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The management of acute venous thromboembolism in clinical practice

Results from the European PREFER in VTE Registry

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Summary

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in Europe. Data from real-world registries are necessary, as clinical trials do not represent the full spectrum of VTE patients seen in clinical practice. We aimed to document the epidemiology, management and outcomes of VTE using data from a large, observational database. PREFER in VTE was an international, non-interventional disease registry conducted between January 2013 and July 2015 in primary and secondary care across seven European countries. Consecutive patients with acute VTE were documented and followed up over 12 months. PREFER in VTE included 3,455 patients with a mean age of 60.8 ± 17.0 years. Overall, 53.0 % were male. The majority of patients were assessed in the hospital setting as inpatients or outpatients (78.5 %). The diagnosis was deep-vein thrombosis (DVT) in 59.5 % and pulmonary embolism (PE) in 40.5 %. The most common comorbidities were the various types of cardiovascular disease (excluding hypertension; 45.5 %), hypertension (42.3 %) and dyslipidaemia (21.1 %). Following the index VTE, a large proportion of patients received initial therapy with heparin (73.2 %), almost half received a vitamin K antagonist (48.7 %) and nearly a quarter received a DOAC (24.5 %). Almost a quarter of all presentations were for recurrent VTE, with >80 % of previous episodes having occurred more than 12 months prior to baseline. In conclusion, PREFER in VTE has provided contemporary insights into VTE patients and their real-world management, including their baseline characteristics, risk factors, disease history, symptoms and signs, initial therapy and outcomes.

Keywords

Venous thromboembolism, anticoagulation, registry, direct oral anticoagulants, vitamin K antagonists

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Introduction

Deep-vein thrombosis (DVT) and pulmonary embolism (PE; collectively termed venous thromboembolism [VTE]) are major healthcare burdens in Europe. Indeed, VTE is highly prevalent in Europe and is the third most frequent cardiovascular (CV) disease (1, 2).

Though data from a number of prior VTE registries have been reported (3, 4), a great deal of the available information on the clinical management of VTE is drawn from patients included in clinical trials. Due to complex inclusion and exclusion criteria, these patients are often not representative of the full spectrum of VTE patients. Furthermore, the management of patients with VTE has changed substantially following the introduction of new forms of patient care, such as home treatment, office-based care, and the development of new direct oral anticoagulants (DOACs). The majority of the modifications to management strategies are related to the intrinsic features of the available agents (i.e. larger therapeutic windows removing the necessity for close laboratory monitoring) while others (such as reduced hospital stay) are related to socioeconomic and health economic factors. Considering that neither the degree of implementation nor impact of these amendments appear to have been quantified in a real-world setting, acquisition of contemporary epidemiology data on the management of VTE in Europe is warranted.

Based on this background, we developed an international, non-interventional, prospective disease registry enrolling consecutive VTE patients in both primary and secondary care across different

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countries in Europe (5). The aim was to document the epidemiology, management and outcomes of VTE in a large population that was not limited by stringent clinical trial inclusion/exclusion criteria.

Materials and methods

PREFER in VTE was a prospective, non-interventional, disease registry including patients from seven European countries (Austria, France, Germany, Italy, Spain, Switzerland and the UK). For the present analysis, Germany (D), Austria (A), and Switzerland (CH) were combined into one region, henceforth referred to as "DACH". Prior to study commencement, the registry protocol was approved by the responsible ethics committees for the participating countries and the relevant hospital-based institutional review boards. All patients enrolled in the registry first provided written informed consent. The design and methods of the *PREFER in VTE* registry have previously been described (5), though a brief overview of the design, patient inclusion criteria and data collection methods is provided below.

Patients

Patients eligible for participation in the registry were aged at least 18 years, had symptomatic, objectively confirmed acute VTE (either first-time or recurrent) diagnosed in the last two weeks and were not simultaneously participating in a double blind interventional study. Patients were enrolled between January 2013 and 2014, and those in the present study were followed up through to July 2015.

Data collection

Baseline data were collected in hospitals (on an in- or outpatient basis) or specialised centres at the time of acute VTE diagnosis. The physician was responsible for the input of data pertaining to the period prior to baseline, which was based on a medical history and examination of the patient's medical records. Follow-up data were collected at 1 month (either during a visit or telephone interview) and at 3, 6 and 12 months via a telephone interview with a medically-trained professional. Specially designed patient diaries were kept by each participant to aid their responses to the interview questions and limit recall bias. Furthermore, clear guidelines were adhered to by interviewers in order to standardise the data collection process across the population.

Definitions

Acute VTE was defined as either distal or proximal DVT, PE or both. Cancer was defined as being active if patients were receiving ongoing treatment, whereas a history of cancer was applicable to all patients with a cancer diagnosis. Cardiovascular disease was defined as one of the following: documented coronary artery disease or vascular disease (e.g. peripheral artery disease or aortic plaque), transient ischaemic attack (TIA); stroke; congestive heart failure or left ventricular systolic dysfunction. Hypertension was defined as a blood pressure >130/80 mmHg in patients with diabetes, and a SBP >140 mmHg or diastolic blood pressure (DBP) >90 mmHg in those without diabetes. Liver disease was considered present in patients with chronic hepatic disease or biochemical evidence of significant hepatic derangement. Renal insufficiency was classed into mild (reduction of the glomerular filtration rate [GFR] to 60–89 ml/min with kidney damage), moderate (reduction in GFR to 30–59 ml/min), severe (reduction in GFR to 15–29 ml/min) or end-stage renal disease.

Bleeding risk was assessed using the HAS-BLED score. In this score, one point is awarded for each of the following, up to a maximum of 9 points: hypertension (systolic blood pressure [SBP] >160 mmHg); abnormal renal function (transplantation, chronic dialysis, or serum creatinine ≥200 µmol/L); abnormal liver function (chronic hepatic disease or biochemical evidence of significant hepatic derangement); stroke (history of stroke); bleeding history or predisposition (anaemia); labile INR (time in therapeutic range <60 %); advanced age (>65 years); concomitant drugs/alcohol (one point for use of antiplatelet agents and/or non-steroidal anti-inflammatory drugs, plus one point for excessive alcohol consumption) (6). To assess bleeding outcomes, the International Society of Thrombosis and Haemostasis (ISTH) definitions of major, clinically relevant non-major (CRNM) and nuisance bleeding were used (7).

