

## ARTICLE

# Edoxaban for the Long-Term Therapy of Venous Thromboembolism: Should the Criteria for Dose Reduction be Revised?

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Edoxaban is used for venous thromboembolism (VTE) treatment. Real-life data are lacking about its use in long-term therapy. We aimed to assess the efficacy and the safety of edoxaban for long-term VTE treatment in a real-life setting. Patients with VTE included in the Registro Informatizado Enfermedad TromboEmbólica (RIETE) registry, receiving edoxaban 60 or 30 mg daily were prospectively followed up to validate the benefit of using different dosages. The main outcome was the composite of VTE recurrences or major bleeding in patients with or without criteria for dose reduction. Multivariable analysis to identify predictors for the composite outcome was performed. From October 2015 to November 2019, 562 patients received edoxaban for long-term therapy. Most (94%) of the 416 patients not meeting criteria for dose reduction received 60 mg daily, and 92 patients meeting criteria (63%) received 30 mg daily. During treatment, two patients developed recurrent VTE, six had major bleeding and nine died (2 from fatal bleeding). Among patients not meeting criteria for dose reduction, those receiving 30 mg daily had a higher rate of the composite event (hazard ratio (HR) 8.37; 95% confidence interval (CI) 1.12–42.4) and a significant higher mortality rate (HR 31.1; 95% CI 4.63–262) than those receiving 60 mg. Among patients meeting criteria for dose reduction, those receiving 60 mg daily had no events, and a nonsignificantly higher mortality rate (HR 5.04; 95% CI 0.54–133) than those receiving 30 mg daily. In conclusion, edoxaban seems to be effective and safe for long-term VTE treatment in real life. Criteria for dose reduction should be reformulated.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ We know the efficacy and safety of edoxaban in long-term treatment of venous thromboembolism from randomized trials only. Real-life data are lacking.

### WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Are the recommended doses of edoxaban safe and effective?

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Edoxaban seems to be effective and safe, but the criteria for dose reduction have scarce influence on outcome.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ Further studies are needed to more precisely identify those patients in whom the dose should be reduced.

Current guidelines of antithrombotic therapy,<sup>1,2</sup> based on the evidence from randomized trials,<sup>3–7</sup> recommend the use of direct oral anticoagulants (DOACs) as initial and long-term therapy in patients with venous thromboembolism (VTE). However, the pivotal trials where their indication

was based applied strict exclusion criteria, aimed to exclude patients with a presumed high risk of bleeding. The International Regulatory Authorities encourage the pharmaceutical companies to develop postauthorization safety studies that should start shortly after the approval of the

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new drugs. Edoxaban is among the last DOACs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Unlike other DOACs (dabigatran, rivaroxaban, or apixaban),<sup>8–11</sup> edoxaban currently can provide data only from the pivotal randomized trial. Two postauthorization safety studies have been commissioned by the EMA, but conclusive data are not yet available.<sup>12,13</sup>

In the current study, we used the data from the Registro Informatizado Enfermedad TromboEmbólica (RIETE), a prospective multinational registry of patients with objectively confirmed VTE (ClinicalTrials.gov identifier: NCT02832245), to assess the efficacy and safety of edoxaban for long-term therapy of VTE in real-life clinical practice.<sup>14,15</sup> According to the product label, the recommended dose of edoxaban for long-term therapy is 60 mg daily, but this dose should be reduced to 30 mg daily in patients with creatinine clearance (CrCl) levels 15–50 mL/minute, body weight  $\leq$  60 kg, or concomitant use of P-glycoprotein inhibitors, because they are perceived as being at increased risk for bleeding. Thus, we compared the rate of the composite of VTE recurrences or major bleeding during the course of edoxaban therapy in patients receiving recommended vs. non-recommended doses of edoxaban.

## METHODS

### Study design

Edoxaban was first marketed in Europe for VTE therapy on April 2015, and the first patient receiving edoxaban in RIETE was recruited in October 2015. Thus, we used prospectively collected data from consecutive patients enrolled in the RIETE registry from October 2015 to November 2019. Only patients receiving edoxaban after at least 5 days of initial therapy with a parenteral anticoagulant (unfractionated heparin, low-molecular-weight heparin, or fondaparinux) were considered. The major outcome was the composite of symptomatic VTE recurrences or major bleeding occurring during the course of edoxaban therapy.

