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Full Length Article

Pulmonary embolism in Europe - Burden of illness in relationship to healthcare resource utilization and return to work

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A B S T R A C T

Objectives: Pulmonary embolism (PE) is associated with a substantial economic burden. However evidence from patients in Europe is scarce. The aim of this study was to report the impacts of PE on healthcare resource utilization (HCRU) and return to work using the PREFER in VTE registry.

Methods: The PREFER in VTE registry was a prospective, observational, multicenter study in seven European countries, aiming to provide data concerning treatment patterns, HCRU, mortality, quality of life and work-loss. Patients with a first-time or recurrent PE were included and followed up at 1, 3, 6 and 12 months. Treatment patterns, re-hospitalization rates, length of hospital stays (LOS), and ambulatory/office visits, as well as proportion of patients returning to work, were assessed. Subgroups by country and with/without active cancer were examined separately. Zero-inflated negative binomial and Cox regression were applied to investigate the relationship between baseline characteristics and LOS and return to work, respectively.

Results: Amongst 1399 patients with PE, 53.2% were male and the average age was 62.3 ± 17.1 years old. Overall, patients were treated with combinations of heparin, vitamin K antagonists (VKA) and the non-VKA oral anticoagulants (NOACs) (50.0% treated with the combination of heparin with VKA). Patients with active cancer were primarily treated with heparin (84.9%). NOACs were used more frequently in DACH (Germany, Austria and Switzerland) and France (55.2% and 32.6%) compared to Italy and Spain (4.5% and 6.1%). The VTE-related re-hospitalization rate within 12 months and the average LOS varied substantially between countries, from 26.2% in UK to 12.3% in France, and from 12.9 days in Italy to 3.9 days in France. PE patients were often co-managed by general practitioners in France and DACH (> 84%), and less frequently in other countries (< 47%). The regression results confirmed the country variation of HCRU. Of the employed patients (n = 385), 60% returned to work at 1 month but 27.8% had not after one year. PE patients with DVT were more likely to return to work. Active cancer was a significant predictor for not returning to work, as well as smoking history.

Conclusions: Medical treatment of PE differed between patients with active cancer and patients without active cancer. VTE-related resource utilization differed markedly between countries. While the reported 'not return to work' was high for patients with PE, this may at least in part reflect the presence of co-morbidities such as cancer.

1. Introduction

Pulmonary embolism (PE) due to thrombosis (blood clot) in a lung artery is a relatively common cardiovascular emergency [1,2]. The blood clot commonly travels to the lung arteries from a vein in the leg [1]. PE and deep vein thrombosis (DVT; when the thrombosis occurs in the deep veins, most often in the legs) are two clinical presentations of venous thromboembolism (VTE), with PE being a more severe manifestation. Empirical estimates of PE incidence rates, based on European cohort studies, range from 0.15 per 1000 population per year in Spain [3], 0.189 in Italy [4], 0.342 in the UK [5], 0.50 in Norway [6], 0.51 in Denmark [7], to 0.60 in France [8]. The rates vary partially depending on the setting of the study and the age of the study population. In contrast to population cohort studies, an incidence-based epidemiological model estimated that the PE incidence rate is 0.95 per 1000 population per year and the occurrence of PE events is almost a

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third of a million per year in the European Union (EU) [9].

VTE is associated with increased mortality and morbidity. VTE may occur in isolation but also as a complication of underlying diseases such as cancer, medical conditions, and surgical procedures. Most of the evidence concerning the burden of VTE has been generated in the United States (US); it has been estimated that 547,596 VTE events occur annually among US adults (18 years and above) with 277,549 PE, and 78,511 PE with DVT events [10]. Moreover, a recent review estimated the costs associated with the annual incidence of VTE events at $7–10 billion each year (limited to direct medical cost only) [11]. More specifically, a cost modelling study estimated that US VTE annual costs (including indirect costs) range from $13.5 to 69.3 billion (2011 US Dollars) with $4.5 to 39.3 billion of these costs being preventable if improved prophylaxis measures were put in place [12]. Publications on the burden of VTE in Europe are relatively scarce. A previously published modeling study – based on the data from 6 European countries - estimated that 434,723 PE events and 610,138 post-thrombotic syndrome (PTS) events occurs per annum in the EU. The number of VTE-related deaths was estimated at 543,454 across the EU per annum [9]. The annual VTE costs for the EU, using the same decision tree model as previously reported in the US [12], range from €1.5 to 13.2 billion while preventable costs range from €0.5 to 7.3 billion (2014 Euros) [13]. However, due to the cost assumptions applied in the study, for instance the use of median costs, the total EU cost is likely to be underestimated.

Immediate treatment of PE is highly effective. Initial treatment is aimed at life-saving restoration of blood flow through obstructed pulmonary arteries or at the prevention of potentially fatal recurrences [2]. Traditionally, treatment of PE has consisted of heparin overlapping with dose-adjusted vitamin K antagonists (VKAs). The introduction of the non-VKA oral anticoagulants (NOACs) offers more treatment options.

This study aims to contribute to current scientific knowledge regarding the burden of PE in Europe based on real world data as collected in the PREFER in VTE registry (Prevention of thromboembolic events- European registry in venous thromboembolism). The focus is on resource utilization and return to work of patients with PE. Analyses of mortality and health related quality of life data are reported elsewhere [14]. Specific attention is given to the differences per country, the difference between patients with active cancer and those without, and the association between the burden of the disease and baseline characteristics.

2. Methods

2.1. Setting and study population

The PREFER in VTE registry was a prospective, observational, multicenter study with a follow-up of 12 months. The registry enrolled 3545 consecutive patients from 381 centers (311 active centers i.e., centers that enrolled at least one patient) in seven European countries including Austria, France, Germany, Italy, Spain, Switzerland, and the UK between January 2013 and July 2014. The study protocol has been previously described elsewhere [15]. 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.

Briefly, patients were eligible to be enrolled into the registry if they were at least 18 years old, had a symptomatic, objectively confirmed first time or recurrent acute VTE (the index event) defined as either distal or proximal DVT, PE or both. Eligible patients were recruited within two weeks of the occurrence of the index event. At baseline patients were assessed in terms of their demographics, disease, previous clinical events, risk factors, comorbidities, and presented PE/DVT symptoms, as well as by their previous treatments. At 1, 3, 6 and 12 months follow up, information regarding the occurrence of clinical events, treatments, resource utilization, health related quality of life, and treatment satisfaction during each follow up interval was collected from patients. The current analyses include PE patients only. PE patients were defined as patients that had either a PE with DVT or a PE without DVT. A total of 1399 PE patients were recruited in the PREFER in VTE registry.

