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Original article

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

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ABSTRACT

Introduction: Edoxaban has proven its efficacy and safety in the ENGAGE AF-TIMI 48 and HOKUSAI-VTE clinical trials. Clinical practice patients, however, may differ from those enolled in clinical trials. We aimed to compare patients from the HOKUSAI-VTE clinical trial with those treated in clinical practice.
Materials and Methods: ETNA-VTE-Europe is a prospective, non-interventional post-authorisation safety study conducted in eight European countries.
Results: A total of 2,879 patients presenting with acute symptomatic venous thromboembolism (VTE) were enrolled at 339 sites. Of the 2,680 patients with complete data, 23.6% reported prior VTE and 2.8% had a history of bleeding. Patients in ETNA-VTE were older (65vs.57 years), more likely to be female (46.5vs.39.8%) and had a higher prevalence of chronic venous insufficiency (11.1vs.1.6%) than those in the European cohort of the HOKUSAI-VTE trial (n = 1,512). Bodyweight and creatinine clearance were substantially lower in clinical practice. Edoxaban dosing was adherent to label in 90% of patients, with higher (60 mg) and lower than recommended doses (30 mg) used in 6.6% and 3.3% of the patients, respectively. Heparin lead-in was used in 84.7% of the patients overall, and was more frequently used in patients with PE than patients with DVT only (91.3% vs. 80.1%; $p < 0.0001$).
Conclusions: These data reinforce the largely appropriate use of edoxaban in routine clinical practice, where the

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major bleeding; DACH, Austria, Switzerland and Germany; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; NVAF, non-valvular atrial fibrillation; PASS, post-authorisation safety study; PE, pulmonary embolism; UK/IE, United Kingdom/Ireland; VTE, venous thromboembolism

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study population differs from those in prior randomised controlled trials.
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1. Introduction

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). It has an incidence of approximately 1–2 per 1,000 person-years in Europe [1]. While both events increase the probability of subsequent recurrent VTE [2], case fatality is higher after PE than after DVT [3–5].

For years, low molecular and unfractionated heparin and vitamin-K antagonists (VKAs) provided the only treatment options for patients suffering from VTE. Since then, new non-vitamin K antagonist oral anticoagulants (NOACs) have become available, of which edoxaban – a direct inhibitor of factor Xa – is one example. Knowledge about edoxaban has predominantly been derived from the three large clinical trials: ENGAGE AF-TIMI 48, HOKUSAI-VTE and HOKUSAI-VTE Cancer [6–8]. These trials investigated the clinical efficacy and safety of edoxaban in patients with atrial fibrillation (AF) not triggered by rheumatic valvular disease or mechanical heart valves, the treatment and secondary prevention of acute VTE, and cancer-associated VTE, respectively.

While clinical trials use stringent inclusion and exclusion criteria for patient selection prior to treatment, the treatment of patients in clinical practice are not constrained by the same criteria. There is a clear need for real-world experience with edoxaban and, in particular, the prescribing practices of clinicians using this medication. Furthermore, specific procedures within the clinical trials, such as the requirement for heparin lead-in, may not be followed in clinical practice. Finally, learnings from these larger trials, such as drug interactions, are likely to impact the use of the drug in clinical practice.

For these reasons, and in accordance with the regulatory requirements of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), we established a prospective, non-interventional post-authorisation safety study (PASS). With the "Edoxaban Treatment in routine cliNical prActice for patients with acute Venous ThromboEmbolism in Europe" (ETNA-VTE-Europe) study, we aimed to gain further insight into the use of edoxaban in routine clinical practice, including compliance to the summary of product characteristics (SmPC), the use of a heparin lead-in, dosing patterns and the consideration of concomitant diseases. This information from routine clinical practice was compared to the European cohort from the HOKUSAI-VTE trial population.

2. Materials and methods

ETNA-VTE-Europe was conducted in eight European countries (Austria, Belgium, Germany, Ireland, Italy, the Netherlands, Switzerland and the United Kingdom) [9]. Approval from the responsible Ethics Committees and Institutional Review Boards was obtained and compliance with the Declaration of Helsinki was ensured throughout the study. Patients provided written Informed consent prior to enrolment.

