

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.^[1,2] In addition, VTE is the third cause of vascular death after myocardial infarction and stroke.^[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.^[3,5-7]

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

Rivaroxaban is a once-daily direct factor Xa inhibitor indicated for the management of VTE.^[12] In the EINSTEIN-DVT study, rivaroxaban was as effective and safe as standard therapy for acute treatment of symptomatic DVT.^[13] In the continued-treatment study, compared with placebo, rivaroxaban 20 mg once daily was superior in terms of efficacy, without a significant increase in the risk of major bleeding.^[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.^[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.^[15] Besides, lower doses of rivaroxaban have shown efficacy in the prevention of VTE in the extended phase (beyond the first 3–6 months).^[16]

The strict inclusion/exclusion criteria of clinical trials may limit the external validity of these studies.^[17] In this context, observational studies may provide relevant information and may

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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 Marañón 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

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±9.8
Body mass index (Kg/m ²)	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	
Antiplatelets (%)	18.9
Withdrawal of antiplatelets at the moment of starting anticoagulation (%)	81
Statins (%)	25.5
Venous thromboembolism risk factors	
Previous deep venous thrombosis or pulmonary embolism (%)	22.5
Immobilization ≥4 days for medical reasons different to surgery in the last 2 months (%)	16.2
Any surgery in the previous 2 months (%)	9.0
Hormonal therapy in the last 2 months (%)	7.3
Cancer (%)	6.3
>6-h journey in the last 3 weeks (%)	2.7
Postpartum period (<2 months) (%)	0.9
Provoked events (≥1 venous thromboembolism risk factor) (%)	40.9

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 2
Number of patients with a bleeding event according to the RIETE and HAS-BLED scores.

	Bleeding		P
	Yes	No	
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%	

drugs was required and in 1 patient mechanical thrombectomy and in other patient pulmonary embolectomy were performed.

After a mean follow-up 530 ± 464 days (median follow-up of 405 days), 3.9% of patients died. The causes of death were: infection (1.8%), heart failure (0.9%) and liver failure (0.9%). VTE recurrence was observed in 2.7% of patients (DVT in 2 patients and superficial vein thrombosis in 1 patient). None of the patients with VTE recurrence were receiving anticoagulants. As a result, VTE recurrence was not associated with failure of anticoagulant treatment.

A first bleeding complication occurred in 8.1% while receiving rivaroxaban; all events were minor bleeding. Bleeding events similarly occurred in DVT and PE patients, regardless treatment with rivaroxaban. Overall, major bleeding occurred in 2 cases during the study period (1 patient was taking acenocumarol and the other enoxaparin). The number of patients with a bleeding event according to the RIETE and HAS-BLED scores was shown in Table 2. Bleeding events were independent of the RIETE score ($P = .52$) or HAS-BLED score ($P = .094$). In 26.7% of the cases the bleeding had a gastrointestinal origin, in other 26.7% the urinary tract, in 13.3% epistaxis, and in other 13.3% menorrhagia. A second hemorrhage occurred in 3 patients (1 patient was taking rivaroxaban, another patient acenocumarol and the last one clopidogrel). None of these were major bleeding.

Overall, 91 patients (82%) met all the inclusion criteria for the EINSTEIN studies and 20 patients (18%) had at least 1 exclusion criteria. VTE recurrence ($P = .48$) and total bleeding events ($P = .34$) were independent of patients met inclusion criteria for the EINSTEIN studies. However, the 2 cases of major bleeding occurred in patients with any exclusion criteria (vs 0 in patients who met all the inclusion criteria; $P = .057$). None of the patients with major bleeding were taking rivaroxaban.

5. Discussion

In this prospective study, a wide cohort of patients presented with VTE, either DVT or PE, treated with rivaroxaban in a VTE unit of a tertiary hospital was analyzed. Mean age was 64 years and 56% of patients had at least another concomitant condition at the moment of VTE. Similarly, in other studies performed in “real-life” patients with VTE and treated with rivaroxaban, mean age was 58 to 62 years and patients had a low prevalence of concomitant diseases.^[20,25] Recent data from the RIETE study have shown that among patients with VTE, LMWH is the most frequently used drug as initial therapy in France, Italy and Spain.^[30] These data suggest that despite clinical trials have shown that rivaroxaban exhibit a better benefit-risk profile than

standard therapy in a wide spectrum of the VTE population (only 18% of our patients did not meet criteria to be included in the EINSTEIN studies),^[13–15] and that in contrast to some other DOACs, rivaroxaban can be used in the acute setting without parenteral anticoagulation,^[31] 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,^[32] in a recent study of VTE patients treated with rivaroxaban, only 48% of patients were hospitalised.^[25] 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.^[33,34] These data suggest that treating VTE patients with rivaroxaban could facilitate outpatient 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.^[35] 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.^[19] 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.^[23] 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.^[24,26,36]

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 uncenter 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 and 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

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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References

