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ETNA VTE Europe: A contemporary snapshot of VTE patients treated with edoxaban in clinical practice across eight European countries

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Introduction

- Edoxaban is a non-vitamin K antagonist oral anticoagulant (NOAC) that is approved for the treatment/secondary prevention of acute venous thromboembolism (VTE; deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) in adults, based on its comparable efficacy and superior safety compared with warfarin in a broad spectrum of patients with VTE during the Hokusai-VTE trial[1]
- Although randomised controlled trials are the gold standard for comparing treatments and interventions, real world evidence (RWE) provides a better representation of the range and distribution of patients and management patterns in clinical practice
  - Consequently, RWE should be used to complement RCT data to establish whether the results observed in RCTs are applicable to community practice
- ETNA-VTE-Europe (NCT02943993) was initiated in agreement with the European Medicines Agency (EMA) to assess benefits and risks of edoxaban in the treatment and secondary prevention of VTE for up to 18 months in routine clinical practice
- Using an observational study design, we aimed to compare Hokusai-VTE patients with those treated in clinical practice during ETNA-VTE Europe, and to expand the knowledge about edoxaban's clinical effectiveness and safety in the treatment and prevention of VTE

Methods

- ETNA-VTE-Europe is a prospective, non-interventional post-authorisation safety study conducted in eight European countries[4]
- The study included patients with an initial or recurrent acute VTE that occurred ≤2 weeks prior to enrolment and in which a decision (at the treating physician's discretion) to use edoxaban had already been made
- Descriptive comparisons of Hokusai-VTE and ETNA-VTE Europe are presented
- Exploratory comparisons between subgroups (DVT vs PE ± PE) were performed using a Chi-square test for categorical variables and a Wilcoxon test for continuous variables

Results

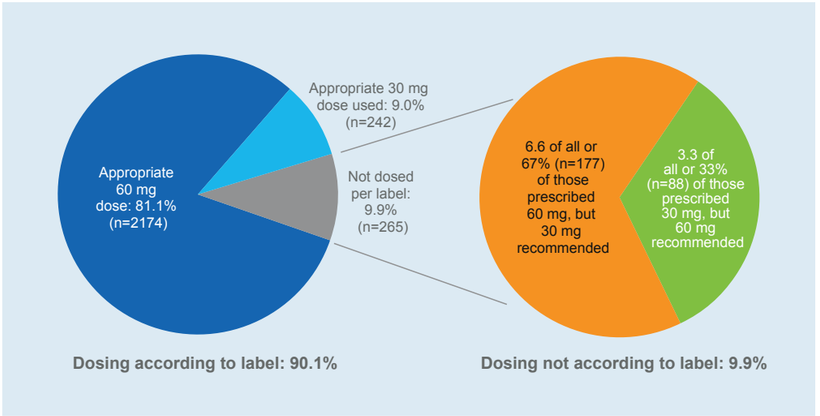
- A total of 2879 patients presenting with acute VTE (median age 65 years, 46.5% female) were enrolled at 339 sites (133 office-based physicians and 206 hospitals)
- Of the 2680 patients with complete data, 23.6% reported prior VTE, 2.9% prior stroke, and 2.8% had a history of bleeding (**Table 1**)
- Patients in ETNA-VTE were older (65 versus 57 years), more likely to be female (46.5% versus 39.8%) and had a higher prevalence of chronic venous insufficiency (11.1% versus 1.6%) than in the European cohort of the Hokusai-VTE clinical trial (n=1512; **Table 1**)
  - Body weight and creatinine clearance (CrCl) were notably lower in clinical practice; more patients had a body weight ≤60 kg (9.3% vs 5.6%) and a CrCl ≤50 ml/min (10.2% vs 4.1%)
- In ETNA-VTE, 90.1% of edoxaban dosing was adherent to the label (**Figure 1**)
  - 6.6% of patients qualifying for dose reduction were incorrectly prescribed edoxaban 60 mg
  - 3.3% of patients were dose-reduced to 30 mg without a formal indication to do so
- Heparin lead-in was used in 84.7% of patients and was more frequently used in PE than DVT patients (91.3% vs. 80.1%; p<0.0001)

Table 1. Patient characteristics from ETNA-VTE (overall and by VTE presentation) and the Hokusai-VTE clinical trial

