Real-life treatment of venous thromboembolism with direct oral anticoagulants: The influence of recommended dosing and regimens

Javier Trujillo-Santos[1]; Pierpaolo Di Micco[2]; Francesco Dentali[3]; James Douketis[4]; José Antonio Díaz-Peromingo[5]; Manuel Jesús Núñez[6]; Inmaculada Cañas[7]; Daniela Mastroiacovo[8]; Marta Saraiva De Sousa[9]; Manuel Monreal[10]; RIETE Investigators*

[1]Department of Internal Medicine, Hospital General Universitario Santa Lucía, Murcia, Spain; [2]Department of Internal Medicine and Emergency Room, Ospedale Buon Consiglio Fatebenefratelli, Naples, Italy; [3]Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; [4]Department of Medicine, St. Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada; [5]Department of Internal Medicine, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain; [6]Department of Internal Medicine, Complejo Hospitalario de Pontevedra, Pontevedra, Spain; [7]Department of Internal Medicine, Hospital General de Granollers, Barcelona, Spain; [8]Department of Angiology, Ospedale SS. Filippo e Nicola, Avezzano, Italy; [9]Department of Internal Medicine, Centro Hospitalar Gaia/Espinho, EPE. Vila Nova de Gaia, Portugal; [10]Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol de Badalona, Universidad Católica de Murcia, Murcia, Spain

Summary

In patients with venous thromboembolism (VTE), the influence on outcome of using direct oral anticoagulants (DOACs) at non-recommended doses or regimens (once vs twice daily) has not been investigated yet. We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry to compare the outcomes in patients with VTE receiving DOACs according to the recommendations of the product label versus in those receiving non-recommended doses and/or regimens. The major outcomes were the rate of VTE recurrences, major bleeding and death during the course of therapy. As of March 2016, 1635 VTE patients had received DOACs for initial therapy and 1725 for long-term therapy. For initial therapy, 287 of 1591 patients (18 %) on rivaroxaban and 22 of 44 (50 %) on apixaban did not receive the recommended therapy. For long-term therapy, 217 of 1611 patients (14 %) on rivaroxaban, 29 of 81 (36 %) on apixaban and 15 of 33 (46 %) on dabigatran did not receive the recommended therapy. During the course of therapy with DOACs, eight patients developed VTE recurrences, 14 had major bleeding and 13 died. Patients receiving DOACs at non-recommended doses and/or regimens experienced a higher rate of VTE recurrences (adjusted HR: 10.5; 95 %CI: 1.28–85.9) and a similar rate of major bleeding (adjusted HR: 1.04; 95 %CI: 0.36–3.03) or death (adjusted HR: 1.41; 95 %CI: 0.46–4.29) than those receiving the recommended doses and regimens. In our cohort, a non-negligible proportion of VTE patients received non-recommended doses and/or regimens of DOACs. This use may be associated with worse outcomes.

Keywords

Clinical studies, pulmonary embolism, deep-vein thrombosis

Correspondence to:
Prof. Manuel Monreal, MD, PhD
Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol
Carretera del Canyet s. n., 08916 Barcelona, Spain
E-mail: mmonreal.germanstrias@gencat.cat

* A full list of RIETE investigators is given in the Appendix.

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Introduction

Current guidelines of antithrombotic therapy recommend the use of dabigatran, rivaroxaban, apixaban or edoxaban as long-term anticoagulant therapy in patients with venous thromboembolism (VTE) (1). The risk reduction of recurrent VTE with all of the direct oral anticoagulants (DOACs) appears to be similar to the risk reduction with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA), while the risk of bleeding (particularly intracranial) is less with the DOACs than with VKA therapy (2–7). Some studies have recently reported that in real life a number of VTE patients were prescribed DOACs at lower than recommended doses (8, 9). The influence on outcomes of these off label dosing recommendations needs to be further investigated.