Statistics

All binary and categorical outcomes were expressed as frequencies (percentages). Means and standard deviations (SD) were given for normally distributed numerical variables and medians were used for non-parametric data. For all data presented here, values are based on the number of patients for whom the particular data point was available and fully completed, with corresponding denominators. Missing/unknown values are excluded for each factor. Statistical comparisons were carried out using Chi-square and t-tests, with a p-value <0.05 considered significant.

Results

In the *PREFER in VTE* registry, 3,464 patients were initially registered. Of these, 3,455 (99.7 %) had evaluable baseline data and were included in the current analysis (Figure 1). In the overall population, the majority were assessed at a hospital (78.6 %) as inpatients or outpatients, with only a small proportion undergoing office-based assessment (21.4 %). The hospital assessment rate was higher for PE than for DVT patients (92.5 % vs 69.1 %; p<0.0001).

Patient characteristics

For all patients included in the analysis, the total mean age was 60.8 years, 53.0 % were male, the mean body mass index (BMI) was 27.9 kg/m^2, 31.5 % had a history of smoking, and 17.3 % a his-

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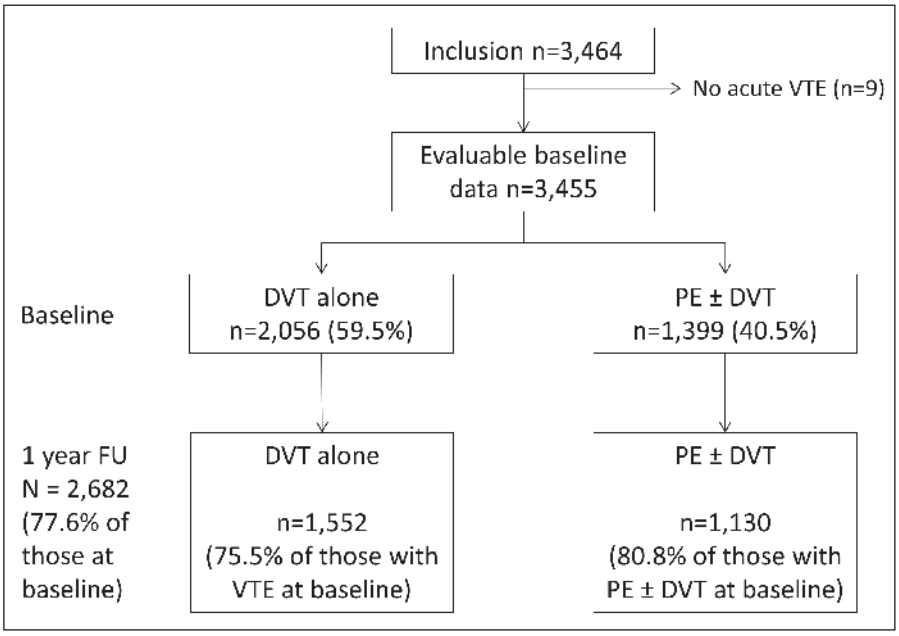

Figure 1: Patient flow. DVT, deep-vein thrombosis; PE, pulmonary embolism.

tory of alcohol use (Table 1). No substantial differences between DVT only and PE ± DVT groups were seen with respect to these demographics. Common comorbidities were CV disease (45.5%), followed by hypertension (42.3%), and dyslipidaemia (21.1%). Each of these comorbidities were more prevalent in patients with PE ± DVT than in those with DVT alone. Before baseline examination, coronary artery disease was present in 3.8% of all patients, myocardial infarction (MI) and atrial fibrillation (AF) had occurred in 3.3% and 3.5%, respectively, 2.3% had suffered a transient ischaemic attack (TIA) and 2.4% had experienced a stroke. Both AF and arterial embolization were more common in the PE patients.

VTE-related history and bleeding risk

A history of varicose veins (20.2%) and cancer (16.0%) were prevalent in the study population, with similar proportions seen in the DVT only and PE ± DV groups (Table 2). Overall, 23.5% of patients had a history of VTE, applying to a significantly higher proportion of the DVT only compared to the PE ± DVT group (25.7% vs 20.2%; p=0.0002) (Table 2). More DVT than PE ± DVT patients had experienced a previous DVT episode (24.5% vs 15.3%; p<0.0001), while more PE ± DVT than DVT patients had experienced a previous PE episode (10.0% vs 5.2%; p<0.0001).

The majority of previous DVTs had occurred >12 months before baseline (82.7%) and had resulted in hospitalisation in 42.2% of cases. Similarly, the majority of previous PE episodes (84.5%) had also occurred >12 months before baseline, though a substantially higher proportion of patients had been hospitalised as a result (84.2%). Of the patients with a previous DVT episode, 12.3% were receiving ongoing VTE treatment at baseline. Of patients with a previous PE episode, 13.1% were receiving ongoing VTE treatment at baseline. This corresponded to only a small proportion of the overall population.

A total of 133 out of 3,451 patients had a history of bleeding events before the baseline visit (Table 3). Of those bleeding events, CRNM bleeding was the most common (51.1%). Seventeen patients (12.8%) had a history of intracerebral bleeding. Based on the HAS-BLED score, bleeding risk was low in the majority of patients (56.7% had a 0 or 1 points assigned) with no major difference between patients experiencing DVT only (59.4%) and PE ± DVT (52.7%) (Figure 2). Patients with 2 or more points on the HAS-BLED score made up >40% of the cohort. Fourteen percent had a HAS-BLED score of 3 or more points (12.9% DVT, 15.5% PE ± DVT), indicating high risk. The frequencies of individual elements of the HAS-BLED score were also fairly similar between groups.

VTE diagnosis (overall and by type of VTE)

Upon diagnosis, the most frequent symptoms and signs in relation to DVT were pain (82.8%) and the swelling of extremities (73.3%) (Table 4). The most frequent symptoms of PE were dyspnea (75.6%) and chest pain (45.5%). Only 2.2% of DVT patients and 6.9% of PE patients were asymptomatic at the time of diagnosis. The median time between onset of symptoms and first medical contact was 19 hours (h). This was longer for the DVT population (48 h) compared to patients suffering from PE (7 h).

In the DVT population, the majority of patients were diagnosed using ultrasound (98.6%), with a median of 4 days between symptom onset and ultrasound diagnosis. CT/MRI was used for 1.9% of diagnoses, and venography for 1.6%.