According to the product label, the recommended dose of edoxaban is 60 mg once daily following initial therapy with heparin, low-molecular-weight heparin, or fondaparinux for at least 5 days. However, this dose should be reduced to 30 mg once daily in patients who meet any of the following criteria: moderate renal impairment (CrCl levels 15–50 mL/minute), body weight  $\leq$  60 kg, or concomitant use of potent P-glycoprotein inhibitors. Thus, we compared the rates of the composite outcome in patients receiving edoxaban at recommended doses vs. those receiving non-recommended doses in the two clinical scenarios (in patients meeting criteria for dose reduction and in those not meeting criteria).

### Patients

The rationale and methodology of RIETE has been previously reported elsewhere.<sup>15</sup> In brief, RIETE started in Spain in 2001 and in subsequent years has expanded the sites in several countries. For this study, we only included patients with acute symptomatic VTE confirmed by objective tests (compression ultrasonography for suspected deep vein thrombosis (DVT); ventilation-perfusion lung scan, helical computed tomography (CT) scan, or conventional

angiography for suspected pulmonary embolism (PE)). All patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention.

### Variables

The following parameters were recorded in RIETE: clinical status, including coexisting conditions such as chronic heart or lung disease, recent bleeding, anemia, or renal insufficiency; risk factors for VTE; the treatment received upon VTE diagnosis (drug, doses, regimen, and duration), and the outcomes during follow-up. Immobilized patients were defined as nonsurgical patients who had been immobilized (i.e., total bed rest with or without bathroom privileges) for  $\geq$  4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE. Active cancer was defined as newly diagnosed cancer or when receiving antineoplastic therapy of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support, or combined therapies). Unprovoked VTE was considered in the absence of active cancer, recent immobility, surgery, estrogen use, pregnancy, or postpartum. Recent major bleeding was considered in patients having suffered major bleeding  $<$  30 days prior to VTE. Anemia was defined as hemoglobin levels  $<$  13 g/dL for men and  $<$  12 g/dL for women. CrCl levels at baseline were measured using the Cockcroft–Gault formula.

### Follow-up

All patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. All patients were followed up for at least 3 months. During follow-up, special attention was paid to any signs or symptoms suggesting recurrent DVT, PE, or major bleeding. Each episode of clinically suspected recurrent DVT or PE was documented by repeat objective imaging. Bleeding complications were classified as “major” if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal, intraocular, hemopericardium, or intracranial, or when they were fatal.<sup>5,15</sup> Fatal bleeding was defined as any death occurring  $<$  10 days after a major bleeding episode, in the absence of any alternative cause of death.<sup>15</sup> Fatal PE, in the absence of autopsy, was defined as any death occurring  $<$  10 days after PE diagnosis, in the absence of any alternative cause of death.

### Statistical analyses

Categorical variables were compared using the  $\chi^2$  test (two-sided) and Fisher’s exact test (two-sided). Continuous variables were compared using Student *t*-test. The incidence rates of VTE recurrences or major bleeding appearing during the course of therapy with edoxaban were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratios (HRs) and 95% confidence intervals (CIs). Then, a multivariable analysis was performed to identify independent predictors for the composite of VTE recurrences or major bleeding. Because we anticipated different mortality risks between

subgroups, risks of the composite event were assessed using competing risk models, with mortality (not due to recurrent VTE or major bleeding, respectively) as the competing risk. Covariates entering in the model were selected by a significance level of  $P < 0.10$  on univariable analysis, or by a well-known association reported in the literature. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program (version 25.0 for Windows; SPSS, Chicago, IL).

### Institutional review board approval

All patients provided oral or written informed consent to their participation in the registry, according to the requirements of the institutional review boards within each enrolling center.