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicentre, ongoing, international (Spain, Belgium, Czech Republic, France, Greece, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, United States, Canada, Ecuador and Venezuela enroll patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (10–14). Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment patterns and outcomes in patients diagnosed with VTE. Using the RIETE cohort, the current study compared the clinical characteristics and outcomes during the course of therapy of patients prescribed the recommended

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doses and regimens of DOACs versus those prescribed differently (non-recommended doses, non-recommended regimens or both).

Patients and methods

Inclusion criteria

Consecutive patients with acute, symptomatic deep-vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography 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 legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. This analysis was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) and by the Institutional Review Board of NorthShore University Health System (Evanston, IL, USA).

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralised coordinating centre through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

Study design

We conducted a retrospective study that used prospectively collected data from consecutive patients enrolled in the RIETE registry. For this study, only patients treated with DOACs (either initially or for long-term therapy) were considered. Our aim was to compare the clinical characteristics and outcomes of patients treated with DOACs according to the recommendations of the product label versus in those who were treated differently (non-recommended doses, non-recommended regimens or both). Patients were considered to receive the recommended therapy if the DOAC was started within the first 72 hours (h) after VTE diagnosis and were prescribed: 1) rivaroxaban 15 mg twice daily for 21 ± 2 days (initial therapy) and then 20 mg once daily (long-term therapy); 2) apixaban 10 mg twice daily for 7 ± 2 days and then 5 mg twice daily; or 3) dabigatran 150 mg twice daily beyond the first 7 ± 2 days of parenteral anticoagulant therapy.

The major outcome was the rate of VTE recurrences, major bleeding or death occurring during the course of therapy with DOACs. Comparisons were made separately for initial and long-term therapy and for every DOAC. Bleeding events were classified as 'major' if they were overt and required a transfusion of two units or more of blood, or were retroperitoneal, spinal or intracranial, or when they were fatal, as previously reported (4).

Baseline variables

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any co-existing or underlying conditions; risk factors for VTE; diagnostics tools used for diagnosis; laboratory data; the treatment received upon VTE diagnosis (drugs, doses, regimen and duration); and the outcome during the course of anticoagulation. Immobilised patients were defined as non-surgical patients who had been immobilised (i.e. total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to VTE. Surgical patients were defined as those who underwent a surgical intervention in the two months prior to VTE. Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Patients with recent surgery, recent immobilisation ≥4 days, estrogen use, pregnancy, puerperium or recent travel >6 h were considered to have transient risk factors for VTE. Patients without cancer or transient risk factors were considered to have idiopathic VTE. Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e. there was no standardisation of treatment). Patients were followed-up during the course of therapy in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications 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 centres. However, if staff at the coordinating centre were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

Categorical variables were compared using the Chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Continuous variables were compared using Student t-test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated, and a p-value <0.05 was considered to be statistically significant. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio (15). In order to measure predictors of outcomes, a multivariable

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analysis was performed using a Cox proportional hazard regression analysis. Covariates entering in the multivariable analysis were those with a p value <0.02 in the univariate analysis. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

Role of the funding source

The sponsors of the study (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the

Table 1: Clinical characteristics of the patients according to the use of DOACs for initial and for long-term therapy.