In the PE population the majority of patients were diagnosed using CT/MRI (81.7%) with a median delay of 2 days between onset of symptoms and CT/MRI diagnosis. A further 17.5% were diagnosed using echocardiography, and less than 10% were diag-

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Table 1: Patient characteristics at baseline.

	Total (N=3,455)	DVT only (n=2,056)	PE ± DVT (n=1,399)	P-value PE ± DVT vs DVT only
Age, years	60.8 ± 16.97	59.8 ± 16.84	62.3 ± 17.05	0.60
Male gender	1832/3455 (53.0)	1088/2056 (52.9)	744/1399 (53.2)	0.88
BMI, kg/m^2	27.9 ± 5.57	27.7 ± 5.28	28.2 ± 5.95	<0.0001
Smoking history	1083/3443 (31.5)	621/2049 (30.3)	462/1394 (33.1)	0.08
Current smoker	469/1080 (43.4)	303/618 (49.0)	166/462 (35.9)	<0.0001
Alcohol use	594/3443 (17.3)	377/2050 (18.4)	217/1393 (15.6)	0.03
Comorbidities				
Hypertension	1461/3451 (42.3)	814/2053 (39.6)	647/1398 (46.3)	0.0001
Vascular disease (PAD, aorticplaque)	211/3451 (6.1)	112/2054 (5.5)	99/1397 (7.1)	0.05
Dyslipidaemia	729/3451 (21.1)	360/2054 (17.5)	369/1397 (26.4)	<0.0001
Diabetes	356/3451 (10.3)	200/2053 (9.7)	156/1398 (11.2)	0.18
Cardiovascular disease(excluding hypertension)	1571/3449 (45.5)	871/2051 (42.5)	700/1398 (50.1)	0.0001
Renal disease	213/3447 (6.2)	123/2049 (6.0)	90/1398 (6.4)	0.60
GFR 60–89 ml/min	67/212 (31.6)	40/123 (32.5)	27/89 (30.3)	
GFR 30–59 ml/min	103/212 (48.6)	61/123 (49.6)	42/89 (47.2)	
GFR 15–29 ml/min	35/212 (16.5)	17/123 (13.8)	18/89 (20.2)	
ESRD (GFR <15 ml/min / permanent renal replacement therapy)	7/212 (3.3)	5/123 (4.1)	2/89 (2.2)	
Liver disease	89/3451 (2.6)	53/2053 (2.6)	36/1398 (2.6)	0.99
History of cardiovascular events				
Myocardial infarction	115/3450 (3.3)	63/2052 (3.1)	52/1398 (3.7)	0.30
Coronary artery disease	131/3451 (3.8)	78/2054 (3.8)	53/1397 (3.8)	0.996
Percutaneous coronary intervention	71/3450 (2.1)	37/2053 (1.8)	34/1397 (2.4)	0.20
Coronary artery bypass graft	28/3450 (0.8)	18/2052 (0.9)	10/1398 (0.7)	0.60
Atrial fibrillation	120/3451 (3.5)	54/2053 (2.6)	66/1398 (4.7)	0.001
Stroke	83/3451 (2.4)	45/2053 (2.2)	38/1398 (2.7)	0.32
Transient ischaemic attacks	78/3451 (2.3)	41/2053 (2.0)	37/1398 (2.6)	0.21
Arterial embolization	29/3452 (0.8)	8/2054 (0.4)	21/1398 (1.5)	0.0004
Cardiac valve replacement	13/3451 (0.4)	8/2054 (0.4)	5/1397 (0.4)	0.88

Continuous data are given as mean ± SD, categorical data are given as n/N (%); BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; GFR, glomerular filtration rate; ESRD, end-stage renal disease.

nosed using perfusion scan, pulmonary angiography, venous study or ventilation scan.

VTE treatment strategy

At baseline, the majority of patients in the overall population (73.2%) were documented as receiving heparin, with a significant number receiving vitamin K antagonists (VKAs, 49.3%) and DOACs (24.9%). In general, a greater proportion of PE ± DVT patients appeared to be taking heparin and VKAs than patients with DVT alone (84.9% and 58.0%, vs 65.2% and 43.3%, respectively), while the opposite was true for DOACs (21.5% vs 27.2%, respectively) (Figure 3A). For the subset of countries in which DOACs were launched at study initiation, the aforementioned trend was also evident (Figure 3B). However, the proportion of patients taking DOACs was generally higher than the overall population for both study groups (42.1% of DVT patients and 35.9% of PE ± DVT patients) and fewer patients were receiving heparin in the

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Table 2: VTE-related risk factors.

	Total (N=3,455)	DVT only (n=2,056)	PE ± DVT (n=1,399)	p-value PE ± DVT vs. DVT only
Previous first episode of VTE	812/3453 (23.5)	529/2055 (25.7)	283/1398 (20.2)	0.0002
Previous episode of DVT	718/3452 (20.8)	504/2055 (24.5)	214/1397 (15.3)	<0.0001
Previous episode of PE	246/3448 (7.1)	106/2053 (5.2)	140/1395 (10.0)	<0.0001
Varicose veins	699/3453 (20.2)	455/2055 (22.1)	244/1398 (17.5)	0.0008
Chronic venous insufficiency	538/3451 (15.6)	340/2053 (16.6)	198/1398 (14.2)	0.06
History of cancer	552/3451 (16.0)	323/2054 (15.7)	229/1397 (16.4)	0.60
Active cancer / ongoing treatment	294/552 (53.3)	174/323 (53.9)	120/229 (52.4)	0.73
Major surgery or trauma within past three months	490/3453 (14.2)	295/2055 (14.4)	195/1398 (13.9)	0.74
Bone fractures/soft tissue trauma	394/3450 (11.4)	255/2053 (12.4)	139/1397 (9.9)	0.03
>5 days in bed	369/3451 (10.7)	204/2054 (9.9)	165/1397 (11.8)	0.08
Chronic respiratory disease	305/3451 (8.8)	155/2053 (7.5)	150/1398 (10.7)	0.001
Arthritis	264/3451 (7.6)	180/2053 (8.8)	84/1398 (6.0)	0.003
Known thrombophilic conditions	226/3455 (6.5)	155/2056 (7.5)	71/1399 (5.1)	0.004
CHF or LVSD	141/3450 (4.1)	58/2052 (2.8)	83/1398 (5.9)	<0.0001
Infectious diseases				0.38
Current	53/3451 (1.5)	27/2053 (1.3)	26/1398 (1.9)	
Recent (<3 months)	65/3451 (1.9)	41/2053 (2.0)	24/1398 (1.7)	
Lower extremity paralysis	39/3450 (1.1)	24/2053 (1.2)	15/1397 (1.1)	0.80
Intravenous drug abuse	11/3451 (0.3)	9/2053 (0.4)	2/1398 (0.1)	0.13
Use of estrogens	231/3452 (6.7)	142/2054 (6.9)	89/1398 (6.4)	0.53
Females only	223/1621 (13.8)	136/967 (14.1)	87/654 (13.3)	0.65
Pregnancy†	29/2697 (1.1)	24/1533 (1.6)	5/1164 (0.4)	0.005
Puerperium	34/3454 (1.0)	23/2056 (1.1)	11/1398 (0.8)	0.33

