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ARTICLE

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

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Background

- Edoxaban is among the last DOACs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of venous thromboembolism (VTE) .
- 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 ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors.
- Unlike other DOACs edoxaban currently can provide data only from the pivotal randomized trial.

Aim of the study

- To assess the efficacy and safety of edoxaban for long-term therapy of VTE in real-life clinical practice comparing the rate of the composite of VTE recurrences or major bleeding during therapy in patients receiving recommended vs. non-recommended doses of the drug.

Methods

- Data from the Registro Informatizado Enfermedad TromboEmbólica (RIETE), a prospective multinational registry of patients with objectively confirmed VTE.
- Consecutive patients enrolled in the RIETE registry from October 2015 to November 2019 receiving edoxaban for the treatment of VTE.
- All patients were followed up for at least 3 months.
- The major outcome was the composite of symptomatic VTE recurrences or major bleeding occurring during edoxaban therapy.

Results (I)

- 562 patients: of these, 146 (26%) met 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): they were significantly older (74 ± 14 vs. 62 ± 15 years; P < 0.001), weighed less (73 ± 12 vs. 82 ± 13 kg; P < 0.01), and had lower CrCl levels at baseline (79 ± 24 vs. 99 ± 34 mL/minute; P < 0.001) than those receiving recommended doses.
- 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.

Results (II)

- Among 146 patients meeting criteria for dose-reduction, 54 (37%) received non-recommended doses (60 mg instead of 30 mg daily) of edoxaban: they were younger (71 ± 17 vs. 79 ± 17 years; $P < 0.05$) and had higher CrCl levels at baseline (57 ± 29 vs. 47 ± 27 mL/minute) than those receiving 30 mg daily.
- During edoxaban therapy, no patient had VTE recurrences; none of the 54 patients meeting criteria for dose reduction but receiving 60 mg daily developed major bleeding.

	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
tients, N	*23*	*393*	*54*	*92*
nical 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%)
sk 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%)
cent 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%)
derlying 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%)
boratory 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
tial 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%)
ents during initial therapy				
VTE recurrences	2 (0.51%)	1 (4.3%)	0	0
Major bleeding	0	0	1 (1.1%)	0

values refer to comparisons between patients with non-recommended vs. those on recommended doses of edoxaban.
Cl, creatinine clearance; DVT, deep vein thrombosis; VTE, venous thromboembolism.
< 0.001; $P = 0.01$; $P = 0.002$; $P = 0.005$; $P = 0.048$; $P = 0.025$.

Clinical characteristics of patients according to criteri dose reduction and use recommended doses edoxaban

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	
		Weight > 60 kg and CrCl levels > 50 mL/minute			
Patients, N		***23***		***393***	
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	-	-
Patients, N		**Weight ≤ 60 kg or CrCl levels ≤ 50 mL/minute**			
		54		***92***	
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.
*$P = 0.04$; $P = 0.001$.

Conclusions

- This is the first real-life study on patients receiving edoxaban for long-term therapy of VTE.
- The study validate the effectiveness and safety of edoxaban for long-term therapy of VTE in real life.
- During edoxaban therapy, patients receiving 30 mg daily had an 8-fold higher rate of the composite event than those receiving 60 mg.
- These 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.
- There might be a useful basis for future controlled clinical trials comparing different therapeutic strategies; waiting for new data, these results should caution clinicians against empirically dose reducing based on off-label recommendations.