Parameter	HOKUSAI-VTE*† N=1512	ETNA-VTE N=2680	ETNA-VTE DVT only N=1559	ETNA-VTE PE ± DVT N=1121	p-value DVT vs. PE
Age, years	57 (45–69)	65 (52–76)	64 (51–75)	66 (54–76)	0.0052
Female patients	601 (39.8)	1246 (46.5)	706 (45.3)	540 (48.2)	0.1577
Body weight, kg	84.0 (73.9–95.3)	80 (70–92)	80 (70–90)	81 (70–94)	0.0031
Acute VTE diagnosis					
DVT only	854 (56.5)	1559 (58.2)	1559 (100.0)	0 (0.0)	N/A
PE with or without DVT	658 (43.5)	1121 (41.8)	0 (0.0)	1121 (100.0)	N/A
Hypertension	563 (37.3%)	1150 (42.9)	627 (40.2)	523 (46.7)	0.0006
Medical history					
Diabetes mellitus	115 (7.6)	298 (11.1)	168 (10.8)	130 (11.6)	0.4561
Chronic Venous Insufficiency	24 (1.6)	297 (11.1)	214 (13.7)	83 (7.4)	<0.0001
Cancer	136 (9.0)	253 (9.4)	132 (8.5)	120 (10.7)	0.0566
Stroke	18 (1.2)	79 (2.9)	29 (1.9)	50 (4.5)	0.0001
Bleeding history	N/A	76 (2.8)	29 (1.9)	47 (4.2)	0.0003
Frailty	N/A	330 (12.3)	176 (11.3)	154 (13.8)	0.0196
CrCL‡§, ml/min	104.3 (79.0–128.9)	90.1 (65.7–117.7)	91.2 (65.5–120.4)	89.3 (65.9–115.0)	0.2238
VTE history					
Prior DVT	180 (11.8)	434 (16.2)	310 (19.9)	124 (11.1)	<0.0001
Prior PE (with or without DVT)	107 (7.1)	199 (7.4)	73 (4.7)	126 (11.2)	<0.0001
Edoxaban dose, 60 mg	1371 (90.7)	2351 (87.7)	1349 (86.5)	1002 (89.4)	0.0317

Values are n (%) or medians with IQRs; N/A, not available from the HOKUSAI-VTE dataset or incompatible definition; a Chi-square test was used for categorical variables and a Wilcoxon test for continuous variables. Note that the HOKUSAI-VTE population was confined those enrolled in Europe and those receiving Edoxaban. Frailty was not further defined in the observational plan and instead based on physician definition.*Only corresponding ETNA-VTE European countries were included in the reported Hokusai-VTE cohort (Germany, Austria, Ireland, Netherlands, Italy, Switzerland, Great Britain, Belgium); †mITT and safety population including edoxaban and warfarin patients; ‡Recalculated based on patient variables; §Cockroft-Gault formula. **CrCl**, creatinine clearance; **DVT**, deep vein thrombosis; **PE**, pulmonary embolism; **VTE**, venous thromboembolism

Figure 1. Dosing according to edoxaban label based on bodyweight, creatinine clearance and P-gp inhibitor use



- Based on the proportions of patients fulfilling the dose reduction criteria for edoxaban (**Table 2**), use of edoxaban 30 mg was in line with the SmPC[5] in 241 of the 329 (73.3%) patients that were prescribed a 30 mg dose

Table 2. Patients fulfilling the dose reduction criteria for edoxaban

	Body weight ≤60 kg	CrCl*,† ≤50 ml/min	Any of Body weight, CrCl or PgP use
Total (N=2680)	241 (9.3)	245 (10.2)	419 (15.6)
Belgium, Netherlands, Luxembourg (N=692)	43 (6.6)	43 (6.9)	76 (11.0)
Austria, Germany, Switzerland (N=1012)	73 (7.4)	77 (9.3)	135 (13.3)
Italy (N=847)	118 (14.0)	119 (14.4)	197 (23.3)
Ireland/UK (N=129)	7 (5.7)	5 (4.4)	11 (8.5)
VTE type			
DVT only (N=1559)	142 (9.3)	133 (10.0)	241 (15.5)
PE ± DVT (N=1121)	99 (9.1)	112 (10.5)	178 (15.9)
Dosing			
30 mg (N=329)	130 (39.9)	165 (53.1)	241 (73.3)
60 mg (N=2351)	111 (4.9)	80 (3.8)	178 (7.6)

Values are n (%); PgP inhibitor use was not reported due to low number of patients who underwent dose reduction following this criteria (n=2). *Recalculated based on patient variables; †Cockroft-Gault formula. **CrCl**, creatinine clearance; **DVT**, deep vein thrombosis; **PgP**, P-glycoprotein; **PE**, pulmonary embolism; **VTE**, venous thromboembolism

Conclusions

- **The data describe a clinical practice population of VTE patients that is partially different to prior randomised controlled trials**
  - **The clinical practice population was older and had more comorbidities**
- **Edoxaban is largely used adequately in these patients, respecting the recommendations for treatment initiation, dosing, and dose adjustments in special patient populations**

References

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Declaration of interest

ETNA-VTE Europe