Continuous data are given as mean ± SD, categorical data are given as n/N (%); †Pregnancy was not evaluated from the beginning but was added to the eCRF at a later stage in the study; BMI, body mass index; DVT, deep vein thrombosis; eCRF, electronic case report form; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; CHF, congestive heart failure; LVSD, left ventricular systolic dysfunction.

DVT group (56.6%). DOACs were more frequently used in younger patients, those without renal impairment, those at low risk of bleeding, and those with fewer comorbidities (such as diabetes).

At 1-month follow-up, the most prevalent treatment in the overall population was VKA (53.4%) followed by DOACs (25.4%) and heparin (18.9%). In general, a greater proportion of patients with DVT only were taking heparin (20.2% vs 16.9%) or DOACs (27.6% vs 22.2%) compared to PE ± DVT patients (Figure 3C). Conversely, use of VKAs was more prevalent in the PE ± DVT group (61.8% vs 47.7%). Again, the same trends were true for countries in which DOACs were launched at study initiation (Figure 3D). However, the proportion of patients treated with DOACs at 1 month was generally higher (42.6% and 35.9% for DVT and PE ± DVT groups, respectively) with lower levels of heparin use (11.6% and 9.6% for DVT and PE ± DVT groups, respectively) than in the corresponding overall groups.

Outcomes 12 months after diagnosis

Twelve months after diagnosis, 230 patients had died (6.7% of all those 3,455 patients evaluable at baseline), with similar rates in each group. The PE recurrence rate was generally low (1.3% overall), the DVT recurrence was higher (3.9%), largely owing to a higher proportion of DVT only patients experiencing a further DVT event (5.6% vs 1.7% for PE ± DVT patients; p<0.0001). Major bleeding occurred in 1.5%, clinically-relevant non-major bleeding (CRNM) in 3.1%, and 4.2% of patients experienced nuisance bleeding. The only difference between groups was found for CRNM bleeding, with significantly more events occurring in the PE ± DVT group (4.2% vs 2.3%; p=0.008). In those having a fol-

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Table 3: History of bleeding events.

	Total (N=3,455)	DVT only (n=2,056)	PE ± DVT (n=1,399)	p-value PE ± DVT vs. DVT only
Total bleeding	133/3451 (3.9)	74/2053 (3.6)	59/1398 (4.2)	0.3562
Major bleeding	36/133 (27.1)	19/74 (25.7)	17/59 (28.8)	
CRNM bleeding	68/133 (51.1)	36/74 (48.6)	32/59 (54.2)	
Nuisance bleeding	29/133 (21.8)	19/74 (25.7)	10/59 (16.9)	
Gastrointestinal*	46/133 (34.6)	28/74 (37.8)	18/59 (30.5)	0.3773
Major bleeding	12/46 (26.1)	6/28 (21.4)	6/18 (33.3)	
CRNM bleeding	23/46 (50.0)	14/28 (50.0)	9/18 (50.0)	
Nuisance bleeding	11/46 (23.9)	8/28 (28.6)	3/18 (16.7)	
Intracerebral	17/133 (12.8)	6/74 (8.1)	11/59 (18.6)	0.0706
Other	72/133 (54.1)	42/74 (56.8)	30/59 (50.8)	0.4968
Major bleeding	16/72 (22.2)	11/42 (26.2)	5/30 (16.7)	
CRNM bleeding	37/72 (51.4)	19/42 (45.2)	18/30 (60.0)	
Nuisance bleeding	19/72 (26.4)	12/42 (28.6)	7/30 (23.3)	

All data are given as n/N (%). Multiple reasons could be given for a bleeding event. CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; *patients may have had major and/or CNRM and/or nuisance bleeding.

low-up at 12 months available, rates of the individual components of the non-fatal ischaemic events (MI, stroke, TIA and arterial embolism) were extremely low (≤0.5%) and similar between groups, with the exception of arterial embolisation, which was more prevalent in DVT only patients (0.5% vs 0.1% for PE ± DVT patients; p=0.045) (Table 5). Hospital admission occurred in 17.5% of patients overall, though greater numbers of PE ± DVT patients were hospitalised (21.5%) compared to DVT only patients (14.5%; p<0.0001).

Discussion

PREFER in VTE was a multinational registry which enrolled over 3,400 patients from seven European countries (5). This multicentre observational database aimed to document VTE clinical management practices and patient outcomes in a wide-ranging sample of sites. These encompassed the spectrum of care from small to specialist primary care practices, small to very large secondary care institutions, and both academic and non-academic sites. *PREFER in VTE* therefore provides a snapshot of the VTE landscape in Western European countries, including the real-world use of new DOACs.

Patient characteristics

Patients in the *PREFER in VTE* registry were generally older (average 61 years) compared to those in recent phase 3 clinical trials (ranging from 55 to 58 years) (8). Conversely, our patients were similar in age or younger than those in inception cohorts (ranging from 62–65 years) (9, 10). About half (53%) of the PREFER in VTE patients were males compared with 53.0–61% in clinical trials (8). However, most VTE inception cohorts show higher percentages of females (9, 10). This is likely to be partly due to recurrences being more common in males; hence registries and clinical trials contain a higher proportion of male subjects, despite first episodes being more common in females. The mean BMI was 27.9 kg/m^2, similar to what has been described in both clinical trials and inception cohorts (8, 10, 11). The frequency of risk factors for VTE (such as cancer and a past history of VTE) were similar to clinical trials. Over 23% of all presentations were for recurrent VTE disease, with the majority of previous episodes (>80%) having occurred more than 12 months previously. This is consistent with the view that VTE should be considered as a chronic disease (12). Around 4% of patients had experienced bleeding prior to developing the index VTE. Given that such patients have not been included in clinical trials, their clinical course is of interest.