2.1. Setting

In order to represent the regional distributions of centres, healthcare settings, specialties and approaches to VTE treatment, a sequential site selection process was implemented. This involved identification of

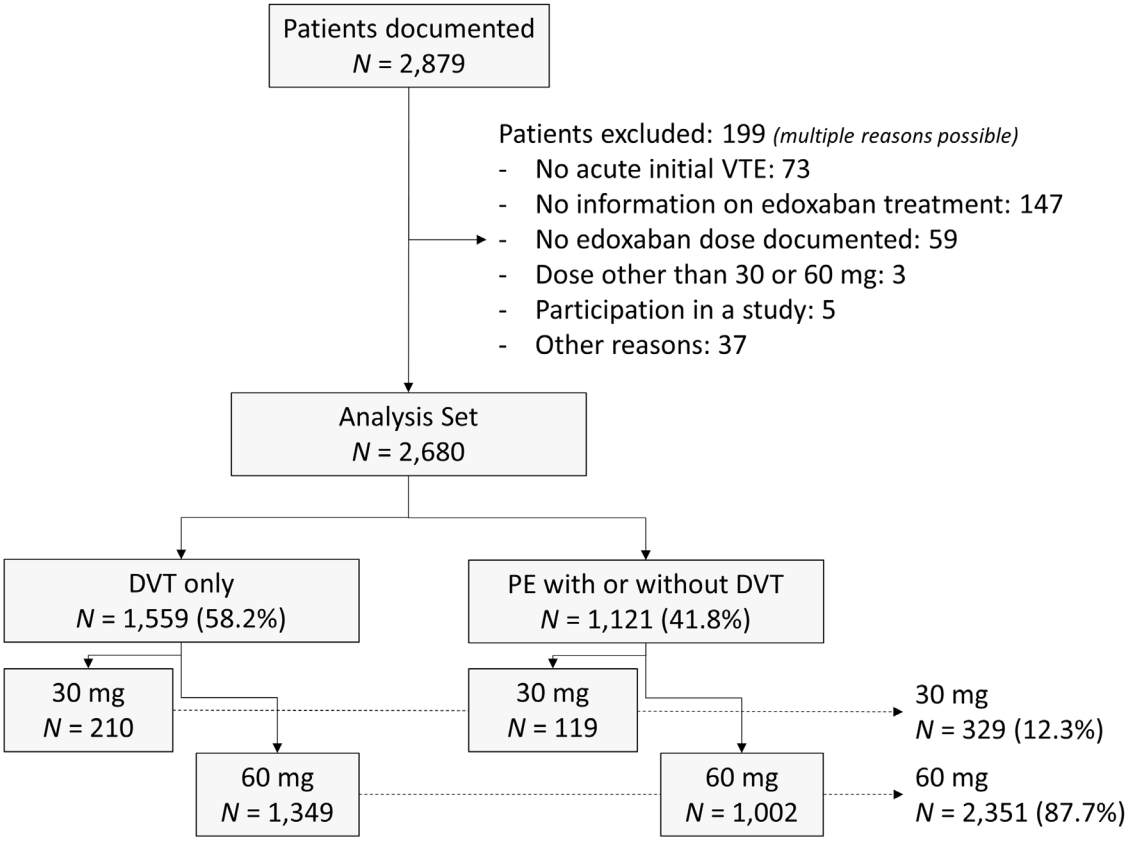

Fig. 1. Patients documented and analysed by subgroup. DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

potential sites, acquisition of relevant institutional details, assessment of suitability and invitation to participate. To be considered eligible, sites were required to have access to acute VTE patients, the ability to access the study Electronic Data Capture system, record data in English and have adequate time and staff to perform all study-related documentation activities. Sites also agreed to complete a screening log with the aim of maximising the potential for consecutive enrolment of those patients receiving edoxaban, and to perform follow-ups according to routine clinical practice.

2.2. Patient population

Patient recruitment took place in two waves. The first wave was from Q4, 2016 until Q2 2018 (Switzerland and Germany) and the second was from Q1 2017 until Q4 2018 (all other countries). The recruitment period was 2 years in each country [9]. The study included patients with initial or recurrent acute VTE (distal or proximal DVT and/or PE) that had occurred no more than two weeks prior to enrolment and in which a decision, at the discretion of the treating physician, to use edoxaban had already been made. The use of concomitant treatment and changes to medication were unrestricted. Study exclusion criteria were a lack of written informed consent and participation in a simultaneous interventional study.