## RESULTS

Since October 2015 to November 2019, 22,015 patients with VTE were recruited in RIETE, of whom 562 (2.6%) received edoxaban for long-term therapy (Figure 1). Of these, 146 (26%) met criteria for dose reduction: because of body weight  $\leq 60$  kg in 43 patients, CrCl levels  $\leq 50$  mL/minute in 73 patients, and both conditions in 30 patients. No data are available for concomitant intake of P-glycoprotein inhibitors because it was an item not included in the registry.

### Patients not meeting criteria for dose reduction

Among 416 patients not meeting criteria for dose reduction, 23 (5.5%) received non-recommended doses of edoxaban (30 mg daily). Patients receiving non-recommended doses were significantly older ( $74 \pm 14$  vs.  $62 \pm 15$  years;  $P < 0.001$ ), weighed less ( $73 \pm 12$  vs.  $82 \pm 13$  kg;  $P < 0.01$ ), and had lower CrCl levels at baseline ( $79 \pm 24$  vs.  $99 \pm 34$  mL/minute;  $P < 0.001$ ) than those receiving recommended doses (Table 1). They also were nonsignificantly more likely to have active cancer. During initial therapy with parenteral anticoagulants (before starting edoxaban), three patients had

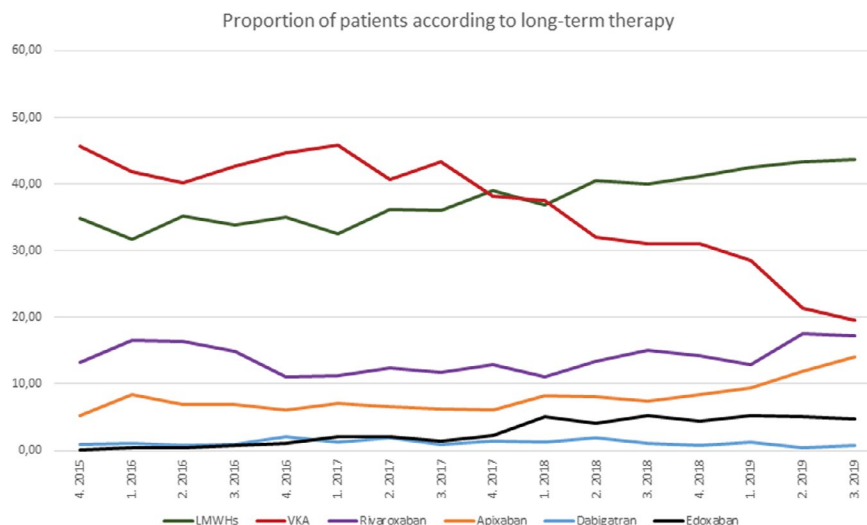
developed VTE recurrences, no patient had major bleeding. Most patients in both subgroups (81% vs. 70%) were initially treated with low-molecular-weight heparin, with a median duration from VTE diagnosis to start of edoxaban therapy of 7 days (Table 2). Median duration of edoxaban therapy was similar in patients receiving recommended or non-recommended doses.

During the course of therapy, two patients developed recurrent DVT, five had major bleeding (gastrointestinal 2, vaginal 1, hemoptysis 1, and hematoma 1), and five patients died (because of bleeding 2, heart failure 1, multi-organ failure 1, and unknown 1). No patient developed PE recurrences. Patients receiving non-recommended doses of edoxaban (30 mg daily) had a significantly higher rate of the composite outcome (HR 8.37; 95% CI 1.12–42.4) and a higher mortality rate (HR 31.1; 95% CI 4.63–262) than those receiving 60 mg daily (Table 3).

### Patients meeting criteria for dose reduction

Among 146 patients in this subgroup, 54 (37%) received non-recommended doses (60 mg instead of 30 mg daily) of edoxaban. Patients receiving non-recommended doses were younger ( $71 \pm 17$  vs.  $79 \pm 17$  years;  $P < 0.05$ ) and had higher CrCl levels at baseline ( $57 \pm 29$  vs.  $47 \pm 27$  mL/minute) than those receiving 30 mg daily (Table 1). One patient had developed major bleeding before starting edoxaban, and no patient had VTE recurrences. Median time elapsed from VTE diagnosis to the start of edoxaban was similar in both subgroups (7 days). Median duration of therapy was also similar.