Our study may supplement the information already obtained from databases such as the Registro Informatizado de Enfermedad ThromboEmbólica (RIETE) registry, an ongoing, international, prospective registry of acute VTE patients which was started in 2001 (3). In a 2010 analysis including 22,133 patients, the proportion of patients diagnosed with PE was slightly higher compared to the present study (PE: 47% vs 41%), as was the mean age (65 vs 60 years) (13). This may be for a number of reasons related to differences in study design. Although RIETE also excluded individuals participating in clinical trials, analyses tend to pool data from patients who were diagnosed over a wide range of years (i.e. between 2001 and 2008) (13). Conversely, the present analysis is based on those diagnosed between 2013–2014. This means that patient

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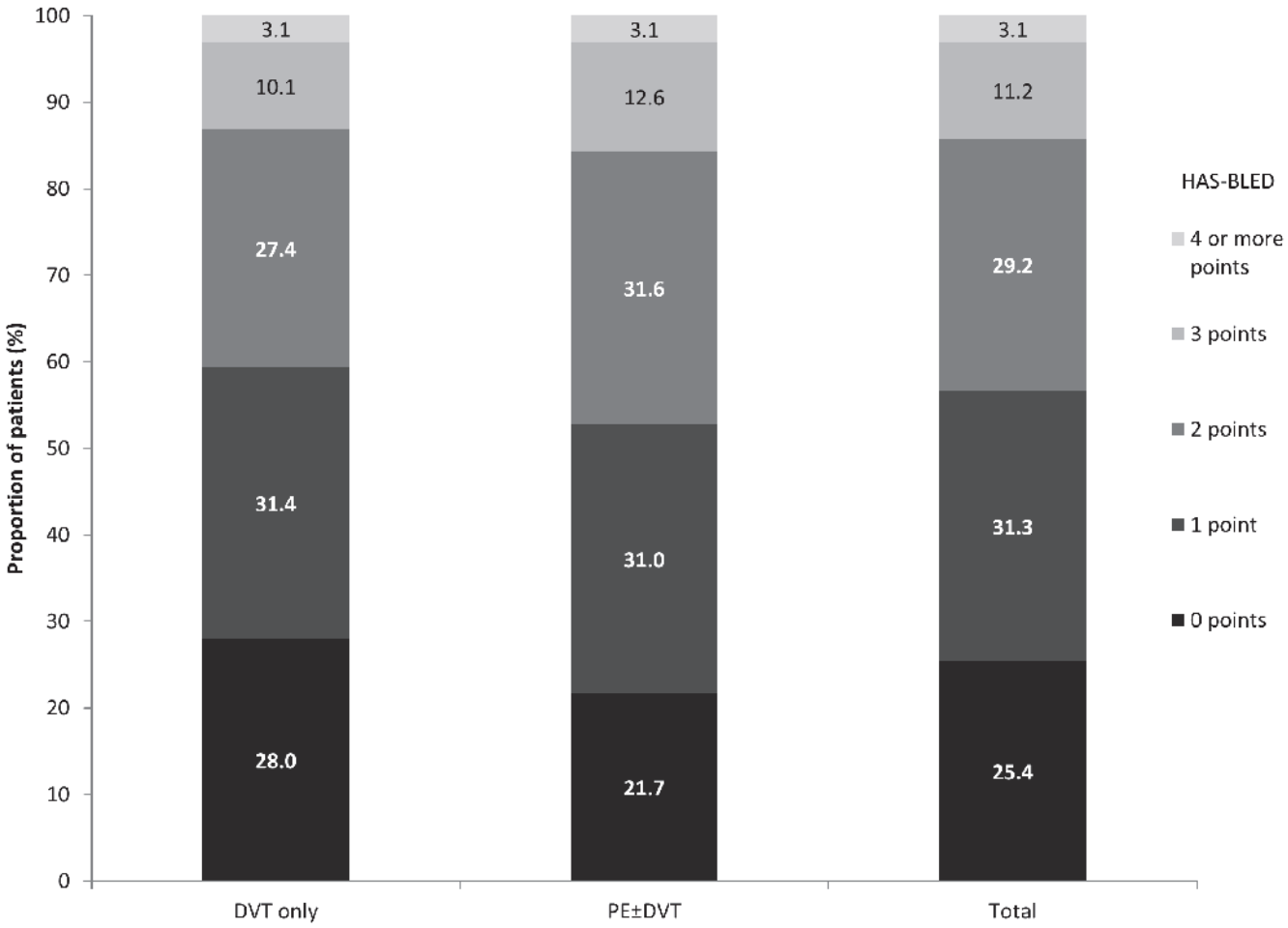

	DVT	PE ± DVT	Total
Hypertension* (%)	1195 (61.0)	893 (65.3)	2088 (62.8)
Age >65 years (%)	849 (41.3)	705 ((50.4)	1554 (45.0)
Medication usage predisposing to bleeding** (%)	206 (10.0)	172 (12.3)	378 (11.0)
Renal disease‡ (%)	123 (6.0)	90 (6.4)	213 (6.2)
Liver disease‡‡ (%)	53 (2.6)	36 (2.6)	89 (2.6)
Stroke history (%)	45 (2.2)	38 (2.7)	83 (2.4)
Alcohol or drug usage history (%)	52 (2.5)	32 (2.3)	84 (2.4)
Labile INR§ (%)	23 (1.1)	14 (1.0)	37 (1.1)
Prior major bleeding or predisposition to bleeding (%)			

Figure 2: Bleeding risk by type of VTE according to overall HAS-BLED score and individual components (n=3,292). DVT, deep-vein thrombosis; PE, pulmonary embolism. In the HAS-BLED score, one point is assigned for each of the criteria in the lower panel (9 points max). *Systolic blood pressure >160 mmHg. **Antiplatelet agents or non-steroidal anti-inflammatory drugs. ‡Dialysis, transplant, Cr >2.26 mg/dl or >200 µmol/l. ‡‡Cirrhosis or bilirubin >2× normal or AST/ALT/AP >3× normal. §time in therapeutic range <60 %.

