 points: intermediate risk; ≥ 3 points: high risk).[28,29] Whether patients met inclusion criteria for the EINSTEIN studies was also analyzed.[13,14]

The dose of rivaroxaban was adjusted to the recommendations for patients with VTE according to the drug data sheet.

3. Statistical analysis
Qualitative variables were expressed as absolute and relative frequencies, and quantitative variables were expressed as measures of central tendency and dispersion (mean and standard deviation [SD] or median and interquartile range [IQR] in the case of variables with a non-normal distribution). To compare proportions, the chi-square test or Fisher test were used, according to the sample size. To compare 2 means, the Mann–Whitney U test was performed. Statistical significance was set at a P value < .05. The statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

4. Results
A total of 111 patients were included in the study (all patients had a history of VTE, received rivaroxaban at some point and were follow-up regardless patients remained on rivaroxaban). Mean age was 63.8 ± 17.4 years (53.2% men). The 54.1% of patients presented with DVT, 32.4% with PE, 13.5% with both conditions simultaneously. 61% of patients were admitted to hospital. VTE risk factors are presented in Table 1. The 40.9% of patients had at least one VTE risk factor with 59.1% of the events being unprovoked. Seven patients (6.3%) had cancer, all of them with a different origin. The origin of the cancer was as follows: breast, stomach, pancreas, bladder, prostate, hematologic, and biliary. Baseline characteristics of the sample are available in Table 1.

Overall, 71.7% (n = 79) of patients received rivaroxaban during the acute phase (first 10 days) of VTE, 95.5% (n = 106) as long-term therapy (from day 10 onwards), and 10.8% (n = 12) after suffering complications (bleeding or recurrence). In 26.4% of patients low-molecular-weight heparin were used, mainly during the acute phase or after complications. Overall, mean duration of treatment with rivaroxaban was 5.5 ± 9.5 months. Patients were followed-up regardless of the duration of rivaroxaban therapy. In 10 patients, treatment with fibrinolytic

Table 1

| Baseline clinical characteristics of the study population (n = 111). |
|-----------------|-----------------|
| Variable        | Value           |
| Biodemographic data |                |
| Age (years)     | 63.8 ± 17.4     |
| Sex, male (%)   | 53.2            |
| Caucasian (%)   | 97.3            |
| Latin American (%) | 2.7        |
| Physical examination |            |
| Body weight (Kg) | 77.5 ± 13.7     |
| Height (cm)     | 168.1 ± 8.8     |
| Body mass index (Kg/m²) | 27.5 ± 3.9 |
| Systolic blood pressure (mmHg) | 131.3 ± 25.5 |
| Cardiovascular disease |          |
| Hypertension (%) | 43.2           |
| Current smokers (%) | 16.2      |
| Diabetes (%)    | 11.7            |
| Previous ischemic heart disease (%) | 7.2       |
| Previous cerebrovascular disease (%) | 7.2     |
| Atrial fibrillation (%) | 7.2      |
| Heart failure (%) | 3.6           |
| Peripheral artery disease (%) | 3.6       |
| Other concomitant diseases |          |
| Chronic kidney disease (%) | 18.9   |
| Creatinine clearance 45–60 mL/min | 11.7   |
| Creatinine clearance 30–44 mL/min | 7.2    |
| Creatinine clearance <30 mL/min | 0        |
| Depression (%)   | 12.6            |
| Chronic obstructive pulmonary disease (%) | 10.8  |
| Thyroid disease (%) | 6.3          |
| Dementia (%)     | 2.7             |
| Alcoholism (%)   | 1.8             |
| Cirrhosis (%)    | 0.9             |
| Any concomitant disease at the moment of VTE (%) | 55.9 |
| Concomitant treatments |         |
| Antplatelets (%) | 18.9           |
| Withdrawal of antplatelets at the moment of starting antiagulation (%) | 81       |
| Statins (%)      | 25.5            |
| Venous thromboembolism risk factors |                  |
| Previous deep venous thrombosis or pulmonary embolism (%) | 22.5 |
| Immobilization ≥4 days for medical reasons | 16.2 |
| different to surgery in the last 2 months (%) |            |
| Any surgery in the previous 2 months (%) | 9.0      |
| Hormonal therapy in the last 2 months (%) | 7.3      |
| Cancer (%)       | 6.3             |
| Postpartum period (<2 months) (%) | 0.9       |
| Provoked events (≥1 venous thromboembolism risk factor) (%) | 40.9 |

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Table 2

| Number of patients with a bleeding event according to the RIETE and HAS-BLED scores. |
|---------------------------------|-------------|-------------|-------------|
|                                  | Yes  | No  | P     |
| RIETE                           |      |      |       |
| 0 (n = 35)                      | 8.6% | 91.4% | .52   |
| 1–4 (n = 75)                    | 16%  | 84%  |       |
| > 4 (n = 1)                     | 0%   | 100% |       |
| HAS-BLED                        |      |      |       |
| 0 (n = 42)                      | 7.1% | 92.9% | .094  |
| 1 (n = 22)                      | 27.2%| 72.8% |       |
| 2 (n = 30)                      | 13.3%| 86.7% |       |
| ≥3 (n = 17)                     | 11.8%| 88.2% |       |