	Initial, Rivaroxaban	Initial, Apixaban	Long-term, Rivaroxaban	Long-term, Apixaban	Long-term, Dabigatran
Patients, N	1,591	44	1,611	81	33
Clinical characteristics,					
Gender (male)	867 (55 %)	20 (46 %)	882 (55 %)	34 (42 %)*	12 (36 %)*
Age (years ± SD)	58 ± 18	63 ± 18	57 ± 18	64 ± 18†	58 ± 21
Body weight (kg ± SD)	81 ± 17	71 ± 12‡	81 ± 17	72 ± 14‡	82 ± 19
Risk factors for VTE					
Cancer	111 (7.0 %)	3 (6.8 %)	110 (6.8 %)	6 (7.4 %)	4 (12 %)
Surgery	183 (12 %)	5 (14 %)	185 (12 %)	12 (15 %)	5 (15 %)
Immobility	244 (15 %)	13 (30 %)*	249 (16 %)	19 (24 %)	5 (15 %)
Oestrogen intake	177 (11 %)	5 (11 %)	181 (12 %)	7 (8.6 %)	7 (18 %)
Pregnancy/puerperium	12 (0.8 %)	1 (2.3 %)	13 (0.8 %)	1 (1.2 %)	0
None of the above	662 (42 %)	18 (41 %)	665 (41 %)	31 (38 %)	11 (33 %)
Prior VTE	310 (20 %)	4 (9.1 %)	318 (20 %)	10 (12 %)	5 (15 %)
Underlying diseases					
Chronic lung disease	131 (8.2 %)	8 (18 %)*	131 (8.1 %)	10 (12 %)	4 (12 %)
Chronic heart failure	77 (4.8 %)	5 (11 %)*	73 (4.5 %)	9 (11 %)†	5 (15 %)†
Recent major bleeding	17 (1.1 %)	2 (4.5 %)	16 (1.0 %)	2 (2.5 %)	1 (3.0 %)
Laboratory tests					
CrCl levels <30 ml/min	15 (2.1 %)	1 (4.2 %)	12 (1.6 %)	3 (6.4 %)*	1 (4.8 %)
Anaemia	277 (18 %)	12 (27 %)	281 (18 %)	26 (32 %)‡	11 (33 %)*
VTE characteristics					
Symptomatic PE	849 (53 %)	23 (52 %)	868 (54 %)	41 (51 %)	17 (52 %)
Drug administration					
Daily doses					
Recommended doses	1,315 (83 %)	22 (50 %)	1,432 (89 %)	53 (65 %)	18 (55 %)
Lower than recommended	275 (17 %)	22 (50 %)	66 (4.1 %)	22 (27 %)	15 (45 %)
Higher than recommended	1 (0.06 %)	0	113 (7.0 %)	6 (7.4 %)	0
Regimen					
Every 12 hours	1,234 (78 %)	40 (91 %)	125 (7.8 %)	72 (89 %)	24 (73 %)
Every 24 hours	158 (9.9 %)	2 (4.5 %)	1,136 (71 %)	4 (4.9 %)	1 (3.0 %)
Not provided	199 (13 %)	2 (4.5 %)	350 (22 %)	5 (6.2 %)	8 (24 %)
Recommended therapy	1,193 (75 %)	22 (50 %)	1,081 (67 %)	50 (62 %)	16 (49 %)
Not recommended	287 (18 %)	22 (50 %)	217 (14 %)	29 (36 %)	15 (46 %)
Non-recommended doses and regimen	147 (9.2 %)	2 (4.5 %)	32 (2.0 %)	3 (3.7 %)	1 (3.0 %)

Comparisons between other DOACs vs. rivaroxaban: *p <0.05; †p <0.01; ‡p <0.001. DOACs, direct oral anticoagulants; SD, standard deviation; VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism.

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data in the study and had final responsibility for the decision to submit for publication.

Results

As of March 2016, 1635 VTE patients had received DOACs initially (rivaroxaban 1591, apixaban 44) and 1725 for long-term therapy (rivaroxaban 1611, apixaban 81, dabigatran 33). Half of them initially presented with PE, with no differences among subgroups. Their clinical characteristics appear in ►Table 1.

For initial therapy, 276 patients receiving rivaroxaban (17%) and 22 on apixaban (50%) did not receive the recommended daily doses (30 and 20 mg, respectively). Moreover, 158 patients on rivaroxaban (9.9%) and two patients on apixaban (4.5%) were prescribed the drug once daily (►Table 1). As for long-term therapy, 179 patients on rivaroxaban (11%), 28 on apixaban (35%) and 15 on dabigatran (45%) did not receive the recommended doses (20, 10 and 300 mg daily, respectively). In addition, 125 patients on rivaroxaban (7.8%) were prescribed the drug twice daily, while four patients on apixaban (4.9%) and one on dabigatran (3.0%) were prescribed once daily. Thus, for initial therapy at least 287 pa-

Table 2: Clinical characteristics of the patients, according to prescribed doses and regimen (once vs twice daily). Patients with no information on regimen are not included.