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numbers are significantly larger in RIETE analyses, though the registry is less geared towards identifying recent shifts in the clinical landscape which may lead to different results. Secondly, the majority of RIETE patients were diagnosed at hospitals in Spain, as well as some in France, Italy, Israel and Brazil. This suggests that sociodemographic biases are likely to be different compared to the present study. Furthermore, hospital diagnosis in the RIETE analysis occurred either following symptomatic emergency room presentation or during hospitalisation for another cause, with both settings indicating more severe disease, high comorbidity levels, and more specialised care. Conversely, the mixture of sites in the *PREFER in VTE* registry allows for the inclusion of patients diagnosed in a range of settings, and therefore a greater diversity of VTE presentation. Interestingly, despite the aforementioned differences, the reported rates of bleeding events prior to baseline were fairly comparable in RIETE and *PREFER in VTE* studies (3.0% vs 3.9%, respectively), suggesting that this may be a consistent factor in VTE patients. Unlike RIETE, our study routinely collected data on factors such as resource utilisation, Quality of Life, and the convenience/burden of anticoagulation treatment, with both general and VTE-specific assessments carried out. Both registries provide valuable and interesting data which may be used to broaden our understanding of the VTE clinical landscape. It will be interesting to compare the results of *PREFER in VTE* with upcoming European registries, such as the Global Anticoagulant Registry in the Field for Venous Thromboembolism (GARFIELD-VTE) (14).

Symptoms and signs of VTE

The presentation of symptoms and signs and the methods used for diagnosis in the present study were consistent with previous data (15, 16). Asymptomatic PE and DVT made up 6.9% and 2.2% of the cohort, respectively. A large difference in the time between clinical onset of symptoms and the time of diagnostic testing was seen between DVT and PE patients, with a shorter duration in the latter population. This is expected, given that PE is the more serious form of VTE presentation. Patients not usually enrolled in clinical trials were included in the registry, including those with a history of bleeding (3.9%), women who are pregnant (1.1%) or in puerperium (1.0%), and intravenous drug users (0.3%).

Comorbidity and bleeding risk

In the present study, we used the HAS-BLED score as the principal measure of bleeding risk. Scores were not seen to vary greatly between DVT and PE patients, with over 40% of the total population having a value consistent with moderate-to-high risk. Comorbidities were not infrequent; renal impairment and liver disease are important factors to be considered in bleeding risk assessment and occurred in 6.2% and 2.6% of patients, respectively. The clinical course of these patients will be of substantial interest, as patients with higher bleeding risk profiles are not typically included in clinical trials.

Although the HAS-BLED score itself was not originally intended for use in assessing VTE patients, having been developed for AF patients (6), each of its individual components is a validated risk factor for bleeding in VTE outlined by the 2016 CHEST Guideline and Expert Panel Report on Antithrombotic Therapy for VTE Disease (17). This is with the exception of hypertension, which was recently identified as a predictor for bleeding in 8,240 VTE patients treated with a factor Xa inhibitor or warfarin (18). Indeed, 2016 ESC Guidelines for the Management of AF state that all of the HAS-BLED components should be used for the identification of modifiable risk factors in anticoagulated patients (19). Furthermore, several groups have presented evidence for the use of the HAS-BLED score in VTE populations (20, 21), with one reporting HAS-BLED to show the highest predictive value compared to other bleeding-risk assessment scores during the first three months of anticoagulation (21). However, it is worth noting that robust validation of HAS-BLED in a large population is currently lacking. The present study provides some new evidence regarding the distribution of bleeding risk between DVT and PE patients as assessed with the HAS-BLED score, which may be informative to a number of researchers in the field. Nonetheless, there are other risk factors for bleeding in VTE patients which are not accounted for by HAS-BLED, such as cancer, thrombocytopenia, diabetes, recent surgery, and frequent falls (17). These should

Table 4: Symptoms and signs at baseline.

DVT (n=2,056)	Patients (%)
Pain	1,703/2,056 (82.8)
Swelling of extremity	1,503/2,056 (73.3)
Calf tenderness	604/2,056 (29.4)
Discoloration	333/2,056 (16.2)
Collateral superficial veins	149/2,056 (7.2)
None (asymptomatic)	45/2,056 (2.2)
Other	120/2,056 (5.8)
PE (n=1,399)	
Dyspnea	1058/1,399 (75.6)
Chest pain	637/1,399 (45.5)
Cough	235/1,399 (16.8)
Tachycardia	233/1,399 (16.7)
Tachypnea	226/1,399 (16.2)
Syncope	114/1,399 (8.1)
Palpitations	110/1,399 (7.9)
Fever	109/1,399 (7.8)
None (asymptomatic)	96/1,399 (6.9)
Hemoptysis	48/1,399 (3.4)
Cyanosis	31/1,399 (2.2)
Cardiogenic Shock	21/1,399 (1.5)
Other	106/1,399 (7.6)

All data are given as n/N (%).