2.2. Analyses and statistics

Descriptive statistics of baseline information is provided, including demographics (age, gender, body mass index [BMI], marital status and country), clinical factors (with/without previous VTE event, PE with/without DVT, and (un)provoked[1]), previous clinical events (within 3 years prior to enrollment: myocardial infarction, coronary heart disease, percutaneous coronary intervention, atrial fibrillation, transient ischemic attack, stroke, and bleeding event), risk factors (within past 3 months or ongoing: active cancer, prolonged immobilization[2], > 5 days in bed, varicose veins, and history of major surgery or trauma), comorbidities (hypertension, congestive heart failure, vascular disease, dyslipidemia, diabetes, chronic venous insufficiency, renal disease, liver disease, chronic respiratory disease, arthritis, bone fracture/soft tissue trauma, lower extremity paralysis, alcohol use, smoking history, thrombophilia, and cardiovascular disease), and the presence of PE symptoms. Due to variable patient accessibility to NOACs and different management patterns, subgroups by country and with/without active cancer are examined separately. Active cancer is defined as receiving ongoing treatment for cancer. For regional comparisons, Austria, Switzerland, and Germany were combined into one pre-specified region label (DACH). More detail of clinical variables can be found elsewhere [16].

2.3. Healthcare resource utilization

Treatment medications at baseline, (i.e. the use of heparin, VKA, or NOACs) and the continuing use of the treatment at each follow up were presented. Accumulated VTE-related healthcare resource utilization, in terms of the number of hospitalizations, length of hospital stay (LOS), the use of intensive care unit (ICU), and ambulatory/office visits at 12 months follow up was estimated. Apart for the total sample, descriptive statistics for country and cancer subgroups were also presented. The difference between compared subgroups was evaluated using chi-square test, Kruskal-Wallis equality-of-populations rank test, or Wilcoxon rank-sum test (no normal distribution was assumed), when appropriate.

The dependency between baseline characteristics and LOS was examined using zero-inflated negative binomial regression to address the issue of the outnumbered zero hospitalization day and over-dispersion of the distribution. A zero-inflated negative binomial regression consists of two parts: the first (inflate) part is to predict whether there is an occurrence of LOS (probability of zero or non-zero), whereas the second part is to predict the duration of LOS above zero (non-zero value). The examined baseline characteristics included demographic factors (age, gender, BMI), previous clinical events, clinical factors (except provoked), co-morbidities (except cardiovascular disease), risk factors, and presented PE symptoms. A separate model was fitted to explore the country variation by adding country as an additional co-variate. These analyses were limited to the total sample.

[1] Provoked PE was defined as having prolong immobilization, > 5 days in bed, or history of major surgery or trauma.

[2] Prolonged immobilization was defined as immobilization within the last 3 months or ongoing (e.g., travelling for more than 4 h).

2.4. Return to work

Return to work was expressed as the proportion of patients returning to work during the follow up and when they returned to work. In the study patients were asked whether they returned to work during the follow up, and, if applicable, how soon they returned to work and their productivity level after return in terms of working hours. The analysis was limited to employed patients and an age limit of 65 years at baseline, and a variable indicating how soon patients returning to work was derived. Kaplan-Meier survival analysis was executed to present the rate and time of employed patients returning to work. Furthermore, a multivariate Cox proportion hazards regression was implemented to assess the association between baseline characteristics (the same as those listed above) and returning to work.

2.5. Missing data

As patients were lost to follow up due to death or incomplete information, there was missing data at each cross-sectional measurement. No imputation was conducted for any missing value. However, the difference in terms of baseline characteristics between patients who completed the follow ups and those who did not were tested, using chi square test, Wilcoxon rank sum test, or *t*-test, when appropriate.

3. Results

3.1. Patients' characteristics

Table 1 presents patient characteristics at baseline by countries. Amongst 1399 PE patients at baseline, 25.2% patients were recruited from France, followed by Italy 23.7%, Spain 23.4%, DACH 17.2% and UK 10.5%. Mean age was higher in Italy (67.4 years, SD: 17.1) and lower in DACH (57.8 SD: 16.8), while the percentage of males was higher in the UK (60.5%) and lower in Italy (47.6%). More than 63% of patients had PE with DVT in DACH, whereas the proportion was much lower in the UK (11.6%). Provoked PE was much higher in France (64.0%) than other countries. Additionally, patients in Italy had the highest number of risk factors and highest comorbidity: active cancer rate (12.7%), prolonged immobilization (26.8%: > 5 days in bed (23.2%)), congestive heart failure (13.9%), vascular disease (16.3%), and chronic venous insufficiency (23.5%). Across all countries, the most commonly reported PE symptoms include dyspnea and chest pain, which was greater than 72% and 32%, respectively. The baseline characteristics of the total sample and cancer subgroup can be found elsewhere [14].

3.2. Missing data

Compared to the study sample with 12 months follow up (n = 1130), those with missing data (n = 269) showed a higher prevalence of COPD and active cancer and a lower prevalence of varicose veins. In addition, those with missing data were more likely to smoke. Data were most often incomplete in the UK.

3.3. VTE related healthcare resource utilization

3.3.1. Medication

As shown in Table 2, the proportion of the total sample treated with heparin, VKA, and NOAC at baseline was 85.4%, 57.4% and 21.2%, respectively, and 50.0% of patients were treated with both heparin and VKA. The use of NOAC was highest in DACH (55.2%) followed by France (32.6%), and the UK (10.3%). Spain and Italy had the lowest rates of NOAC use (6.1% and 4.5%, respectively), which was expected because not all NOACs were reimbursed by these healthcare systems at the time of the data collection of the PREFER in VTE registry. Active cancer patients were treated differently compared to those without active cancer (VKA: 13.5% vs. 61.5%, *p*-value < 0.0001; NOACs: 5.9% vs. 22.7%, *p*-value < 0.0001).

Table 2 also presents the proportion of patients who continued to use the baseline treatment at 1-, 3-, 6- and 12-month follow ups. Whereas the majority of patients with active cancer continued to use heparin after baseline (> 70% up to 3 months), the rate of heparin use dropped to 9.0% for patients without active cancer. Moreover, > 77% and 63% of patients without active cancer patients continued to use baseline VKA or NOACs at 6 months, respectively. At 6 months, 22% and 26% of patients who continued to use VKA or NOACs, respectively, had provoked DVT. Of note, in comparison to other countries, Spain and Italy had a higher proportion of patients who continued to use heparin after baseline (23.7% and 15.1% at 3 months, respectively). A similar pattern was observed with patients without active cancer in both countries.