During the course of edoxaban therapy, one patient bled (in the gastrointestinal tract) and four patients died (infection 1, myocardial infarction 1, multi-organ failure 1, and unknown reason 1). No patient had VTE recurrences. Interestingly, none of the 73 patients weighing  $< 60$  kg and none of the 54 patients meeting criteria for dose reduction but receiving 60 mg daily developed major bleeding. The only major bleed appeared in a patient receiving 30 mg daily. However, patients receiving 60 mg daily had a nonsignificantly higher



**Figure 1** Proportion of patients receiving low-molecular-weight heparin (LMWH), vitamin K antagonists (VKAs), or direct oral anticoagulants for long-term therapy over time.

**Table 1 Clinical characteristics of the patients according to criteria for dose reduction and use of recommended doses of edoxaban**

	Weight > 60 kg and CrCl levels > 50 mL/minute		Weight ≤ 60 kg or CrCl levels ≤ 50 mL/minute	
	Non-recommended	Recommended doses	Non-recommended	Recommended doses
<i>Patients, N</i>	23	393	54	92
Clinical characteristics,				
Male sex	9 (39%)	217 (55%)	14 (26%)	17 (18%)
Mean age, years ± SD	74 ± 14*	62 ± 15	71 ± 17*	79 ± 17
Mean body weight, kg ± SD	73 ± 12*	82 ± 13	65 ± 12	63 ± 12
Body weight ≤ 60 kg	0	0	26 (48%)	47 (51%)
Risk factors for VTE,				
Active cancer	6 (26%)	49 (12%)	9 (17%)	8 (8.7%)
Recent surgery	2 (8.7%)	44 (11%)	3 (5.6%)	5 (5.4%)
Recent immobility ≥ 4 days	5 (22%)	65 (17%)	11 (20%)	30 (33%)
Estrogen use	1 (4.3%)	22 (5.6%)	6 (11%)	3 (3.3%)
Pregnancy/puerperium	0	3 (0.76%)	1 (1.9%)	1 (1.1%)
None of the above	12 (52%)	235 (60%)	29 (54%)	47 (51%)
Prior VTE	1 (4.3%)	58 (15%)	7 (13%)	20 (22%)
Underlying diseases				
Chronic lung disease	2 (8.7%)	33 (8.4%)	7 (13%)	9 (9.8%)
Chronic heart failure	2 (8.7%)	15 (3.8%)	6 (11%)	6 (6.5%)
Recent major bleeding	0	7 (1.8%)	1 (1.9%)	1 (1.1%)
Laboratory tests				
Anemia	7 (30%)	86 (22%)	22 (41%)	42 (46%)
CrCl levels, mL/minute ± SD	79 ± 24*	99 ± 34	57 ± 29*	47 ± 27
CrCl levels > 95 mL/minute	7 (30%)	201 (51%)	9 (17%)	9 (9.8%)
CrCl levels ≤ 50 mL/minute	0	0	32 (59%)*	71 (77%)
CrCl levels < 15 mL/minute	0	0	1 (1.9%)	0
Initial VTE presentation				
Pulmonary embolism	10 (43%)	169 (43%)	27 (50%)	37 (40%)
DVT	13 (57%)	206 (52%)	26 (48%)	54 (59%)
Superficial vein thrombosis	0	18 (4.6%)	1 (1.9%)	1 (1.1%)
Events during initial therapy				
VTE recurrences	2 (0.51%)	1 (4.3%)	0	0
Major bleeding	0	0	1 (1.1%)	0

*P* values refer to comparisons between patients with non-recommended vs. those on recommended doses of edoxaban.

CrCl, creatinine clearance; DVT, deep vein thrombosis; VTE, venous thromboembolism.

\**P* < 0.001; *P* = 0.01; *P* = 0.002; *P* = 0.005; *P* = 0.048; *P* = 0.025.

mortality rate (HR 5.04; 95% CI 0.54–133) than those receiving 30 mg daily (**Table 3**).