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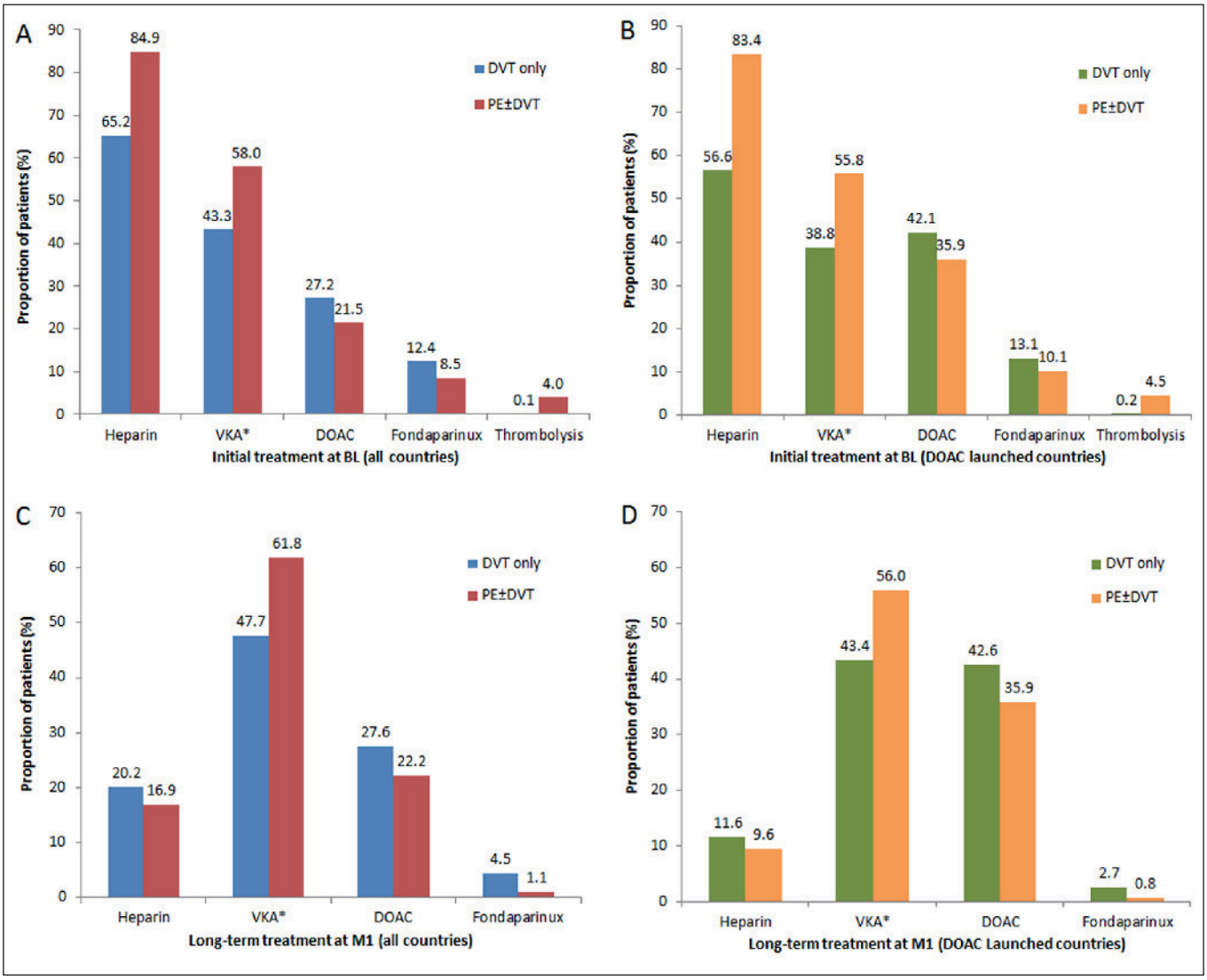

Figure 3: Treatment strategy overall (A and C) and within countries with DOAC launch at study commencement (B and D). DOAC, direct oral anticoagulant; DVT, deep-vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist. Multiple options possible for any one patient. DOAC launched countries are Germany, Austria, Switzerland, France and UK; Non-DOAC countries are Italy and Spain. *Delay in peak effect after initiation (2–5 days).

also be taken into account when determining risk. Several other scores have been suggested for use in the VTE setting, such as VTE-BLEED, which awards points for six clinical variables (active cancer [2 points]; male gender plus uncontrolled arterial hypertension [1 point]; anaemia [1.5 points]; history of bleeding [1.5 points]; age ≥60 years [1.5 points]; and renal dysfunction [1.5 points]) (22). This algorithm, which shares several similarities with the HAS-BLED score, was shown to be strongly predictive for major bleeding in 5,107 VTE patients on stable anticoagulation. Though guidelines currently advocate the presence of 1 (moderate risk) or ≥2 (high risk) out of 11 established risk factors as indicators of a patient's bleeding risk in VTE, further development and validation of existing algorithms such as HAS-BLED and VTE-BLEED may replace such recommendations in future.

VTE treatment

Due to a combination of regulatory statuses, licencing, national and local guidelines and reimbursement at the time of the PREFER in VTE registry, DOAC use varied greatly between countries. Indeed, DOACs were only licensed and reimbursed in DACH, France and the UK. As a result, DOAC data was only fully analysed for these countries. Future analyses of this registry will evaluate the differences in treatment patterns between all included countries.

In the overall registry analysis, almost a quarter of patients were receiving a DOAC at baseline, with little variation between those in the DVT and PE groups (26.8 % vs 21.2 %). During this early phase of therapy, DOACs were more frequently used in younger patients, those without renal impairment, those at low risk of

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Table 5: Overall outcomes of VTE patients 12 months after diagnosis.

	Total (N=3,455)	DVT only (n=2,056)	PE ± DVT (n=1,399)	p-value PE ± DVT vs. DVT only
Total mortality *	230/3,455 (6.7)	128/2,056 (6.2)	102/1,399 (7.3)	0.40
VTE related	11 / 3,455 (0.3)	4 / 2,056 (0.2)	7 / 1,399 (0.5)	0.14
Recurrent VTE **				
Non-fatal PE	30/2,333 (1.3)	12/1,328 (0.9)	18/1,005 (1.8)	0.06
DVT	92/2,341 (3.9)	75/1,337 (5.6)	17/1,337 (1.7)	<0.0001
Bleeding events **				
Major bleeding	35/2,326 (1.5)	18/1,325 (1.4)	17/1,001 (1.7)	0.51
CNRM	72/2,330 (3.1)	30/1,327 (2.3)	42/1,003 (4.2)	0.008
Nuisance	99/2,338 (4.2)	48/1,334 (3.6)	51/1,004 (5.1)	0.08
Non-fatal ischemic events **				
Myocardial infarction	12/2,331 (0.5)	7/1,329 (0.5)	5/1,002 (0.5)	0.93
Stroke	5/2,330 (0.2)	2/1,329 (0.2)	3/1,001 (0.3)	0.44
TIA	9/2,331 (0.4)	5/1,329 (0.4)	4/1,002 (0.4)	0.93
Arterial embolisation	6/2,328 (0.3)	5/1,000 (0.5)	1/1,328 (0.1)	0.045
Hospital admission **	415/2,371 (17.5)	197/1,356 (14.5)	218/1,015 (21.5)	<0.0001

All data are given as n/N (%). Multiple reasons could be given for a bleeding event. CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism. *Proportional to all patients recorded at baseline. **Unless otherwise stated, each denominator refers to the number of patients with complete data for the relevant variable available at 12-month follow-up.