3.3.2. Hospitalization

Table 3 presents the cumulative frequency (percentage) of VTE-related healthcare resource utilization by cancer and country subgroups (the average number of visits and LOS can be found in Appendix Table 1). By the end of the 12-month follow up, 218 out of 1130 patients (19.3%) had been re-hospitalized due to VTE-related events (the reasons for re-hospitalization can be found in Appendix Table 2). If ever re-hospitalized, the average number of repeat hospitalizations was 1.3 with an average LOS of 8.3 days (calculated as the total number of days in hospital divided by the number of patients who were hospitalized). A substantial country variation was observed: the re-hospitalization rate ranged from 26.2% in the UK to 12.3% in France (*p*-value < 0.0001), and LOS ranged from 12.9 days in Italy to 3.9 days in France (*p*-value = 0.0001). Fig. 1 illustrates the accumulated re-hospitalization rate and LOS at each follow up by country. France, DACH and Italy had higher re-hospitalization rates at all time points compared to Spain and the UK; whereas LOS was relatively different between countries with Italy frequently having the longest LOS. Statistically significant differences were also observed between non-cancer and active cancer patients – re-hospitalization rate was 18.4% vs. 32.4% (*p*-value < 0.0001).

The zero-inflated negative binomial regression results (Table 4) suggested that for the first (inflate) part (estimating the probability of having no hospital stay) patients with active cancer, bleeding event, or previous atrial fibrillation had a lower probability of having no hospital day (more likely to be hospitalized). Whereas having PE with DVT or living in France, Italy, or Spain decreased the likelihood of being hospitalized. The second part of the analyses (estimating non-zero values) found that elderly patients and patients with chronic respiratory disease were more likely to have a higher hospital duration, whereas patients living in France, with arthritis, or with previous DVT were likely to have a shorter hospital stay. As there was relatively low variance explained by the models, the results should be interpreted with caution.

3.3.3. Ambulatory/office visit

During the 12-month follow up the majority of the patients visited a physician (88.9%) with an average number of 7.5 visits (Table 3 and Appendix Table 2). Of patients who had at least one physician visit, the recruiting physician and the general practitioner (GP) were most often visited (51.9% and 58.1%, respectively). In comparison, relatively few visits were made to venous institutions or other healthcare professionals. In France and DACH, the proportion of patients who had at least one physician visit visited their GPs in 87.5% and 84.2% of the cases, respectively, suggesting that GP might play a relatively larger role in these countries in co-managing PE patients compared to other countries. Furthermore, active cancer patients did not incur more VTE-related ambulatory/office visits than non-cancer patients. Of note, 6.0% of the total sample did not have any ambulatory/office visits during 12-months follow up and the proportion was even higher in some countries (Italy: 15.1%, the UK: 11.7%).

Table 1
Patients' characteristics at baseline.

Baseline, %	Total n = 1399	France n = 352	DACH n = 241	Italy n = 332	Spain n = 327	UK n = 147	Missing n = 269
Age, years, mean (SD)	62.3 (17.1)*	60.6 (17.2)	57.8 (16.8)	67.4 (17.1)	63.7 (16.8)	59.1 (14.3)	60.8 (18.9)
Under age 65	47.3*	50.3	58.5	33.7	43.7	59.9	46.46
Male	53.2	52.6	56.9	47.6	53.5	60.5	52.8
BMI, mean (SD)	28.2 (6.0)*	27.7 (5.5)	28.7 (6.0)	26.9 (5.1)	28.2 (5.2)	31.1 (8.8)	27.6 (7.2)
Highest graduation	*						
Primary school	32.0	15.6	25.7	50.0	50.5	0	34.2
Secondary school	41.8	44.6	43.6	38.6	30.9	64.0	42.4
Above	21.9	30.1	24.5	9.9	17.1	35.4	19.3
Employment	*						
Employed	29.66	30.7	38.6	18.5	25.0	48.3	29.28
Marital status	*						
Single	14.2	15.6	18.7	13.9	13.8	17.0	17.5
Married/living as married	62.2	61.1	60.6	59.6	65.1	66.7	56.9
Separated/divorced	5.3	6.8	6.2	3.6	2.5	10.2	6.3
Widowed	14.4	11.1	10.0	22.0	17.4	6.1	16.4
Other	1.2	0.6	1.2	1.8	0.6	2.7	1.5
Risk factors (within past 3 months or ongoing)							
Active cancer	8.6*	7.4	2.9	12.7	12.5	2.7	17.1
Prolong immobilization	17.8*	13.4	17.5	26.8	15.0	15.0	21.2
> 5 day in bed	11.8*	7.7	7.1	23.20	10.7	6.1	13.8
Varicose veins	17.5	15.1	16.7	20.5	20.2	11.6	13.0
Major surg. or trauma	14.0	14.5	14.6	16.3	12.2	10.2	13.4
Previous clinical event (within 3 yr. prior to enroll.)							
MI	3.7	3.1	4.6	4.5	2.8	4.1	4.5
CAD	3.8*	2.3	7.5	3.6	2.5	4.8	2.6
PCI	2.4	1.4	4.2	2.7	1.5	3.4	2.2
AF	4.7*	1.7	2.9	10.2	4.6	2.7	5.9
TIA	2.7*	0.3	2.5	7.2	0.9	2.0	4.1
Stroke	2.7	2.3	1.3	3.3	4.3	1.4	3.3
Bleeding event	4.2	4.8	1.3	6.3	3.7	4.1	4.5
Clinical factors							
Previous VTE event	20.2*	25.3	21.2	15.1	19.3	19.7	19.0
With DVT	46.5*	48.9	63.1	56.6	37.3	11.6	44.6
Provoked	27.5*	64.0	25.8	36.5	24.8	21.8	29.0
Comorbidities							
Hypertension	46.3*	38.6	50.8	55.1	48.6	32.0	42.8
CHF	5.9*	1.7	4.2	13.9	4.6	4.1	6.7
Vascular disease	7.1*	3.1	6.3	16.3	4.9	2.0	9.3
Dyslipidemia	26.4*	24.4	26.0	24.7	34.6	17.7	22.0
Diabetes	11.2	9.7	8.8	15.1	10.1	12.2	10.4
Chronic venous insufficiency	14.2*	12.8	6.7	23.5	16.5	3.4	11.2
Renal disease	6.4	5.7	6.3	7.8	6.7	4.8	8.6
Liver disease	2.6	2.0	2.1	4.2	2.1	2.0	3.7
Chronic respiratory disease	10.7*	9.9	4.6	17.8	8.9	10.9	15.6
Arthritis	6.0*	2.6	4.2	5.7	2.8	25.2	5.2
Bone fracture/soft tissue trauma	10.0*	8.2	11.7	13.9	6.4	10.2	11.5
Lower extremity paralysis	1.1*	0.3	0.4	3.0	0.6	0.7	0.7
Alcohol use	15.6*	12.8	16.1	7.6	10.1	51.7	15.7
Smoking history	33.1	29.9	35.3	30.8	33.3	42.2	41.2
Thrombophilia	5.1	4.8	6.2	6.3	4.0	3.4	3.3
Cardiovascular disease	16.8*	10.0	17.9	27.4	14.4	12.9	20.4
PE symptoms present							
Dyspnea	75.6*	72.4	73.4	80.1	72.8	83.0	72.5
Chest pain	45.5*	48.3	43.6	31.9	50.8	61.2	42.4
Cough	16. 8*	13.1	20.3	15.7	14.1	28.6	17.1
Hemoptysis	3.4	4.3	1.7	2.4	4.6	4.1	3.0
Syncope	8.2	9.4	7.1	8.1	8.6	6.1	6.7
Palpitations	7.9*	6.0	6.2	11.1	5.8	12.2	10.8
Fever	7.8	7.4	6.2	9.3	9.0	7.5	6.7
Cyanosis	2.2*	2.0	1.7	4.8	0	2.7	2.6
Tachypnea	16.2	12.5	19.9	18.4	15.0	16.3	17.5
Tachycardia	16.7*	11.1	13.7	27.1	15.3	14.3	18.2
Cardiogenic shock	1.5	2.0	1.7	2.4	0.6	0	2.6
Others	7.6*	9.7	9.5	4.5	1.5	19.7	7.4