2.3. Objectives

The primary objectives of the study have been previously described [9]. The specific objectives of the present analysis of baseline parameters were to 1) describe the overall patient population, including a regional comparison; 2) explore the patient populations by subgroups (either DVT alone or PE with or without DVT); 3) explore differences in patient characteristics between routine clinical practice and those enrolled in the edoxaban HOKUSAI-VTE clinical trial; 4) investigate edoxaban dosing and dosing adequacy; and 5) analyse the frequency and duration of a heparin lead-in.

2.4. Statistics

Data from patients enrolled into ETNA-VTE were screened for protocol compliance and a baseline analysis set was built; it excluded patients with no VTE at baseline, no information on edoxaban treatment and/or dose(s) other than 30/60 mg, parallel participation in a clinical study and no informed consent. Subgroups were defined by edoxaban dose (30 vs. 60 mg) and VTE characteristics (DVT alone vs. PE with or without DVT) and by geographic regions.

For categorical variables, the number of patients and the corresponding percentages are presented. Median and interquartile ranges (IQRs) are shown for continuous variables. Exploratory comparisons between subgroups were performed using a Chi-square test for categorical variables and a Wilcoxon test for continuous variables. The statistical analysis was performed using SAS version 9.4.

3. Results

A total of 2,879 patients were documented at 339 sites representing 133 office-based physicians and 206 hospitals. Of these, 199 patients were excluded from the analysis (reasons presented in **Fig. 1**), resulting in 2,680 evaluable patients.

Table 1
Patient characteristics of those in clinical practice (ETNA-VTE) overall, by VTE presentation and those in clinical trials (HOKUSAI-VTE).

	HOKUSAI-VTE (ETNA-VTE Europe countries[a,b]) [*N* = 1,512]	ETNA-VTE [*N* = 2,680]	ETNA-VTE DVT only [*N* = 1,559]	ETNA-VTE PE ± DVT [*N* = 1,121]	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)	1,246 (46.5)	706 (45.3)	540 (48.2)	0.1577
Bodyweight, 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)	1,559 (58.2)	1,559 (100.0)	0 (0.0)	n.a.
PE with or without DVT	658 (43.5)	1,121 (41.8)	0 (0.0)	1,121 (100.0)	n.a.
Blood Pressure					
SBP, mmHg	130 (120–140)	130 (120–140)	130 (120–140)	130 (120–142)	0.0449
DBP, mmHg	80 (71–86)	80 (70–85)	80 (72–85)	80 (70–86)	0.0118
Hypertension	563 (37.3%)	1,150 (42.9)	627 (40.2)	523 (46.7)	0.0006
Medical history					
Dys-/hyperlipidemia	306 (20.3)	519 (19.4)	283 (18.2)	236 (21.1)	0.0639
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
Hyper-/Hypothyroidism	91 (6.0)	237 (8.8)	123 (7.9)	114 (10.2)	0.0459
COPD	59 (3.9)	177 (6.6)	85 (5.5)	92 (8.2)	0.0043
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	1,371 (90.7)	2,351 (87.7)	1,349 (86.5)	1,002 (89.4)	0.0317
30 mg	141 (9.3)	329 (12.3)	210 (13.5)	119 (10.6)	0.0317

[a] *Only corresponding ETNA-VTE European countries were included in the reported HOKUSAI-VTE cohort (Germany, Austria, Ireland, Netherlands, Italy, Switzerland, Great Britain, Belgium);*

[b] *mITT and safety population including edoxaban and warfarin patients*

Legend: 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.

*Recalculated based on patient variables; **Cockroft-Gault formula

COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DBP, diastolic blood pressure; DVT, deep vein thrombosis; PE, pulmonary embolism; SBP, systolic blood pressure; VTE, venous thromboembolism. Frailty was not further defined in the observational plan and instead based on physician definition.

3.1. Patient characteristics

Patients had a median age of 65 years, 46.5% were female and the median bodyweight was 80 kg (Table 1). Hypertension (42.9%), dys-/hyperlipidemia (19.4%), diabetes mellitus (11.1%) and chronic venous insufficiency (11.1%) were the most common comorbid conditions/risk factors, followed by cancer (9.4%) and hyper-/hypothyroidism (8.8%). Approximately one quarter of patients reported prior VTE (16.2% prior DVT alone; 7.4% prior PE ± DVT), 2.9% had a history of stroke and 2.8% had a history of bleeding.