bleeding (according to HAS-BLED), and those with fewer comorbidities (such as diabetes). Concurrently, a similar registry which enrolled AF patients (PREFER in AF) also noted a low use of DOACs in higher-risk patients (23). This may be considered paradoxical, given that the use of DOACs is thought to be more beneficial in higher-risk patients, especially the elderly. A potential explanation for this may be the reluctance of physicians to treat higher-risk patients with the newer agents at the time of the *PREFER in VTE* registry, likely due to a greater degree of familiarity and confidence using VKAs. Other explanations may include a physicians being unwilling to switch patients from their historical agents, or a lack of understanding of the benefits of new agents. The latter may highlight a need for greater education in this area, especially given that results from pivotal phase III studies suggest that DOACs are as effective as VKAs with improved safety profiles (24–28). Indeed, a meta-analysis comparing the four approved DOACs with warfarin found that all of the DOACs had comparable efficacy with a significantly lower bleeding risk (29). These results and current guidelines suggest that there will be a paradigm shift towards higher DOAC use in the future; however, greater education efforts may be needed for many physicians to become comfortable with DOAC use. Data demonstrating the safe use of a predefined reduced DOAC dose for special subsets of patients (such as those with renal impairment or low bodyweight), may instil greater confidence in the medical professionals prescribing them (24).

Outcomes

Overall outcomes at 12 months showed event rates that were consistent with previous studies (2, 10, 24–28, 30, 31). VTE is a condition associated with significant mortality, and the rates seen were much higher than those found in clinical trial populations (24–28). The higher recurrence rates seen in DVT compared with PE patients may be related to treatment patterns, and this will be examined in future analyses. The rates of major, CRNM and nuisance bleeding and ischemic arterial events were as expected.

Limitations

While registries are generally more representative of a real-world population and not subject to the stringent inclusion/exclusion criteria restrictions of randomised control trials, a certain degree of sampling bias is unavoidable. Indeed, the majority of patients in the present study were diagnosed with VTE in the hospital setting, with approximately 40 % presenting with PE. "Although hospital diagnosis was not necessarily on an in-patient basis, these findings suggest that the registry may be more representative of those with more severe VTE, limiting generalisability. Furthermore, for countries where diagnosis and management predominantly occur outside of a hospital setting owing to differences in healthcare system structure, our findings may not necessarily be applicable. In addition, very elderly, frail patients are less likely to be able to give informed consent and patients who died suddenly due to PE were

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What is known about this topic?

- Venous thromboembolism (VTE) represents a significant healthcare burden and is the third most common cardiovascular disease in Europe.
- Much of the data available for the management of VTE are from clinical trials and may therefore not be representative of the full spectrum of VTE patients.

What does this paper add?

- Analysis of a large European cohort of VTE patients, finding that patients at moderate-to-high risk of bleeding are prevalent amongst those who have a VTE event.
- Almost a quarter of all presentations were for recurrent VTE, with >80 % of previous episodes having occurred more than 12 months prior to baseline; hence VTE should be considered a chronic disease.
- Uptake of direct oral anticoagulants in Europe has been encouraging, with use particularly common in certain lower-risk subgroups.

not included. Patients under 18 and those actively participating in a randomised, double blind interventional study were also ineligible for enrolment, potentially excluding some younger, healthier subjects from the analysis. Finally, while one of the strengths of this registry is the large variety of sites, which reflects efforts to find a representative spread and account for national differences, confinement of study centres to Western Europe may limit extrapolation of findings to other geographical areas.

Of further note is that patient histories, as with most studies, were based on a retrospective review of medical records. Therefore, some incomplete or inaccurate data may be expected, reducing robustness. Furthermore, the degree of detail recorded may have been insufficient to reliably determine certain variables (such as type and severity of prior bleeding events), and the interpretation of data by physicians may have introduced further subjective bias or inaccuracy. Thus, the reliability of data on events prior to baseline is not fully assured.

In terms of the data collected by telephone interview, a standardised patient diary was employed to record relevant events and limit recall bias. Notwithstanding this, the patient's subjective evaluation of factors (such as bleeding severity) may have influenced the data collected. However, interviews were carried out by professionals with the appropriate medical knowledge and training to ensure standardised definitions were adhered to and further information could be sought from the patient's medical practitioners. Therefore, data are assumed to be valid.

Future perspectives

Further analyses of the PREFER in VTE registry will provide new insights into the management of VTE patients in Western Europe. Evaluation of the follow-up data of these patients will provide evidence for the changing clinical landscape in VTE treatment. Additionally, patient satisfaction and health-related quality of life will be analysed based on questionnaires completed at baseline and each follow-up.

Conclusions

The results confirm that VTE is a ubiquitous disorder occurring in many settings, and that in a real-world sample that is unrestricted by the confines of clinical trial inclusion/exclusion criteria, risk factors for bleeding are not uncommon. VTE is also a chronic disease, with initial events often taking place more than a year before subsequent episodes. DOAC use in Europe is fairly common, particularly amongst "lower-risk" patients at present; though this should extend into the higher-risk population as guideline recommendations circulate and physician confidence in DOACs grows. Future analyses from the PREFER in VTE registry are therefore likely to identify changing treatment patterns reflecting recent changes to guideline recommendations.

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Author contributions

All authors have contributed to the design of the registry and/or the preparation of the manuscript. EMF was responsible for the analysis of data. ATC and PB drafted the first version of the manuscript and the remaining authors made substantial revisions to the manuscript. 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 organizations.

Conflicts of interest

The members of the Steering Committee received honoraria for their advice in the planning of the Registry. Giancarlo Agnelli (GA), Rupert Bauersachs (RB), Alexander T. Cohen (ATC), Anselm K. Gitt (AKG), Patrick Mismetti (PM), Manuel Monreal (MM), Stefan N. Willich (SNW) and Peter Bramlage (PB) have received research support and/or honoraria for lectures from a number of pharmaceutical companies including Daiichi Sankyo, the sponsor of the registry. Eva-Maria Fronk (EMF), Petra Laeis (PL) and Wolf-Peter Wolf (WPW) are employees of Daiichi Sankyo Europe GmbH. The members of the Steering Committee received honoraria and travel reimbursements from Daiichi Sankyo Europe GmbH for their participation in Steering Committee Meetings.

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