Table 2

| RIETE | HAS-BLED | P |
|-------|----------|---|
| 0 (n = 35) | 7.1% | 92.9% | .094 |
| 1 (n = 22) | 27.2% | 72.8% |       |
| 2 (n = 30) | 13.3% | 86.7% |       |
| ≥3 (n = 17) | 11.8% | 88.2% |       |

In this prospective, non-interventional, and observational study, the risk of major bleeding (0.8%) and VTE recurrences (1.4%) with rivaroxaban was low. In addition, it has been shown that in routine practice, VTE patients who continue rivaroxaban therapy after the initial 3- or 6-month treatment period have a significantly lower risk for VTE recurrence without significant increased risk for major bleeding. Other studies have confirmed the good results in clinical practice of rivaroxaban regarding effectiveness and safety in VTE patients, that are in accordance with those reported in the pivotal clinical trials. This study has some limitations due to the absence of a control group. Since this was an observational study, some bias could have not been controlled. However, in this prospective study, all patients presented with VTE in the unit were consecutively included. The main strength of this real-life survey is that the patients studied represent the actual population that will receive rivaroxaban in clinical practice. In addition, as all patients were treated in the same VTE unit, this may increase the homogeneity in the management of these patients. On the other hand, since this was a unicenter study, our results cannot necessarily be extended to other populations with a different clinical profile or management.

In this cohort of patients presented with VTE, either DVT or PE, treated with rivaroxaban, only 61% of patients were admitted to hospital and mean hospital length-of-stay was 8.8 days. After a mean follow-up of 530 days, only 3.9% of patients died and VTE recurrence occurred in 2.9% of patients. Among anticoagulated patients, no VTE recurrence occurred. Overall, a first bleeding complication occurred in 13.5% of patients during standard therapy in a wide spectrum of the VTE population. 18% of our patients did not meet criteria to be included in the EINSTEIN studies, and that in contrast to some other DOACs, rivaroxaban can be used in the acute setting without parenteral anticoagulation, the use of rivaroxaban in this context is still low and limited to some type of patients. This may be related with the lack of reimbursement of rivaroxaban for this indication in Spain.

In our study, 61% of patients with VTE were admitted to hospital. Despite in the last years it has been reported an increase in the incidence of hospitalized PE patients, in a recent study of VTE patients treated with rivaroxaban, only 48% of patients were hospitalised. In addition, different studies have shown that treatment with rivaroxaban could be associated with a reduction of hospital length-of-stay among VTE patients compared with standard therapy. These data suggest that treating VTE patients with rivaroxaban could facilitate out-patient management and in case of admission, hospital length-of-stay could significantly be reduced and secondarily, this translates into cost savings.

In our study, after a mean follow-up of 530 days, only 3.9% of patients died, and VTE recurrence occurred in 2.9% of patients. Remarkably, among anticoagulated patients, no VTE recurrence occurred. While receiving rivaroxaban, a first bleeding complication occurred in 8.1%, with no major bleeding events. Remarkably, bleeding events were independent of the RIETE or HAS-BLED scores, and no major bleeding occurred while taking rivaroxaban. Data from the RIETE registry have shown that risk-adjusted rates of all-cause mortality have decreased from 6.6% in the first period (2001–2005) to 4.9% in the last period (2010–2013), mainly due to improvements in the management of these patients. However, there is much room for improvement, and rivaroxaban could be of help in this context.

Thus, in XALIA, a multicenter, prospective, non-interventional, and observational study, the risk of major bleeding (0.8%) and VTE recurrences (1.4%) with rivaroxaban was low. In addition, it has been shown that in routine practice, VTE patients who continue rivaroxaban therapy after the initial 3- or 6-month treatment period have a significantly lower risk for VTE recurrence without significant increased risk for major bleeding. Other studies have confirmed the good results in clinical practice of rivaroxaban regarding effectiveness and safety in VTE patients, that are in accordance with those reported in the pivotal clinical trials. This study has some limitations due to the absence of a control group. Since this was an observational study, some bias could have not been controlled. However, in this prospective study, all patients presented with VTE in the unit were consecutively included. The main strength of this real-life survey is that the patients studied represent the actual population that will receive rivaroxaban in clinical practice. In addition, as all patients were treated in the same VTE unit, this may increase the homogeneity in the management of these patients. On the other hand, since this was a unicenter study, our results cannot necessarily be extended to other populations with a different clinical profile or management.

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the whole follow-up period. In patients receiving rivaroxaban, a first bleeding complication occurred in 8.1%; all events were minor bleeding.

In conclusion, our study supports the current literature data and the similar results of real-life VTE patients with those enrolled in the rivaroxaban pivotal clinical trials. Rivaroxaban may facilitate outpatient treatment and should be considered as a first-line therapy for the management of VTE patients.

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