The majority of patients were included from Austria/Germany/Switzerland (DACH; n = 1,012; 37.8%), followed by Italy (n = 847; 31.6%) and Belgium/Netherland/Luxembourg (Benelux; n = 692; 25.8%) while fewer patients were included from the UK/Ireland (n = 129; 4.8%) (Table 2). Patients in Italy tended to be older (median 69 years), more frail (18.9%), included more female patients (50.6%) and patients had a lower bodyweight (median 75 kg) than those patients from other countries. Italian patients also had a higher relative rate of DVT (68.4%) vs. PE ± DVT (31.6%) compared to the other countries.

3.2. Patient characteristics by initial VTE type

In total, 1,559 patients (58.2%) were included based on a diagnosis of DVT alone and 1,121 suffered from PE ± DVT (41.8%) (Table 1). Patients with DVT alone and those suffering from PE ± DVT had similar patient characteristics overall (Table 1). Almost a two-fold higher frequency of prior DVT (19.9% vs. 11.1%; $p < 0.0001$) and of chronic venous insufficiency (13.7 vs. 7.4; $p < 0.0001$) was seen in DVT patients compared to PE patients.

3.3. A comparison of clinical practice vs. clinical trial populations

Patients in clinical practice had characteristics partially distinct from edoxaban patients in the HOKUSAI-VTE trial (Table 1). Patients in clinical practice were typically older (median 65 vs. 57 years) and more often female (46.5 vs. 39.8%). While comorbid conditions and risk factors were not substantially different overall, there was a much higher prevalence of chronic venous insufficiency in clinical practice (11.1 vs. 1.6%).

Patients from clinical practice had a lower bodyweight than those in the clinical trial (80 vs. 84 kg) resulting in more patients having a critical bodyweight ≤60 kg (9.3 vs. 5.6%) (Table 1). This was particularly evident for patients from Italy, where 14.0% patients had a bodyweight ≤60 kg. Creatinine clearance (CrCl) was lower in clinical practice (90.1 vs. 104.3 ml/min) and more patients had a critical CrCl ≤50 ml/min (10.2 vs. 4.1%), again with a particularly high rate in Italy (14.4%).

3.4. Edoxaban dosing and dosing adherence to label recommendations

The SmPC recommends a once daily dose of 60 mg edoxaban for the treatment of DVT and PE, for the prevention of recurrent DVT and PE and for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with ≥1 risk factor. A reduced dose of 30 mg is recommended for patients with renal impairment, low bodyweight (≤60 kg) and for patients receiving specific PgP inhibitors. In clinical practice, a 60 mg dose of edoxaban was used in 2,351 patients (87.7%) and 30 mg in 329 patients (12.3%).

Patients receiving the 30 mg edoxaban dose (Table 4) were substantially older (median 79 vs. 63 years), predominantly female (68.1% vs. 43.5%), had a lower median bodyweight (65 vs. 81 kg) and a higher comorbidity burden, as exemplified by the rates of hypertension (58.7% vs. 40.7%), dys-/hyperlipidemia (27.7% vs. 18.2%), diabetes (16.1% vs. 10.4%), cancer (14.6% vs. 8.7%) and chronic obstructive pulmonary disease (COPD; 12.2% vs. 5.8%). In line with the SmPC, a 30 mg dose of edoxaban was more frequently used in patients with a poor kidney function (CrCl 48.7 vs. 95.5 ml/min),

Table 2
Patients included into ETNA-VTE by geographic region (N = 2,680).