* Statistically significant difference between compared countries.

Table 2
Treatment overtime of the total sample and by subgroups.

	Total sample		Without active cancer		With active cancer	
	%	n	%	n	%	n
Heparin (LMWH and UFH)						
BL	85.4	(1191/1395)	85.4	(1090/1276)	84.9	(101/119)
LMWH	*84.0*	*(985/1173)*	*83.8*	*(898/1072)*	*86.1*	*(87/101)*
Continue. 1 m	19.4	(198/1023)	14.3	(134/938)	75.3	(64/85)
LMWH	*97.5*	*(192/197)*	*97.0*	*(129/133)*	*98.4*	*(63/64)*
Continue. 3 m	13.5	(131/967)	9.0	(81/897)	71.4	(50/70)
LMWH	*99.2*	*(127/128)*	*98.7*	*(77/78)*	*100*	*(50/50)*
Continue. 6 m	9.7	(94/968)	6.6	(60/907)	55.7	(34/61)
LMWH	*98.9*	*(92/93)*	*100*	*(59/59)*	*97.1*	*(33/34)*
Continue. 12 m	5.4	(50/918)	3.9	(34/873)	35.6	(16/45)
LMWH	*96*	*(48/50)*	*94.1*	*(32/34)*	*100*	*(16/16)*
VKA						
BL	57.4	(801/1395)	61.5	(785/1276)	13.4	(16/119)
Continue. 1 m	94.9	(695/732)	94.9	(682/719)	100.0	(13/13)
Continue. 3 m	89.7	(618/689)	89.8	(608/677)	83.3	(10/12)
Continue. 6 m	77.8	(534/686)	77.9	(526/675)	72.7	(8/11)
Continue. 12 m	56.8	(356/627)	56.8	(353/621)	50.0	(3/6)
NOACs						
BL	21.2	(296/1394)	22.7	(289/1275)	5.9	(7/119)
Continue. 1 m	91.2	(248/272)	90.9	(241/265)	100.0	(7/7)
Continue. 3 m	82.3	(214/260)	82.6	(209/253)	71.4	(5/7)
Continue. 6 m	63.1	(159/252)	63.0	(155/246)	66.7	(4/6)
Continue. 12 m	45.5	(110/242)	45.6	(108/237)	40.0	(2/5)

	France		DACH		Italy		Spain		UK	
	%	n	%	n	%	n	%	n	%	n
Heparin (LMWH and UFH)										
BL	85.8	(302/352)	80.8	(193/239)	80.1	(265/331)	94.2	(308/327)	84.2	(123/146)
LMWH	*77.7*	*(233/300)*	*73.5*	*(136/185)*	*78.8*	*(204/259)*	*95.1*	*(291/306)*	*98.4*	*(121/123)*
Continue. 1 m	12.7	(35/276)	8.6	(14/163)	20.6	(47/228)	35.0	(91/260)	11.5	(11/96)
LMWH	*97.1*	*(34/35)*	*100*	*(13/13)*	*95.7*	*(45/47)*	*97.8*	*(89/91)*	*100*	*(11/11)*
Continue. 3 m	10.7	(29/271)	4.8	(7/146)	15.1	(31/205)	23.7	(61/257)	3.4	(3/88)
LMWH	*96.6*	*(28/29)*	*100*	*(7/7)*	*100*	*(29/29)*	*100*	*(60/60)*	*100*	*(3/3)*
Continue. 6 m	8.2	(22/268)	2.7	(4/147)	12.0	(25/208)	16.1	(41/254)	2.2	(2/91)
LMWH	*95.5*	*(21/22)*	*100*	*(4/4)*	*100*	*(24/24)*	*100*	*(41/41)*	*100*	*(2/2)*
Continue. 12 m	3.9	(10/257)	2.8	(4/142)	6.2	(12/195)	9.9	(24/242)	0.0	(0/82)
LMWH	*80*	*(8/10)*	*100*	*(4/4)*	*100*	*(12/12)*	*100*	*(24/24)*	–	
VKA										
BL	56.6	(198/350)	37.3	(90/241)	66.8	(221/331)	53.2	(174/327)	80.8	(118/146)
Continue. 1 m	95.1	(176/185)	89.0	(73/82)	96.1	(196/204)	94.8	(146/154)	97.2	(104/107)
Continue. 3 m	91.0	(172/189)	79.2	(57/72)	92.6	(176/190)	89.4	(135/151)	89.7	(78/87)
Continue. 6 m	80.9	(148/183)	69.3	(52/75)	85.4	(164/192)	77.3	(116/150)	62.8	(54/86)
Continue. 12 m	59.3	(105/177)	53.6	(37/69)	65.2	(103/158)	53.4	(78/146)	42.9	(33/77)
NOACs										
BL	32.6	(114/350)	55.2	(132/239)	4.5	(15/332)	6.1	(20/327)	10.3	(15/146)
Continue. 1 m	92.5	(99/107)	88.3	(106/120)	91.7	(11/12)	100.0	(19/19)	92.9	(13/14)
Continue. 3 m	81.0	(85/105)	83.8	(93/111)	76.9	(10/13)	83.3	(15/18)	84.6	(11/13)
Continue. 6 m	57.8	(59/102)	69.8	(74/106)	58.3	(7/12)	55.6	(10/18)	64.3	(9/14)
Continue. 12 m	37.6	(38/101)	51.5	(53/103)	44.4	(4/9)	52.9	(9/17)	50.0	(6/12)