- Bartholomew JR. Update on the management of venous thromboembolism. *Cleve Clin J Med* 2017;84:39–46. Review. Erratum in: *Cleve Clin J Med*. 2018;85:189.
- Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015;12:464–74.
- Salmerón Febres LM, Cuenca Manteca J. Direct oral anticoagulants in the treatment of venous thromboembolic disease. *Ann Vasc Surg* 2017;42:337–50.
- Sogaard KK, Schmidt M, Pedersen L, et al. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014;130:829–36.
- Larsen TB, Lip GY, Gorst-Rasmussen A. Anticoagulant therapy after venous thromboembolism and 10-year mortality. *Int J Cardiol* 2016;208:72–8.
- Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–69.
- Grosse SD, Nelson RE, Nyarko KA, et al. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res* 2016;137:3–10.
- Witt DM, Clark NP, Kaatz S, et al. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:187–205.
- Nakamura M, Yamada N, Ito M. Novel anticoagulant therapy of venous thromboembolism: current status and future directions. *Ann Vasc Dis* 2017;10:92–8.
- Beyer-Westendorf J, Ageno W. Benefit-risk profile of non-vitamin K antagonist oral anticoagulants in the management of venous thromboembolism. *Thromb Haemost* 2015;113:231–46.
- Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis* 2016;41:206–32.
- European Medicines Agency (EMA). Xarelto (“Summary of Product Characteristics”. Updated 24 October 2017. Available at: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf.
- Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
- Investigators EINSTEIN-PE, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
- Prins MH, Lensing AW, Bauersachs R, et al. 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.
- Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med* 2017;376:1211–22.
- van Deudekom FJ, Postmus I, van der Ham DJ, et al. External validity of randomized controlled trials in older adults, a systematic review. *PLoS One* 2017;12:e0174053.
- Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 2014;124:955–62.
- Agno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016;3:e12–21.
- Jara-Palomares L, Sanchez-Oro-Gomez R, Elias-Hernandez T, et al. Rivaroxaban for the treatment of venous thromboembolism. A “real-life” perspective in 103 patients. *Thromb Res* 2014;134:617–21.
- Chu A, Limberg J. Rivaroxaban program for acute venous thromboembolism upon ED discharge, with focus on utility of commercially available dose pack. *Am J Emerg Med* 2017;35:1910–4.
- Imberti D, Barillari G. eXperience VTE Italian Group. Real-life management of venous thromboembolism with rivaroxaban: results from experience VTE, an Italian epidemiological survey. *Clin Appl Thromb Hemost* 2018;24:241–7.
- Khorana AA, Berger JS, Wells PS, et al. Risk for venous thromboembolism recurrence among rivaroxaban-treated patients who continued versus discontinued therapy: analyses among patients with VTE. *Clin Ther* 2017;39:1396–408.
- Coleman CI, Bunz TJ, Turpie AGG. Effectiveness and safety of rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism. *Thromb Haemost* 2017;117:1841–7.
- Pesavento R, Iori I. Gruppo Italiano Survey TEV. Use of rivaroxaban in real-life treatment of venous thromboembolism: results of the TEV Survey, an Italian epidemiological study. *G Ital Cardiol (Rome)* 2017;18:239–46.
- Sindet-Pedersen C, Langtved Pallisgaard J, Staerk L, et al. Comparative safety and effectiveness of rivaroxaban versus VKAs in patients with venous thromboembolism. A Danish nationwide registry-based study. *Thromb Haemost* 2017;117:1182–91.
- Gaertner S, Cordeanu EM, Nouri S, et al. Rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMO-TEV observational study): analysis of 6-month outcomes. *Int J Cardiol* 2017;226:103–9.
- Ruiz-Giménez N, Suárez C, González R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008;100:26–31.
- Pisters R, Lane DA, Nieuwlaar R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart survey. *Chest* 2010;138:1093–100.
- Maurizot A, Bura-Rivière A, Grilki K, et al. Venous thromboembolic disease: comparison of management practices in France, Italy and Spain. *J Med Vasc* 2017;42:6–13.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315–52.
- de Miguel-Díez J, Jiménez-García R, Jiménez D, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. *Eur Respir J* 2014;44:942–50.

- [33] Weeda ER, Wells PS, Peacock WF, et al. Hospital length-of-stay and costs among pulmonary embolism patients treated with rivaroxaban versus parenteral bridging to warfarin. *Intern Emerg Med* 2017;12:311–8.
- [34] Coleman CI, Fermann GJ, Weeda ER, et al. Is rivaroxaban associated with shorter hospital stays and reduced costs versus parenteral bridging to warfarin among patients with pulmonary embolism? *Clin Appl Thromb Hemost* 2017;23:830–7.
- [35] Jiménez D, de Miguel-Díez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. *J Am Coll Cardiol* 2016;67:162–70.
- [36] Larsen TB, Skjøth F, Kjældgaard JN, et al. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. *Lancet Haematol* 2017;4:e237–44.