	Belgium, Netherlands, Luxembourg [N = 692; 25.8%]	Austria, Germany, Switzerland [N = 1,012; 37.8%]	Italy [N = 847; 31.6%]	Ireland, UK [N = 129; 4.8%]
Age, years	61 (49–70)	65 (53–76)	69 (54–79)	59 (45–72)
Female patients	298 (43.1)	466 (46.0)	428 (50.5)	54 (41.9)
Body weight, kg	83 (73–95)	83 (72–95)	75 (66–85)	85.5 (74–97)
Acute VTE diagnosis				
DVT only	307 (44.4)	610 (60.3)	579 (68.4)	63 (48.8)
PE with or without DVT	385 (55.6)	402 (39.7)	268 (31.6)	66 (51.2)
Medical history				
Diabetes mellitus	70 (10.1)	129 (12.7)	90 (10.6)	9 (7.0)
Dys-/Hyperlipidemia	139 (20.1)	194 (19.2)	166 (19.6)	20 (15.5)
Hyper-/Hypothyroidism	39 (5.6)	139 (13.7)	53 (6.3)	6 (4.7)
COPD	40 (5.8)	56 (5.5)	69 (8.1)	12 (9.3)
Cancer	68 (9.8)	90 (8.9)	85 (10.0)	10 (7.8)
Chronic Venous Insufficiency	34 (4.9)	145 (14.3)	117 (13.8)	1 (0.8)
Bleeding history	9 (1.3)	46 (4.5)	17 (2.0)	4 (3.1)
Stroke	19 (2.7)	30 (3.0)	29 (3.4)	1 (0.8)
Blood Pressure				
SBP, mmHg	131 (120–147)	131 (121–144)	130 (120–140)	130 (120–146)
DBP, mmHg	80 (73–90)	80 (70–85)	80 (70–80)	79 (70–88)
Hypertension	225 (32.5)	508 (50.2)	385 (45.5)	32 (24.8)
Frailty	47 (6.8)	112 (11.1)	160 (18.9)	11 (8.5)
CrCl*,**, ml/min	98.2 (75.1–123.3)	89.4 (66.0–117.5)	81.7 (60.5–110.2)	104.0 (77.0–132.7)
Venous thromboembolism				
Prior DVT	116 (16.8)	176 (17.4)	123 (14.5)	19 (14.7)
Prior PE	70 (10.1)	84 (8.3)	35 (4.1)	10 (7.8)
Edoxaban dose				
60 mg	636 (91.9)	923 (91.2)	676 (79.8)	116 (89.9)
30 mg	56 (8.1)	89 (8.8)	171 (20.2)	13 (10.1)

Legend: Values are n (%) or medians and IQRs; *Recalculated based on patient variables; **Cockroft-Gault formula
COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DBP, diastolic blood pressure; DVT, deep vein thrombosis; PE, pulmonary embolism; SBP, systolic blood pressure; VTE, venous thromboembolism. Frailty was not further defined in the observational plan and instead based on physician definition.

The SmPC-recommended edoxaban dose (based on bodyweight, CrCl and PgP inhibitor use) was given to 90.1% of the patients (60 mg: 81.1%, 30 mg: 9.0%). A dose of 60 mg of edoxaban, which did not follow the SmPC recommendations, was seen in 6.6% of the patients and was more frequently used than a 30 mg edoxaban dose that did not follow SmPC recommendations (3.3%) (**Supplementary Figure 1**).

According to the SmPC, the daily edoxaban dose of 60 mg should be adjusted to 30 mg if any of the following criteria is fulfilled: bodyweight ≤60 kg (n = 241; 9.3%), 15–50 ml/min CrCl (n = 245; 10.2%) or use of a specific PgP inhibitor (n = 2; 0.1%) (**Table 3**). Based on these criteria, the use of the 30 mg edoxaban dose was in line with the SmPC in 241 of the 329 patients who were prescribed a 30 mg dose (73.3%).

Conversely, 178 of the 2,351 patients who received a 60 mg dose (7.6%) should have received the SmPC-recommended 30 mg edoxaban dose. The patients with the higher-than-recommended dose were younger (median 75 vs. 80 years) and had a better renal function (CrCl 55.1 [IQR 45.3–81.3] vs. 44.2 [36.4–53.7] ml/min) than those receiving the 30 mg dose based on the SmPC recommendations.

3.5. Heparin lead-in

Heparin lead-in was used in 84.7% of the patients overall, and was more frequently used in patients with PE than patients with DVT only (91.3% vs. 80.1%; p < 0.0001) (**Supplementary Table 1**). Heparin lead-in usage was similar among those receiving both the 30 mg and 60 mg doses of edoxaban. The median number of days for the heparin lead-in was 6 (IQR 5–7). Taking the use and recommended length of a heparin lead-in from the SmPC into account, 66.4% of the patients were treated according to the label. The use of heparin lead-in was lowest in Ireland/UK with only 72.9% of patients receiving it compared with 88.2% patients in the Benelux countries.

4. Discussion

The study provides much needed information on the real-world experience of clinician's prescribing practises for edoxaban and gives a contemporary snapshot of patients treated with edoxaban in clinical practice across eight European countries. It illustrates that patients enrolled in clinical trials differ from patients in everyday clinical practice, that clinical trial design may influence clinical practice (e.g., the use of a heparin lead-in) and how the findings from clinical trials change clinical practice treatment patterns in special populations (edoxaban usage in patients with low bodyweight, poor kidney function and those receiving concomitant medication). Finally, the data allow quantification and characterisation of routine edoxaban use beyond the clinical trial setting.