	Low doses	Recommended doses	High doses	Once daily	Twice daily
Initial therapy, Rivaroxaban					
Patients, N=1,591	275	1,315	1	158	1,234
Age >70 years	89 (32%)	362 (28%)	0	58 (37%)*	342 (28%)
Body weight <60kg	19 (6.9%)	100 (7.6%)	0	8 (5.1%)	95 (7.7%)
Active cancer	34 (12%)‡	77 (5.9%)	0	19 (12%)†	77 (6.2%)
CrCl levels <30 ml/min	7 (5.5%)†	8 (1.3%)	0	4 (5.7%)*	8 (1.4%)
Initial therapy, Apixaban					
Patients, N=44	22	22	0	2	40
Age >70 years	8 (36%)†	12 (55%)	-	0	19 (48%)
Body weight <60kg	6 (27%)	2 (9.1%)	-	1 (50%)	6 (15%)
Active cancer	3 (14%)	0	-	0	3 (7.5%)
CrCl levels <30 ml/min	1 (7.7%)	0	-	0	1 (2.5%)
Long-term therapy, Rivaroxaban					
Patients, N=1,611	66	1,432	113	1,136	125
Age >70 years	45 (68%)‡	370 (26%)	27 (24%)	323 (28%)	38 (39%)
Body weight <60kg	10 (15%)*	100 (7.0%)	12 (11%)	82 (7.2%)	13 (10%)
Active cancer	16 (24%)‡	92 (6.4%)	2 (1.8%)*	2 (1.6%)	86 (7.6%)*
CrCl levels <30 ml/min	6 (9.1%)‡	13 (0.9%)	0	1 (0.09%)	14 (1.2%)
Long-term therapy, Apixaban					
Patients, N=81	22	53	6	4	72
Age >70 years	13 (59%)	24 (45%)	4 (67%)	1 (25%)	38 (53%)
Body weight <60kg	5 (23%)	7 (13%)	2 (33%)	2 (50%)	11 (15%)
Active cancer	4 (18%)*	2 (3.8%)	0	0	6 (8.3%)
CrCl levels <30 ml/min	1 (4.5%)†	0	0	0	4 (5.6%)
Long-term therapy, Dabigatran					
Patients, N=33	15	18	0	1	24
Age >70 years	10 (67%)†	3 (17%)	-	1 (100%)	7 (29%)
Body weight <60kg	1 (6.7%)	2 (11%)	-	0	3 (13%)
Active cancer	1 (6.7%)	3 (17%)	-	0	3 (13%)
CrCl levels <30 ml/min	1 (6.7%)	0	-	0	1 (4.2%)

Comparisons between non-recommended versus recommended doses and/or regimen: *p <0.05; †p <0.01; ‡p <0.001. CrCl, creatinine clearance levels.