On competing risk multivariable analysis, after adjusting for patient's age, sex, body weight, cancer, transient risk factors for VTE, chronic heart or lung disease, anemia, CrCl levels at baseline, initial VTE presentation, and the daily dose of edoxaban, only patients with active cancer (HR 7.40; 95% CI 1.83–30.0), chronic heart failure (HR 10.9; 95% CI 1.80–66.3), or initially presenting with PE (HR 8.97; 95% CI 1.05–76.7) were at an increased risk for the composite event (**Table 4**). The HR for the composite event of patients with CrCl levels ≤ 50 mL/minute was 0.36 (95% CI 0.03–3.49), and the HR for body weight ≤ 60 kg was impossible to calculate because no patient weighing ≤ 60 kg in our cohort bled.

## DISCUSSION

This is the first real-life study on patients receiving edoxaban for long-term therapy of VTE. After a median of 106 days of

therapy, 2 patients (0.36%) developed recurrent DVT and 6 (1.07%) suffered major bleeding, 2 of which were fatal. No patient had recurrent PE. These results compare favorably with those obtained in the pivotal trial that served to approve the indication of edoxaban for secondary prevention of VTE.<sup>5</sup> In the HOKUSAI trial, 3,385 patients received edoxaban 60 mg daily for 3–12 months, and 733 received 30 mg daily. Our patients were older (71 vs. 56 years), more likely to have active cancer (13% vs. 9.2%), or CrCl levels 30–50 mL/minute (14% vs. 6.5%) than those in HOKUSAI. Moreover, 4.6% of patients in our cohort (none in HOKUSAI) had CrCl levels < 30 mL/minute. During the course of therapy, their rate of VTE recurrences (3.2%) was 10-fold higher than in our cohort, and their rate of major bleeding was similar (1.4%). Therefore, our findings validate the effectiveness and safety of edoxaban in a cohort of real-life patients with VTE (with no exclusion criteria), as those recruited in HOKUSAI.

According to the product label, the recommended dose of edoxaban for long-term therapy of VTE is 60 mg daily,

**Table 2 Treatment details and clinical outcomes during edoxaban therapy**

	Weight > 60 kg and CrCl levels >50 mL/minute		Weight ≤ 60 kg or CrCl levels ≤ 50 mL/minute	
	Non-recommended	Recommended doses	Non- recommended	Recommended doses
<i>Patients, N</i>	23	393	54	92
Initial therapy (before edoxaban)				
Median days (IQR)	8 (6–37)	7 (5–14)	7 (5–13)	7 (5–11)
Over 10 days	10 (43%)	132 (34%)	16 (30%)	26 (28%)
LMWH	16 (70%)	319 (81%)	44 (81%)	73 (79%)
Unfractionated heparin	2 (8.7%)	7 (1.8%)	2 (3.7%)	1 (1.1%)
Thrombolytics	0	3 (0.76%)	2 (3.7%)	1 (1.1%)
Fondaparinux	4 (17%)	55 (14%)	5 (9.3%)	12 (13%)
Inferior vena cava filter	0	7 (1.8%)	0	0
Edoxaban therapy				
60 mg once daily	-	393 (100%)	54 (100%)	-
30 mg once daily	23 (100%)	-	-	92 (100%)
Mean days (± SD)	136 ± 91	165 ± 149	145 ± 107	142 ± 130
Median days (IQR)	107 (69–196)	111 (87–190)	101 (84–187)	96 (84–178)
Over 90 days	13 (57%)	262 (67%)	31 (57%)	53 (58%)

CrCl, creatinine clearance; IQR, interquartile range; LMWH, low-molecular-weight heparin.