4.1. ETNA-VTE patient population

The clinical management of acute VTE has been documented in a number of national (MASTER, SWIVTER II [10, 11]), European (PREFER in VTE [12]) and global (RIETE, GARFIELD-VTE, RECOVERY, XALIA [13–16]) registries. PREFER in VTE is the closest matching registry to our study with respect to design and setting [12]. It included 3,455 patients with acute DVT and/or PE in 381 sites in seven European countries and was conducted at a time when edoxaban was not readily available. As such the ETNA-VTE trial adds the edoxaban perspective to these data. While patients in ETNA-VTE matched those in PREFER in VTE with respect to many patient characteristics, patients were about 4 years older in ETNA-VTE and had a lower rate of chronic venous insufficiency. The rate of a prior bleeding history was also slightly lower in ETNA-VTE than in PREFER in VTE. Taken together this difference should be carefully taken into account when comparing the two datasets.

To compare patients in clinical practice versus those in the prior HOKUSAI-VTE trial [7], we confined the trial patients to the ones from corresponding European countries. It was particularly evident that patients in clinical practice were older, more often female and had a higher prevalence of chronic venous insufficiency than patients in the HOKUSAI-VTE clinical trial. The latter finding is potentially due to different interrogation and should be interpreted with caution. Bodyweight and creatinine clearance were also lower in clinical practice with more patients having a low (≤60 kg) bodyweight and a CrCl ≤50 ml/min. This may be not surprising as women in general, and elderly women in particular, are frequently underrepresented in clinical trials [17]. Dose adjustment was already mandated in the HOKUSAI-VTE trial for low bodyweight and for those with a low creatinine clearance, but it appears that fewer patients with these parameters were enrolled in the trial than seen in clinical practice.

4.2. Edoxaban dosing and dosing adherence to label recommendations

Edoxaban dosing was according to label in 90% of the patients. Only 6.6% of patients received a higher and 3.3% of the patients a lower than recommended dose. The SmPC mandates a dose reduction from 60 to 30 mg edoxaban when the patient's bodyweight is ≤60 kg, creatinine clearance is ≤50 ml/min and they are receiving concomitant PgP inhibitor.

With the limitations of comparing data from different registries, which imply different clinical settings and populations, the rate of appropriate dosing seen in ETNA-VTE seems to be reassuring. Moudallel *et al.* described rates of appropriate dosing of 70.3% for apixaban, 76.4% for dabigatran and 78.1% for rivaroxaban before and during hospital admission (no specific inclusion diagnosis and age ≥60 years

Table 3
Specific patient populations

	Body weight ≤ 60 kg n (%)	CrCl*,** ≤ 50 ml/min n (%)	Any of Body weight, CrCl or PgP use n (%)
Total (*N* = 2,680]	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* = 1,012]	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* = 1,559]	142 (9.3)	133 (10.0)	241 (15.5)
PE ± DVT (*N* = 1,121]	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* = 2,351]	111 (4.9)	80 (3.8)	178 (7.6)

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

Table 4
Baseline characteristics separately by edoxaban dose and by recommended/non-recommended edoxaban dose