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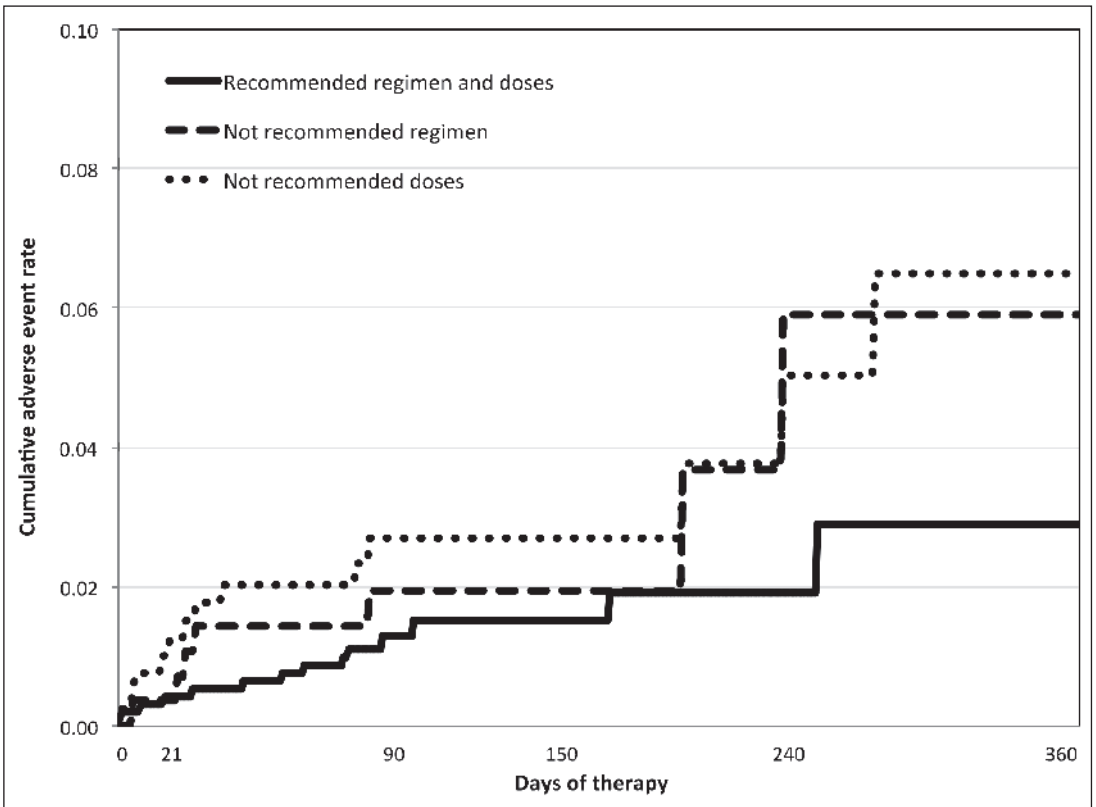

Days of therapy	0	21	90	150	240	360
Recommended doses and regimens	963	920	763	364	133	51
	0	4 (0.4%)	10 (1.0%)	12 (1.2%)	13 (1.3%)	14 (1.5%)
Not recommended regimens	282	279	226	127	45	21
	0	1 (0.4%)	4 (1.4%)	5 (1.8%)	6 (2.1%)	7 (2.5%)
Not recommended doses	416	391	313	188	79	37
	0	5 (1.2%)	8 (1.9%)	10 (2.4%)	11 (2.6%)	13 (3.1%)

Figure 1: Cumulative rate of the composite outcome (VTE recurrences, major bleeding or death) according to the use of recommended doses and/or regimens.

tients on rivaroxaban (18%) and 22 on apixaban (50%) did not receive the recommended doses and/or regimens. For long-term therapy, 217 patients on rivaroxaban (14%), 29 on apixaban (36%) and 15 on dabigatran (46%) did not receive the recommended therapy.

Among patients treated with rivaroxaban for initial therapy, those receiving doses <30 mg daily (lower than recommended) were most likely to have cancer or CrCl levels <30 ml/minute (min) than those receiving 30 mg daily (▶Table 2). Patients on rivaroxaban once daily were most likely aged >70 years or to have active cancer or CrCl levels <30 ml/min than those on the drug twice daily. As for patients on apixaban, those receiving doses <20 mg daily also were most likely aged >70 years than those receiving 20 mg daily.

For long-term therapy, patients on rivaroxaban receiving doses <20 mg daily (lower than recommended) were most likely aged >70 years, weighed <60 kg or had cancer or CrCl levels <30 ml/min compared with those on 20 mg daily, while those on higher doses were less likely to have active cancer (▶Table 2). Patients on rivaroxaban twice daily (against the recommendations) most likely had active cancer than those on once daily. Patients on apixaban <10 mg daily also were most likely to have active cancer or CrCl levels <30 ml/min than those receiving 10 mg daily. There is information on only 33 patients receiving dabigatran for long-term therapy, and those receiving <300 mg daily most likely were aged >70 years as well.

During the course of therapy with DOACs (either initial, long-term or both), five patients presented with DVT recurrences, three with PE recurrences, 14 had major bleeding (intracranial 4, gastrointestinal 3, menorrhagia 2) and 13 died (fatal PE one, sudden unexpected death 2, disseminated cancer 2, heart failure 2, other 5). Most adverse events (15 of 20, 75%) appeared within the first three months of therapy (▶Figure 1).