**Table 3 Clinical outcomes during edoxaban therapy according to the existence of criteria for dose reduction and the use of recommended vs. non-recommended doses**

	Non-recommended doses		Recommended doses		Hazard ratio (95% CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
<b>Weight &gt; 60 kg and CrCl levels &gt; 50 mL/minute</b>					
<i>Patients, N</i>		<b>23</b>		<b>393</b>	
PE recurrences	0	-	0	-	-
DVT recurrences	1	11.8 (0.59–58.1)	1	0.56 (0.03–2.77)	20.9 (0.54–817)
Major bleeding	1	11.6 (0.58–57.5)	4	2.25 (0.71–5.43)	5.18 (0.21–41.2)
Gastrointestinal	1	11.6 (0.58–57.5)	1	0.56 (0.03–2.77)	20.7 (0.53–809)
Hematoma	0	-	1	0.56 (0.03–2.77)	-
Vaginal	0	-	1	0.56 (0.03–2.77)	-
Hemoptysis	0	-	1	0.56 (0.03–2.77)	-
Composite outcome	2	23.5 (3.95–77.8)	5	2.81 (1.03–6.23)	8.37 (1.12–42.4)*
Death	3	35.0 (8.89–95.2)	2	1.12 (0.19–3.71)	31.1 (4.63–262)*
Fatal bleeding	1	11.6 (0.58–57.5)	1	0.56 (0.03–2.77)	20.7 (0.53–809)
Heart failure	1	11.6 (0.58–57.5)	1	0.56 (0.03–2.77)	20.7 (0.53–809)
Unknown reason	1	11.6 (0.58–57.5)	0	-	-
<b>Weight ≤ 60 kg or CrCl levels ≤ 50 mL/minute</b>					
<i>Patients, N</i>		<b>54</b>		<b>92</b>	
PE recurrences	0	-	0	-	-
DVT recurrences	0	-	0	-	-
Major bleeding	0	-	1	2.79 (0.14–13.7)	-
Gastrointestinal	0	-	1	2.79 (0.14–13.7)	-
Composite outcome	0	-	1	2.79 (0.14–13.7)	-
Death	3	14.0 (3.57–38.2)	1	2.79 (0.14–13.7)	5.04 (0.54–133)
Infection	1	4.68 (0.23–23.1)	0	-	-
Myocardial infarction	1	4.68 (0.23–23.1)	0	-	-
Unknown	1	4.68 (0.23–23.1)	0	-	-
Multi-organ failure	0	-	1	2.79 (0.14–13.7)	-

*P* values refer to comparisons between patients with non-recommended vs. those on recommended doses of edoxaban.

CI, confidence interval; CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism.

\**P* = 0.04; *P* = 0.001.

**Table 4 Univariable and multivariable analysis for the composite outcome (recurrent VTE or major bleeding)**

	Univariable analysis	Multivariable analysis (competing risk analysis)
Clinical characteristics		
Male sex	2.14 (0.52–8.65)	1.79 (0.44–7.17)
Age > 70 years	0.71 (0.17–2.98)	0.36 (0.03–3.3)
Body weight ≤ 60 kg	-	-
Risk factors for VTE		
Unprovoked VTE	Ref.	Ref.
Active cancer	7.11 (1.68–30.2)*	7.40 (1.83–30.0)*
Transient risk factors	0.41 (0.05–3.25)	0.54 (0.10–2.76)
Underlying diseases		
Chronic lung disease	1.85 (0.23–14.4)	1.52 (0.38–5.95)
Chronic heart failure	7.21 (1.47–35.4)*	10.9 (1.8–66.3)*
Recent major bleeding	-	-
Laboratory tests		
Anemia	2.89 (0.70–11.8)	1.02 (0.16–6.41)
CrCl levels ≤ 50 mL/minute	0.69 (0.08–5.74)	0.36 (0.03–3.49)
Initial VTE presentation		
Pulmonary embolism	8.47 (1.07–66.8)*	8.97 (1.05–76.7)*
Edoxaban doses,		
30 mg daily	2.54 (0.60–10.7)	4.88 (0.93–25.4)

P values refer to comparisons between patients with non-recommended vs. those on recommended doses of edoxaban.

Results expressed as hazard ratio (95% confidence intervals).

CrCl, creatinine clearance; Ref., reference; VTE, venous thromboembolism.