	Edoxaban overall		Edoxaban as recommended		Edoxaban not as recommended	
	30 mg [N = 329]	60 mg [N = 2,351]	30 mg [N = 241]	60 mg [N = 2,173]	30 mg[N = 88]	60 mg [N = 178]
Age, years	79 (70; 85)	63 (51; 74)	80 (72; 86)	62 (51; 72)	74.0 (67; 81)	75 (55; 82)
≥75 years	208 (63.2)	546 (23.2)	166 (68.9)	451 (20.8)	42 (47.7)	95 (53.4)
Female	224 (68.1)	1,022 (43.5)	174 (72.2)	884 (40.7)	50 (56.8)	138 (77.5)
Bodyweight, kg	65 (56; 80)	81 (72; 93)	60 (54; 70)	83.0 (74; 95)	80 (71; 92)	60 (57; 66)
Acute VTE diagnosis						
DVT only	210 (63.8)	1,349 (57.4)	146 (60.6)	1,254 (57.7)	64 (72.7)	95 (53.4)
PE with or without DVT	119 (36.2)	1,002 (42.6)	95 (39.4)	919 (42.3)	24 (27.3)	83 (46.6)
Blood Pressure						
SBP, mmHg	130 (120; 140)	130 (120; 141)	130 (119; 140)	130 (120; 142)	130 (122; 142)	130 (118.5; 140)
DBP, mmHg	80 (70; 80)	80 (70; 86)	76 (70; 80)	80 (71; 86)	80 (76; 80)	76 (70; 80)
Hypertension	193 (58.7)	957 (40.7)	144 (59.8)	876 (40.3)	49 (55.7)	81 (45.5)
Medical history						
Dys-/Hyperlipidemia	91 (27.7)	428 (18.2)	69 (28.8)	392 (18.0)	22 (25.0)	35 (19.7)
Diabetes mellitus	53 (16.1)	245 (10.4)	43 (17.8)	223 (10.3)	10 (11.4)	22 (12.4)
Chronic venous insufficiency	40 (12.2)	257 (10.9)	33 (13.7)	236 (10.9)	7 (8.0)	21 (11.8)
Cancer	48 (14.6)	205 (8.7)	37 (15.4)	182 (8.4)	11 (12.5)	23 (12.9)
Hyper-/Hypothyroidism	34 (10.3)	203 (8.6)	25 (10.4)	182 (8.4)	9 (10.2)	21 (11.8)
COPD	40 (12.2)	137 (5.8)	31 (12.9)	123 (5.7)	9 (10.2)	14 (7.9)
Stroke	14 (4.3)	65 (2.8)	13 (5.4)	55 (2.5)	1 (1.1)	10 (5.6)
Bleeding history	13 (4.0)	63 (2.7)	8 (3.3)	56 (2.6)	5 (5.7)	7 (3.9)
Major or CRNM bleed	10 (3.0)	40 (1.7)	5 (2.1)	35 (1.6)	5 (5.7)	5 (2.8)
Major bleed	7 (2.1)	16 (0.7)	4 (1.7)	14 (0.6)	3 (3.4)	2 (1.1)
Major GI bleed	1 (0.3)	2 (0.1)	0 (0.0)	2 (0.1)	1 (1.1)	0 (0.0)
Frailty	17 (5.2)	85 (3.6)	94 (39.0)	181 (8.3)	24 (27.3)	31 (17.4)
CrCl*,**, ml/min	48.7 (39.2; 62.8)	95.5 (73.4; 122.5)	44.2 (36.4; 53.7)	98.3 (76.7; 124.9)	63.8 (55.9; 76.7)	55.1 (45.3; 81.3)
Venous thromboembolism						
Prior DVT	54 (16.5)	380 (16.1)	41 (17.0)	355 (16.3)	13 (14.8)	25 (14.0)
Prior PE (± DVT)	19 (5.8)	180 (7.7)	17 (7.1)	176 (8.1)	2 (2.3)	4 (2.2)

Legend: Values are n (%) or medians (IORs); *Recalculated based on patient variables; **Cockroft-Gault formula.
COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRNM, clinically relevant non-major bleeding; DBP, diastolic blood pressure; DVT, deep vein thrombosis; GI, gastrointestinal; PE, pulmonary embolism; SBP, systolic blood pressure; VTE, venous thromboembolism. Frailty was not further defined in the observational plan and instead based on physician definition.

for all NOACs) [18]. Rodriguez *et al.* described similar rates for patients with non-valvular atrial fibrillation. They observed appropriate dosing in 74.9%, 74.4% and 84.2% of patients receiving apixaban, dabigatran and rivaroxaban, respectively [19]. The encouraging adherence rate to the recommended dosing observed in the ETNA-VTE Europe registry suggests that the criteria based on the HOKUSAI-VTE clinical trial are relatively easy to apply to routine clinical practice and are consistent with the clinical needs of the prescribing physicians [7]. Alternatively, ETNA-VTE may represent a selection of centres that were experienced with edoxaban use. A comparison of the appropriate dosing rate with VKAs is more complex, as there is no fixed adequate VKA dose for a given patient [20]. As such, the high rate of appropriate dosing in ETNA-VTE is reassuring for its safety in clinical practice and it implies that dosing guidance is clear and simple.

Both the use of higher and lower-than-label recommended doses is of concern as it might increase the likelihood of bleeding on the one hand and the risk of recurrent VTE on the other. It appears that physicians used the reduced 30 mg edoxaban dose more often in multimorbid, elderly women with poor kidney function and a high risk of bleeding. While this caution may be appropriate, these very same patients are at an increased risk of thromboembolic events, which mandates appropriate anticoagulation. High-dose edoxaban use that is not in line with label was frequently considered in young patients with a good renal function and a low bleeding risk. As the definition of high-dose use not in line with the SmPC in our analysis was based on renal function, bodyweight and PgP inhibitor use, the two latter criteria may not be considered by physicians. This patient group should, therefore, receive particular attention as the risk of bleeding may be increased.