Patients receiving lower than recommended doses of DOACs (either initially or for long-term therapy) had a non-significantly higher rate of VTE recurrences (adjusted HR: 3.36; 95%CI:

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0.78–14.4) and a similar rate of major bleeding or death (▶Table 3). Those receiving the non-recommended regimens (rivaroxaban once daily during initial therapy and then twice daily for long-term therapy; apixaban and dabigatran twice daily for initial and for long-term therapy) experienced a higher rate of VTE recurrences (adjusted HR: 4.50; 95%CI: 0.99–20.4) with no differences in bleeding or death. Overall, patients receiving DOACs at non-recommended doses and/or regimens experienced a significantly higher rate of VTE recurrences (adjusted HR: 10.5; 95%CI: 1.28–85.9) and a similar rate of major bleeding (adjusted HR: 1.04; 95%CI: 0.36–3.03) or death (adjusted HR: 1.41; 95%CI: 0.46–4.29) than those receiving the recommended doses and regimens (▶Table 3).

Discussion

Ours is among the first studies to reveal that a non-negligible proportion of VTE patients in real life are prescribed DOACs at doses or regimens different from those recommended in the product label (8, 9). During initial therapy, one in every five patients (18%)

Table 3: Clinical outcome in patients receiving non-recommended doses or regimen versus recommended doses and regimen of DOACs. Patients with no information on regimen (once vs twice daily) are not included.

	N	Rate (95%CI)	N	Rate (95%CI)	Non-adjusted HR (95%CI)	Adjusted HR (95%CI)
	Low doses		Recommended doses			
Patients, N	375		1,030			
Follow-up (years)	179.89		438.89			
DVT recurrences	3	1.67 (0.34–4.87)	2	0.46 (0.05–1.65)	3.54 (0.59–21.3)	3.54 (0.59–21.3)
PE recurrences	2	1.12 (0.12–4.01)	1	0.23 (0.003–1.27)	5.09 (0.46–56.2)	3.43 (0.28–42.2)
VTE recurrences	5	2.78 (0.90–6.49)	3	0.68 (0.14–2.00)	4.05 (0.96–17.0)	3.36 (0.78–14.4)
Major bleeding	5	2.78 (0.90–6.49)	8	1.82 (0.78–3.59)	1.55 (0.51–4.76)	1.33 (0.43–4.11)
Death	7	3.89 (1.56–8.02)	6	1.37 (0.50–2.98)	2.99 (1.00–8.91)*	1.99 (0.64–6.13)
	High doses		Recommended doses			
Patients, N	115		1,030			
Follow-up (years)	60.65		438.89			
Major bleeding	1	1.65 (0.02–9.17)	8	1.82 (0.78–3.59)	0.99 (0.12–7.95)	0.98 (0.12–7.9)
	Non-recommended regimen		Recommended regimen			
Patients, N	289		1,118			
Follow-up (years)	137.36		480.68			
DVT recurrences	2	1.46 (0.16–5.26)	2	0.42 (0.05–1.50)	3.34 (0.47.23,7)	3.34 (0.47.23,7)
PE recurrences	2	1.46 (0.16–5.26)	1	0.21 (0.003–1.16)	8.21 (0.74–91.4)	13.23 (0.83–210.5)
VTE recurrences	4	2.91 (0.78–7.46)	3	0.62 (0.13–1.82)	4.86 (1.08–21.8)*	4.50 (0.99–20.4)
Major bleeding	2	1.46 (0.16–5.26)	10	2.08 (1.00–3.83)	0.69 (0.15–3.18)	0.64 (0.14–2.94)
Death	2	1.46 (0.16–5.26)	9	1.87 (0.85–3.55)	0.81 (0.18–3.77)	0.42 (0.08–2.29)
	Non-recommended doses or regimen		Recommended doses and regimen			
Patients, N	528		983			
Follow-up (years)	255.33		417.19			
DVT recurrences	4	1.57 (0.42–4.01)	1	0.24 (0.003–1.33)	6.37 (0.71–57.2)	6.35 (0.71–57.0)
PE recurrences	3	1.18 (0.24–3.43)	0	-	-	-
VTE recurrences	7	2.74 (1.10–5.65)	1	0.24 (0.003–1.33)	11.5 (1.41–93.3)*	10.5 (1.28–85.9)*
Major bleeding	6	2.35 (0.86–5.12)	8	1.92 (0.83–3.78)	1.25 (0.43–3.60)	1.04 (0.36–3.03)
Death	7	2.74 (1.10–5.65)	6	1.44 (0.53–3.13)	2.00 (0.67–5.96)	1.41 (0.46–4.29)