LMWH = low molecular weight heparin; UFH = unfractionated heparin; BL = baseline.

A possibility of selection bias associated with analyzed data should be considered. As shown in the missing data section above, the study sample differed from the non-study sample data (due to lost to follow up). The additional analyses show that the re-hospitalization rate and average LOS of the current follow up were higher in the group of patients who did not participate in the next follow up compared to those who participated in the next follow up.

3.3.4. Return to work

385 patients were employed at baseline and under 65 years old (27.5% of the total sample), with the average age of 46.7 years old. Amongst those, 72.2% returned to work by the end of the follow up (12 months). While no statistical difference in the returning-to-work rate was observed between countries (79.3% in DACH to 62.1% in the UK), the active cancer subgroup (n = 18) had a much lower rate (27.8%) compared to the non-cancer group (74.4%, p-value < 0.0001). Fig. 2 presents the Kaplan-Meier estimate of the returning-to-work rate after the index event in the total study sample. Around day 60 more than half of the study population (50.3%) had returned to work. Furthermore, amongst patients who returned to work, 35.3% (95/269) reported reduced working hours at first return with an average of 23 h of work completed per week for 3.1 weeks. For the current work level,

Table 3
Accumulated VTE-related healthcare resource utilization by each country (frequency).

	Total N = 1130		France N = 316		DACH N = 187		Italy N = 258		Spain N = 266		UK N = 103	
	n	%	n	%	n	%	n	%	n	%	n	%
Re-hospitalization	218	19.3%	39	12.3%	45	24.1%	57	22.1%	50	18.8%	27	26.2%
Ambulatory/office visits												
Physician	1005	88.9%	312	98.7%	184	98.4%	192	74.4%	243	91.4%	74	71.8%
Original site	586	51.9%	207	66.3%	92	50.0%	77	40.1%	160	65.8%	50	67.6%
General practitioners	657	58.1%	273	87.5%	155	84.2%	83	43.2%	111	45.7%	35	47.3%
Cardiologists	209	18.5%	127	40.7%	25	13.6%	27	14.1%	24	9.9%	6	8.1%
Internists	170	15.0%	4	1.3%	39	21.2%	52	27.1%	72	29.6%	3	4.1%
Vascular physicians	177	15.7%	77	24.7%	34	18.5%	39	20.3%	22	9.1%	5	6.8%
Pulmonologists	197	17.4%	73	23.4%	24	13.0%	38	19.8%	51	21.0%	11	14.9%
Other physicians	342	30.3%	161	51.6%	50	27.2%	41	21.4%	80	32.9%	10	13.5%
Venous institutions	24	2.1%	1	0.3%	–		16	6.2%	1	0.4%	6	5.8%
Other healthcare profs.	107	9.5%	40	12.7%	10	5.3%	34	13.2%	11	4.1%	12	11.7%
None	68	6.0%	–	12.3%	1	0.5%	39	15.1%	16	6.0%	12	11.7%

	Without active cancer N = 1056		With active cancer N = 74	
	n	%	n	%
Hospitalization	194	18.4%	24	32.4%
Ambulatory/office visits				
Physician	947	89.7%	58	78.4%
Original site	556	58.7%	30	51.7%
General practitioners	634	66.9%	23	39.7%
Cardiologists	202	21.3%	7	12.1%
Internists	161	17.0%	9	15.5%
Vascular physicians	164	17.3%	13	22.4%
Pulmonologists	183	19.3%	14	24.1%
Other physicians	325	34.3%	17	29.3%
Venous institutions	23	2.2%	1	1.4%
Other healthcare profs.	112	10.6%	5	6.8%
None	59	5.6%	9	12.2%

27.8% (76/273) reported reduced working hours with an average of 27 h worked per week for 4.2 weeks. The average working hours per week at baseline was 37.6. The results are presented per country and cancer subgroups in Table 5.

Of note the discrepancy between the initial number at risk in the Kaplan-Meier estimate and the descriptive number stated above is due to the fact that some patients did not report details regarding days of work missed. Patients with zero days off work would automatically be excluded from the Kaplan-Meier analysis.

The Cox regression results suggested that patients were less likely to return to work when having active cancer and a smoking history. Counter-intuitively, the results also suggested that PE patients with DVT were more likely to return to work (Table 6).

4. Discussion

This study investigated the burden of PE in Europe in terms of VTE-related healthcare resource utilization and return to work, and it demonstrated that a number of factors varied significantly. VTE-related re-hospitalization rate and LOS varied substantially between countries. PE patients were often co-managed by GPs in DACH and France, and less so in other countries. The regression results confirmed the country variation in LOS. The study also showed patients with active cancer were primarily treated with heparin, while patients without active cancer received combinations of heparin, VKA, and NOACs. In terms of return to work, 60% of employed patients returned to work within a month, but 27.8% had still not returned after one year. Active cancer was a significant predictor for not returning to work.