\* $P = 0.005$ ;  $P = 0.007$ ;  $P = 0.009$ ;  $P = 0.015$ ;  $P = 0.043$ ;  $P = 0.045$ .

but this dose should be reduced to 30 mg daily in patients with CrCl levels 15–50 mL/minute, body weight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors. This recommendation is mainly based on studies performed in patients receiving the drug for VTE treatment.<sup>16–18</sup> However, none of the 73 patients weighing ≤ 60 kg and only 1 of 103 patients with CrCl levels 15–50 mL/minute in our cohort developed major bleeding. On the other hand, patients with active cancer (4 of 72) or chronic heart failure (2 of 29) had a much higher influence on the risk for the composite outcome. Thus, our findings suggest that the recommendation for dose reduction based on prior studies performed in patients with atrial fibrillation may not be optimal in patients with VTE. Some additional variables (such as cancer or heart failure) may have a higher influence on the risk for bleeding.

Twenty-three of 416 patients (5.5%) not meeting criteria for dose reduction in our cohort received edoxaban 30 mg daily (instead of 60 mg). These patients were older, weighed less, had lower CrCl levels, and were (nonsignificantly) more likely to have active cancer than those receiving 60 mg daily. We hypothesize that these may have been the reasons why their attending doctors prescribed 30 mg instead of the recommended dose of 60 mg daily. During the course of edoxaban therapy, patients receiving 30 mg daily had an 8-fold higher rate of the composite event than those receiving 60 mg. The 20-fold higher rate of VTE recurrences could be, in part, explained by the use of lower doses of edoxaban, but the 5-fold higher rate of major bleeding could not.

No patient meeting criteria for dose reduction developed VTE recurrences. Interestingly also, none of the 54 patients meeting criteria for dose reduction but receiving 60 mg daily

bled. The only major bleeding appeared in a patient receiving 30 mg daily. Thus, our findings suggest that edoxaban seems to be safe in patients with renal insufficiency or low body weight. Similarly, no dose reduction was prescribed in the presence of the same clinical conditions, in all the randomized clinical trials for VTE treatment with rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE) or with apixaban (AMPLIFY), unlike in nonvalvular atrial fibrillation studies in which a dose reduction was scheduled. Certainly, patients receiving 60 mg daily had a 5-fold higher mortality rate, but none of the reported causes of death (heart failure, myocardial infarction, and multi-organ failure) seems to be a potential consequence of anticoagulant therapy.

This study has a number of potential limitations. First, RIETE is an observational registry, and our data are hypothesis-generating. There 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, given the small sample size, there is a risk of overestimation and underestimation, also type I and II errors. In addition, given the median follow-up time was only 4 months, any error occurring in the analysis might be multiplied when using event rate as “per 100 person-years,” especially among the reduced-dose group. However, our study includes subgroups of patients (the very elderly, those with disseminated cancer, or with severe renal failure) that almost never appear in randomized clinical trials. Third, a variety of practitioners entered data into the registry,

which may lend itself to potential inaccuracies in the data being reported. Fourth, in the registry, information about the concomitant use of P-glycoprotein inhibitors was not collected (because few patients with VTE use ciclosporin, dronedarone, erythromycin, or ketoconazole); then, we have no information about potential interactions and/or side effects related to this concomitant administration. Fifth, given the observational nature of the study, the finding of an increased risk for major bleeding in patients receiving a lower than recommended dose is likely to be a result of confounding by indication. Unfortunately, this does not appear to be adjustable given the small number of the study outcomes, which limits the maximum number of independent variables entering into a multivariable Cox proportional hazards regression model. 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 randomized trial, and enhances the generalizability of our findings. The broad range of patients from multiple medical centers, countries, and treatment settings enrolled in the RIETE registry decreased the likelihood of the inclusion of a skewed population in this study.

## CONCLUSION

In summary, our data validate the effectiveness and safety of edoxaban for long-term therapy of VTE in real life. However, the criteria (body weight and renal function) used to recommend a dose reduction seem to have scarce influence on outcome. Further studies are needed, using larger samples of patients receiving edoxaban, to more precisely identify those patients in whom the dose should be reduced.

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