Variables entering in the multivariable analyses: age, body weight, cancer, CrCl levels, initial VTE presentation (PE vs DVT alone), recent major bleeding, anaemia and abnormal platelet count. Comparisons between non-recommended versus recommended doses and/or regimen: *p <0.05. DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; HR, hazard ratio; CI, confidence intervals.

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- **Coordinator of the RIETE Registry:**Monreal M (Spain)
- **RIETE Steering Committee Members:** Decousus H (France), Prandoni P (Italy), Brenner B (Israel).
- **RIETE National Coordinators:**Barba R (Spain), Di Micco P (Italy), Bertoletti L (France), Tzoran I (Israel), Reis A (Portugal), Bosevski M (R. Macedonia), Bounameaux H (Switzerland), Malý R (Czech Republic), Wells P (Canada), Verhamme P (Belgium).
- **RIETE Registry Coordinating Center:** S & H Medical Science Service
- **Members of the RIETE Group: Spain:** Adarraga MD, Aibar MA, Alcalde-Manero M, Alfonso M, Arcelus JI, Ballaz A, Barba R, Barrón M, Barrón-Andrés B, Bascuñana J, Blanco-Molina A, Bueso T, Bustamante A, Cañada G, Cañas I, Casado I, Chic N, del Pozo R, del Toro J, Díaz-Pedroche MC, Díaz-Peromingo JA, Falgá C, Fernández-Aracil C, Fernández-Capitán C, Fidalgo MA, Font C, Font L, Gallego P, García MA, García-Bragado F, Gavín O, Gómez C, Gómez V, González J, González-Marcano D, Grau E, Grimón A, Guijarro R, Guirado L, Gutiérrez J, Hernández-Comes G, Hernández-Blasco L, Jara-Palomares L, Jaras MJ, Jiménez D, Joya MD, Llamas P, Lecumberri R, Lobo JL, López-Jiménez L, López-Reyes R, López-Sáez JB, Lorente MA, Lorenzo A, Maestre A, Marchena PJ, Martín-Martos F, Mestre B, Monreal M, Nieto JA, Nieto S, Núñez MJ, Odriozola M, Otalora S, Otero R, Pedrajas JM, Pérez-Ductor C, Peris ML, Porras JA, Reig O, Riera-Mestre A, Riesco D, Rivas A, Rodríguez C, Rodríguez-Dávila MA, Rosa V, Ruiz-Giménez N, Sahuquillo JC, Sala-Sainz MC, Sampériz A, Sánchez R, Sanz O, Soler S, Sopeña B, Suriñach JM, Trujillo-Santos J, Uresandi F, Valero B, Valle R, Vela J, Vela L, Vila M, Villalobos A, Villalta J; **Belgium:** Vanassche T, Verhamme P; **Canada:** Wells P; **Czech Republic:** Hirmerova J, Malý R; **Ecuador:** del Pozo G, Salgado E, Sánchez GT; **France:** Bertoletti L, Bura-Riviere A, Mahé I, Merah A, Moustafa F; **Israel:** Braester A, Brenner B, Tzoran I; **Italy:** Antonucci G, Barillari G, Bilora F, Bortoluzzi C, Ciammaichella M, Dell' Elce N, Dentali F, Di Micco P, Duce R, Ferrazzi P, Giorgi-Pierfranceschi M, Grandone E, Imbalzano E, Lodigiani C, Maida R, Mastroiacovo D, Pace F, Pesavento R, Pinelli M, Poggio R, Prandoni P, Rota L, Tiraferri E, Tonello D, Tufano A, Visonà A, Zalunardo B; **Latvia:** Drucka E, Kigitovica D, Skride A; **Portugal:** Sousa MS; **Republic of Macedonia:** Bosevski M, Zdraveska M; **Switzerland:** Alatri A, Bounameaux H, Calanca L, Mazzolai L.