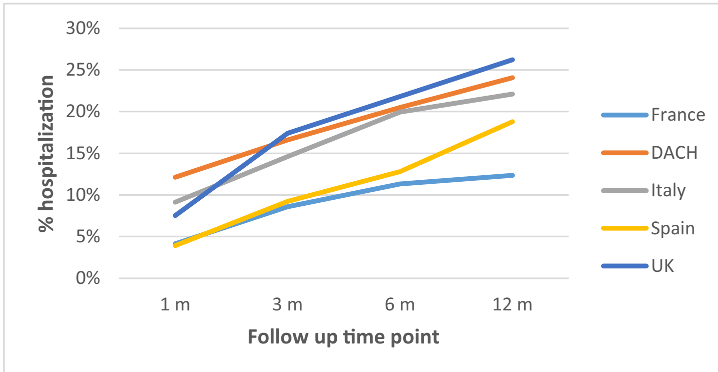
4.1. Treatment pattern

Due to licensing and reimbursement status of NOACs during the PREFER in VTE registry, NOACs use varied substantially across the included countries in our study. This was observed in Spain and Italy where access to NOACS was limited at the moment of the PREFER study conduction. Even amongst the countries where NOACs were fully accessible, NOACs use also varied. For instance, the UK had much lower NOAC use, compared to DACH and France. This could be due to different national or local treatment guidelines and recommendations. It was also observed that the use of heparin after baseline varied greatly among countries. According to treatment guidelines and general practice, heparin is given to patients within the first one to two weeks during the acute phase of the PE event. However, the data shows that more than 23% of the patients in Spain and 15% of the patients in Italy continued to use heparin at 3-month follow up. This pattern was still observed in both countries even after removing active cancer patients from the analysis [data not shown]. Local treatment recommendations and limited access to NOACs explain this observation.

Distinct treatment patterns between PE patients with and without active cancer were observed. The majority of patients with active cancer were initially treated with heparin and continued to use heparin afterwards, whereas patients without active cancer might start with heparin at a similar rate as that of active cancer patients but stop heparin treatment at one month. These observations reflect clinical practice in all countries except for Spain and Italy.

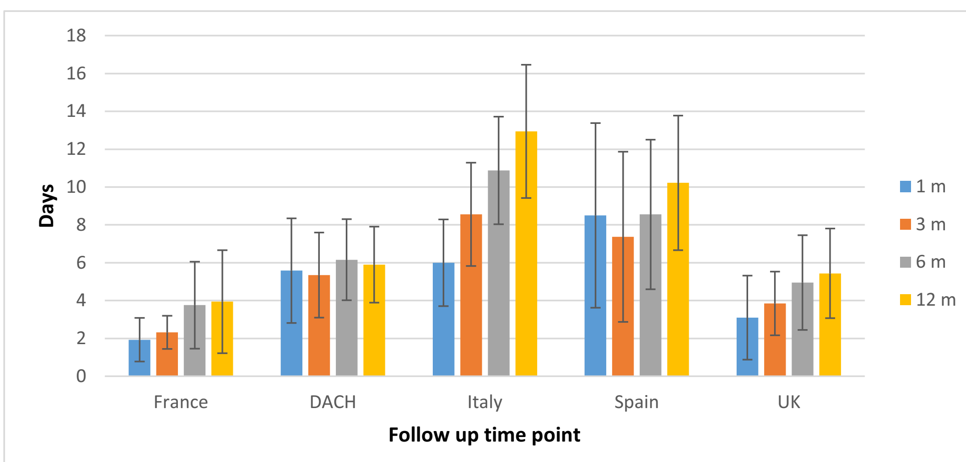
A large proportion of patients who received VKA or NOACs at baseline continued their treatment after 3 months. The standard

a) Percentage of patients being hospitalized



N	1 month	3 month	6 month	12 month
France	338	326	318	316
DACH	223	205	200	187
Italy	307	281	271	258
Spain	307	293	281	266
UK	133	115	110	103

b) Average total hospitalization duration if hospitalized



N	France	DACH	Italy	Spain	UK
1 month	14	24	25	12	10
3 month	28	32	38	27	20
6 month	34	38	50	36	23
12 month	36	41	51	50	25

Fig. 1. Hospitalization by follow-up and country.
a Percentage of patients being hospitalized.
b Average total hospitalization duration if hospitalized.

treatment duration according to treatment guidelines is 3 months, but longer periods of treatment are more often recommended for unprovoked or recurrent PE. Thus, as observed, at 6/12 months, there were 78/57% and 63/45% of patients who continued to use VKA or NOACs, respectively, receiving extended treatment. However, 20% of patients who received extended treatment beyond 3 months had provoked PE which is inconsistent with the current guidelines. In part this discrepancy may be related to the concern about recurrent PE, as PE has a significant mortality rate which may lead to increased concern about stopping anticoagulant therapy. The reason for such practice requires further investigation.

It should be noted that the observed medication use in the current study, to a great extent, reflects the specific case mix of patients included in the PREFER registry, as well as the variation in the disease management across countries.

Table 4
The results of zero-inflated negative binomial regression (length of hospital stay).

	Haz. ratio	Std. err.	P > z	[95% conf. interval]	
Inflate part					
Constant	0.638	0.234	0.006	0.180	1.097
Active cancer	−1.029	0.347	0.003	−1.710	−0.348
Bleeding event	−1.946	0.541	0	−3.006	−0.887
AF	−1.033	0.404	0.011	−1.824	−0.242
PE with DVT	0.488	0.194	0.012	0.109	0.868
France	0.769	0.312	0.014	0.158	1.381
Spain	0.577	0.259	0.026	0.070	1.085
Italy	0.643	0.252	0.011	0.149	1.137
Second part					
Constant	0.773	0.416	0.063	−0.043	1.589
Age	0.019	0.006	0.002	0.007	0.031
Chronic respiratory disease	0.905	0.309	0.003	0.299	1.511
Arthritis	−0.927	0.368	0.012	−1.648	−0.206
Previous VTE event	−0.619	0.248	0.012	−1.105	−0.134
France	−1.370	0.303	0	−1.963	−0.777

Likelihood-ratio test of alpha = 0: chibar2(01) = 1053.61, Pr > =chibar2 = 0.0000.
Vuong test of zero-inflated negative binominal vs. standard negative binomial: z = 3.94, Pr > z = 0.0000.
Goodness of fit: Bayesian information criterion (BIC) 2141.575.

4.2. Re-hospitalization

Similarly, there was a large variation in re-hospitalization rate and LOS between countries. The regression results suggested that in comparison to the UK, France, Italy, and Spain were less likely to have re-hospitalization (Table 4). Patients in France were likely to have a shorter hospital duration, after controlling for case mix across countries (Table 1). However, it should be noted that other factors, such as pressure on cost containment, the healthcare reimbursement system, and the level of adoption for outpatient VTE treatment in clinical practices, might all contribute to the observed variations. A similar country variation in PE mortality rate was observed and a detailed discussion can be found elsewhere [14].

Furthermore, the regression results suggest that patients living in France, those having a previous VTE event and those with a history of arthritis had shorter hospital stays. In France this is likely to be due to the well-established medical infrastructure which allows the out of hospital management of anticoagulation. Patients with previous VTE are likely to be more experienced with anticoagulation and require less education and hence may be discharged early. The reason for the relationship with arthritis and a shorter length of stay and the other finding of PE patients with DVT being more likely to return to work are both currently unknown and may be due to our testing of many variables and the play of chance.