4.3. Use of a heparin lead-in

Heparin lead-in was used in 84.7% of the patients in ETNA-VTE and taking into account the recommended treatment duration of at least 5 days two thirds of patients were treated in accordance with the label and one third were not. The recommendation for a heparin lead-in is based on the HOKUSAI-VTE trial design and is also used for VKA oral anticoagulants [21]. In the HOKUSAI-VTE trial, the heparin lead-in justification was based on real-world practice applicability and the proven global standard of parenteral heparin. According to current labels and guidelines, dabigatran and edoxaban mandate an initial heparin pre-treatment phase of at least 5 days, followed by a switch to the DOAC without overlap [22, 23], while apixaban and rivaroxaban are commenced immediately after the VTE [22, 23], but with higher doses.

Deviations were seen in patients receiving a non-recommended dose of 30 mg and fewer patients with DVT received heparin than those with PE. Moreover, there was a regional variation with far fewer patients receiving heparin in Ireland/UK than in the Benelux states. It appears as if the use of heparin as a lead-in is possibly more influenced by the healthcare system and hospital treatment pathways than by patient and disease (DVT vs. PE) characteristics.

4.4. Strengths and limitations

ETNA-VTE is a prospective, non-interventional registry that serves as a snapshot of clinical practice across eight European countries. For this purpose, consecutive patient inclusion was requested to avoid a patient selection bias that is common in a randomised controlled trial. As such ETNA-VTE covers a much broader patient spectrum and allows insight into patients that were not considered for the clinical trials. To provide a good representation of edoxaban prescribing practices across Europe, data from eight different European countries and a variety of medical practices within each country were included in this study. In an ideal scenario, however, the study would have included patients from each European country.

On the other hand, data collection relies on variables collected during clinical routine practice and a degree of missing data is common for this type of study design. Furthermore, heterogeneous timing, and length and dosing of edoxaban exposure, with or without heparin-lead-in, may prove problematic for the interpretation of long-term results in particular. Finally, the single-arm nature of the study means that direct comparisons with other anticoagulants will not be possible.

5. Conclusions

The study provides much needed information on the real-world experience of clinician's prescribing practises for edoxaban across Europe. In particular, the patient population seen in routine clinical practise is different to patients recruited into prior randomised controlled trials.

Declarations

Ethics approval and consent to participate

Approval from the responsible Ethics Committees and Institutional Review Boards was obtained prior to protocol implementation. Informed consent was obtained from all patients prior to enrolment and compliance with the Declaration of Helsinki was ensured throughout the study.

Consent for publication

Not applicable.

Availability of data and material

Available from the corresponding author upon reasonable request.

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Daiichi Sankyo Europe GmbH, Munich, Germany.

Authors contributions

All authors have contributed to the conceptualization, design and methodology of the registry in collaboration with the Daiichi Sankyo Europe GmbH authors (PL, EMF, WZ, TZ, MCM, PER). ATC, EMF, WZ, MCM, PER, PB, and GA drafted the manuscript. All remaining authors revised the manuscript for important intellectual content. EMF and PER were responsible for the analysis of data. All authors have approved the version to be published. Apart from the selection of the countries, all design aspects were decided by the scientific Steering Committee and executed by independent Contract Research organisations.

Declaration of Competing Interests

The members of the Steering Committee received honoraria for their advice in the planning of the Registry. They also received honoraria and travel reimbursements from Daiichi Sankyo Europe GmbH for their participation in Steering Committee Meetings.

Alexander T. Cohen, David Jimenez, Bernd Brüggenjürgen, and Giancarlo Agnelli have received research support and/or honoraria for lectures from a number of pharmaceutical companies including Daiichi Sankyo, the sponsor of the registry.

Ulrich Hoffmann received honoraria for lectures from Bayer, Daiichi-Sankyo, Leo Pharma, Pfizer, Bristol-Meyers, Aspen, Sanofi-Aventis, Amgen. Advisory board membership for Bayer, Daiichi-Sankyo, Leo Pharma, Sanofi-Aventis and Amgen.

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Supplementary materials

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