What is known about this topic?

- In patients with venous thromboembolism (VTE), the efficacy of the direct oral anticoagulants (DOACs) appears to be similar to that of standard therapy, while the risk of bleeding is lower.

What does this paper add?

- In real life, at least 15% of VTE patients received non-recommended doses and/or regimens of DOACs.
- This use was associated with a higher rate of VTE recurrences, with no benefit in terms of bleeding or mortality.

receiving rivaroxaban and one in every two (50%) on apixaban were prescribed non-recommended doses (most received low doses) or regimens (once daily instead of twice daily). During long-term therapy, one in every seven patients on rivaroxaban (14%), one in every three on apixaban (36%) and one in every two on dabigatran (46%) did receive non-recommended doses and/or regimens. Patients receiving lower than recommended doses were most likely to be elderly or to have cancer or renal insufficiency than those receiving recommended doses. Those on higher than recommended doses of rivaroxaban were less likely to have cancer, and those with non-recommended regimens were most likely to have cancer. Overall, patients receiving DOACs at non-recommended doses and/or regimens had a 10-fold higher rate of VTE recurrences and a similar rate of major bleeding or death than those on recommended therapy. The higher rate of VTE recurrences was confirmed after adjusting for potentially confounding variables (such as patient's age, body weight, recent bleeding, renal function or active cancer). Interestingly, some patients received DOACS during pregnancy and/or puerperium, when DOACs are not generally recommended for these patients.

DOACs have been extensively studied in randomised clinical trials, and the results demonstrated they are at least as effective and safe as conventional therapy in most patients with VTE (2–7, 16–18). However, a number of specific subgroups (such as pregnant women or patients at high risk of bleeding, or with severe renal insufficiency) were excluded in these randomized trials. Moreover, patients weighing <60 kg, aged >70 years or with active cancer were underrepresented. Hence, the efficacy and safety of DOACs within these subgroups have yet to be established. Our data reveal that in real life some patients with severe renal insufficiency or recent major bleeding did receive treatment with DOACs. Moreover, one in every three patients in our cohort was aged >70 years or weighed <60 kg. Many of these patients were prescribed non-recommended doses or regimens, most likely because their doctors were concerned about the risk of bleeding. Our data reveal that using low doses of DOACs did not reduce the risk of bleeding, but increased the risk of VTE recurrences. While the higher rate of VTE recurrences in patients receiving low doses could have been expected, the influence of different regimens on outcomes deserves further explanation.

The present study has potential limitations. First, RIETE is an observational registry, and our data are hypothesis-generating. They might be a useful basis for future controlled clinical trials comparing different therapeutic strategies, but we should be extremely cautious in suggesting changes in treatment strategies based on uncontrolled registry data . On the contrary, our data should caution clinicians against empirically dose reducing based on off label recommendations. Second, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. The main strength of our observation is that the population sample we used describes the effects of anticoagulant therapy in "real world" clinical care, as opposed to in a protocol driven randomised trial, and enhances the generalisability of our findings. The broad range of patients from multiple medical centres, countries, and treatment settings en-

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rolled in the RIETE registry decreased the likelihood of the inclusion of a skewed population in this study.

In summary, in real life a non-negligible proportion of VTE patients were prescribed DOACS at daily doses and/or regimens different from those recommended in the product label. These patients had a higher rate of VTE recurrences with no difference in bleeding than those receiving the drug according to the product label. These data provide evidence that empiric dose reductions may decrease the efficacy while not increasing safety, but more robust data is needed.

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Conflicts of interest
None declared.

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