The key cost driver of the economic burden associated with PE is VTE-related LOS [17]. Most recent studies examine the US setting, whereas only a few studies in the literature report LOS of PE patients in Europe. A study in Belgium with 54 patients reported average LOS as 14.6 days (SD 12.4) in 1998 [18]; and a modeling study in France in 1999 reported an average LOS of 4.6–6.4 days [19]. A more recent German study using local insurance data in 2000–2006 reported average all-cause LOS as 21.4–23.6 days [20]. A Spanish study reported the trend in hospital admission of PE over a 10-year period, where LOS was estimated as 12.7 days in 2002 and decreased to 9.99 in 2011 [21]. In addition, an Italian study collecting data from 160 VTE patients reported a LOS of 12.5 days [22]. In comparison to the number observed in the PREFER in VTE registry, the LOS in Italy and Spain is similar to that reported in the literature; whereas the difference between German figures might be explained by the fact that PREFER in VTE registry is restricted to VTE-related re-hospitalizations only. The shorter LOS in France observed in the PREFER in VTE registry is also reported in the

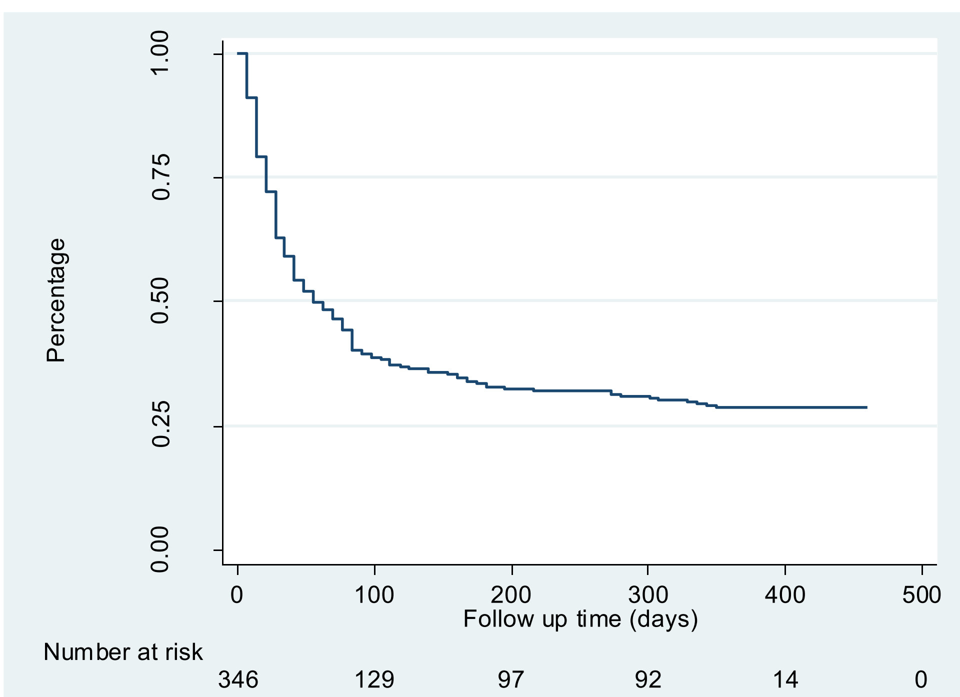


Fig. 2. Kaplan-Meier survival estimate of how soon returning to work after index event.

Table 5
Return to work and working hour/duration, by cancer and country subgroups.

	Total n = 385	Without active cancer n = 367	With active cancer n = 18	France n = 102	DACH n = 87	Italy n = 54	Spain n = 76	UK n = 66
Return to work								
Yes, % (n)	72.2% (278/385)	74.4% (273/367)	27.8% (5/18)	71.6% (73/102)	79.3% (69/87)	74.1% (40/54)	72.4% (55/76)	62.1% (41/66)
First return reduced work								
Yes, % (n)	35.3% (95/269)	35.2% (93/264)	40.0% (2/5)	29.2% (21/72)	34.8% (23/66)	55.6% (20/36)	23.6% (13/55)	45.0% (18/40)
First return reduced work, duration								
n	91	89	2	21	22	17	13	18
Week, mean (SD)	3.12 (3.3)	3.1 (3.3)	2.5 (2.1)	4.8 (4.6)	3.2 (3.8)	3.3 (2.3)	1.6 (0.8)	1.9 (1.3)
First return reduced work, hours								
n	95	93	2	21	23	20	13	18
Hour per week, mean (SD)	22.9 (13.6)	22.9 (13.7)	22.5 (10.6)	29.5 (14.2)	20.7 (11.9)	28.1 (13.2)	10.8 (12.3)	21.1 (9.6)
Current work same as before								
No, % (n)	27.8% (76/273)	27.6% (74/268)	40.0% (2/5)	30.6% (22/72)	22.1% (15/68)	44.7% (17/38)	12.7% (7/55)	37.5% (15/40)
Current work reduced, duration								
n	71	69	2	21	14	14	7	15
week, mean (SD)	4.2 (5.3)	4.2 (5.3)	4.5 (4.9)	4.4 (4.6)	4.6 (4.9)	6.4 (9.0)	2.9 (0.7)	2.1 (1.1)
Current work reduced, hours								
n	76	74	2	22	15	17	7	15
Hour per week, mean (SD)	26.7 (14.5)	26.8 (14.7)	22.5 (10.6)	30.3 (15.8)	25.8 (13.0)	28.2 (14.2)	11.3 (10.5)	27.8 (12.8)

Table 6
Cox regression result.

	Coef.	Std. err.	P > z	[95% conf. interval]	
PE with DVT	1.422	0.187	0.007	1.099	1.841
Active cancer	0.717	0.099	0.017	0.547	0.941
Smoking history	0.186	0.108	0.004	0.059	0.580

Goodness of fit: Bayesian information criterion (BIC) 2525.296

literature.

4.3. Ambulatory/office visit

The European Society of Cardiology recommends that patients on NOACs are followed on a regular basis for on-going review of their treatment, preferably after 1 month initially, and later every 3 months. This study demonstrated that patients were followed-up less regularly than as recommended by these guidelines.

4.4. Return to work

Our study demonstrated 72.2% of PE patients (limited to those employed and under age 65 at baseline) return to work within one year follow-up, with a lower rate for patients with active cancer. This figure is consistent with return to work rate following other major illnesses. The return to work rate within the first year after stroke was reported between 45% to 75%, based on self-reported employment outcomes [23,24]. A more recent Swedish publication, using insurance sickness leave data, reported return to work rate following stroke was 74.7%, at the end of 6-year follow up [25]. Following myocardial infarction (MI), a US study utilizing the data gathered from the VIRGO study reported 84% of patients return to work by 12 months [26].

Publications on long term outcomes of PE/DVT in terms of return to work, or even disability/employment are relatively scarce. A study in Norway investigated work-related disability in patients with VTE compared with those without VTE in a population-based cohort [27]. The study estimated that patients with VTE had between a 17–37% increased risk of work-related disability than those without VTE. The study also indicated that the risk of work-related disability is significantly associated with DVT rather than PE (without DVT) [27]. Our study was not consistent with this finding and showed that PE patients with DVT were more likely to return to work. However, due to the differences in the length of follow up, demographics, clinical characteristics of the study population and research focus, the comparison between these two studies is not straight forward. Our study focused on return to work within 1 year follow-up only, whereas the median duration of follow up was 12.3 years in the Norway study [28].

Of note, the work-loss seen in this study may in part reflect the presence of co-morbidities. This work-loss adds to the indirect costs associated with PE and emphasizes the need for effective primary and secondary preventions and improving the care of PE patients.

4.5. Strengths and limitations

The PREFER in VTE registry provides a rich data source of clinical epidemiology, management and outcomes of VTE patients in a real-world setting. It is one of largest prospective disease registries in VTE and its focus on seven European countries provides a much needed addition to the relatively scarce data on PE from this continent. To the authors' best knowledge, there are no other studies that have explored country variation in VTE-related HCRU and work loss.

A typical limitation of most observational studies is that data may be missing. No corrections such as multiple imputation was made and this needs to be considered in the interpretation of the results. As it is likely that the patients with comorbidities are more often missing, the burden of PE may be underestimated.

5. Conclusion

Pulmonary embolism related healthcare resource utilization and (not) return to work were substantial. 27.8% of employed patients did not return to work after one year. These outcomes differed between countries and between patients with active cancer and those without active cancer. A large amount of country specific information on patient characteristics, re-hospitalization, length of hospital stay, and return to work concerning the excess burden of illness for PE patients was provided to enhance current knowledge on the economic burden for society in Europe.

Appendix A

Table 1
Accumulated VTE-related healthcare resource utilization by each country/cancer subgroups (magnitude)

	Total N = 1130			France N = 316			DACH N = 187			Italy N = 258		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hospitalization												
Number of hospitalization	214	1.3	0.7	38	1.1	0.3	43	1.3	0.9	57	1.5	0.9
Length of hospital stay, total	203	8.3	10.8	36	3.9	8.3	41	5.9	6.6	51	12.9	12.8
Length of hospital stay, per stay	203	6.2	7.3	36	3.2	5.0	41	5.4	6.3	51	8.3	6.3
Days in ICU, total	170	0.3	1.4	30	0.1	0.3	39	0.3	0.8	36	0.1	0.3
Ambulatory/office visits												
Any physician	932	7.6	7.8	293	8.1	5.3	168	11.5	9.2	169	8.3	11.6
Original site	551	2.8	3.8	199	2.4	1.1	84	3.1	3.1	71	5.8	9.0
General practitioners	619	5.2	6.3	258	4.1	3.8	145	8.7	7.5	75	7.4	10.2
Cardiologists	198	1.9	1.8	122	1.8	1.2	23	1.7	1.1	24	2.3	2.9
Internists	164	3.5	4.3	4	9.5	17.0	37	4.4	5.0	48	3.9	3.8
Vascular physicians	169	1.8	1.1	74	1.9	1.2	32	1.7	1.1	36	1.8	1.1
Pulmonologists	188	1.8	1.1	70	1.8	1.2	22	1.9	1.6	36	1.9	0.9
Other physicians	330	2.3	2.2	156	2.2	1.8	49	2.1	1.8	37	2.7	3.3
Venous institutions	23	3.3	3.8	1	1.0	–	–	–	–	16	2.4	2.3
Any other healthcare professionals	104	8.6	37.4	39	6.6	8.8	9	14.3	14.2	26	1.0	1.8

	Spain N = 226			UK N = 103			Without active cancer N = 1056			With active cancer N = 74		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hospitalization												
Number of hospitalization	50	1.2	0.7	26	1.3	0.5	190	1.3	0.7	24	1.3	0.6
Length of hospital stay, total	50	10.2	12.8	25	5.4	6.0	180	7.5	10.0	23	14.5	14.7
Length of hospital stay, per stay	50	8.1	10.2	25	4.1	4.1	180	5.5	5.6	23	11.9	14.1
Days in ICU, total	44	0.7	2.0	21	0.5	2.2	154	0.3	1.3	16	0.9	2.1
Ambulatory/office visits												
Any physician	237	4.7	4.5	65	3.5	3.5	878	7.7	7.9	54	4.8	4.2
Original site	155	2.2	1.2	42	2.0	1.1	522	2.9	3.8	29	2.4	1.4
General practitioners	109	2.3	2.7	32	2.5	2.8	597	5.2	6.3	22	3.4	5.1
Cardiologists	23	1.6	1.0	6	3.7	6.1	191	1.8	1.8	7	2.7	1.9
Internists	72	2.6	2.1	3	1.0	0.0	156	3.5	4.4	8	3.3	2.2
Vascular physicians	22	1.7	0.9	5	0.8	0.4	157	1.8	1.1	12	1.8	0.9
Pulmonologists	50	1.7	1.0	10	1.3	0.5	174	1.8	1.1	14	1.4	0.6
Other physicians	78	2.3	2.6	10	2.2	1.3	313	2.3	2.3	17	1.6	1.0
Venous institutions	1	1.0	–	5	7.2	5.8	22	3.4	3.8	1	1.0	.
Any other healthcare professionals	11	39.3	112.5	19	2.4	2.2	100	8.8	38.1	4	2.3	3.3

Table 2
Reason for re-hospitalization

	%	N
VTE	18.6	(41/221)
Bleeding event	9.3	(20/215)
Other reasons	75.0	(177/236)
Major surgery or trauma	11.4	(24/211)
Stroke	2.8	(6/214)
Arterial embolism	2.4	(5/211)
TIA	1.9	(4/212)
Myocardial infraction	1.4	(3/212)

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