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Full Length Article

Differences in duration of anticoagulation after pulmonary embolism and deep vein thrombosis: Findings from the SWIss Venous ThromboEmbolism Registry (SWIVTER)

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ABSTRACT

Background: Although the two manifestations of venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE), vary considerably, the consensus guidelines recommend similar algorithms for therapeutic anticoagulation in both conditions. Real-world data assessing contemporary management strategies in PE and DVT alone may help tailoring future recommendations towards more individualized patient care.

Methods: In the present analysis, we compared demographics, comorbidities, treatment patterns, and clinical outcomes of PE versus DVT only among 2062 consecutive patients with confirmed VTE enrolled by 11 acute care hospitals between November 2012 and February 2015 in the SWIss Venous ThromboEmbolism Registry (SWIVTER).

Results: Overall, 1246 (60 %) patients were diagnosed with PE. In comparison to DVT alone, PE patients were older (66 vs. 59 years; $p < 0.001$), more frequently had acute and chronic comorbidities, less frequently had prior VTE and hormone replacement, and were less often pregnant. VTE was considered similarly often provoked in patients with PE and DVT alone (33.8 % vs. 33.5 %; $p = 0.88$). Anticoagulation for an indefinite duration was more often prescribed to patients with PE than those with DVT alone (45.7 vs. 19.6 %; $p < 0.001$), and PE diagnosis was the strongest independent predictor of indefinite anticoagulation (OR 3.21; 95 % CI 2.55–4.06; $p < 0.001$). Diagnosis of PE was associated with both increased risk of 90-day mortality (HR 2.31, 95 % CI 1.44–3.71; $p = 0.001$) and major bleeding (HR 3.88, 95 % CI 1.63–9.22; $p = 0.002$).

Conclusions: Our analysis affirms differences in demographics, risk factors, and clinical outcomes of PE versus DVT alone. In routine clinical practice, duration of anticoagulation is being managed differently between the two manifestations of VTE, in contrast to recommendations of the current consensus guidelines.

1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the leading causes of death conjoined by cardiovascular disorders like heart attack and stroke [1,2]. The overall 30-day case fatality of DVT or PE was estimated to be at 1.3 % or 3.9 % and the 90-day case fatality at 3.4 % or 7.0 %, respectively [3]. Most cases of PE occur as complication of

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diagnosed or clinically silent incidental DVT, but a non-negligible portion are reported to be isolated PE without the presence of peripheral or abdominal vein thrombosis at the time of PE diagnosis [4]. The incidence of VTE is associated with a wide range of overlapping risk factors affecting the Virchow's Triad such as age, surgery, or prolonged bed rest, and several distinct risk factors favouring either DVT, like factor V paradox, or PE, such as atrial fibrillation [5–7]. Clinically, the presentation of DVT is often non-specific with major complications being PE and post-thrombotic syndrome, whereas PE presentation can range from totally asymptomatic up to right ventricular dysfunction possibly leading to arrhythmia and sudden death [7,8].

Even though risk factors, disease manifestation, and clinical outcomes of DVT and PE vary considerably, the current consensus guidelines of the American College of Chest Physicians (ACCP) [9,10], American Society of Hematology (ASH) [11,12], and European Society of Cardiology (ESC) [13–15] recommend similar diagnostic and therapeutic algorithms for both VTE manifestations. These recommendations have been summarized in a recent narrative review by N. Wenger et al. [16] The therapeutic algorithm for both VTE manifestations include prognostic risk stratification, anticoagulation, and in selected patients, reperfusion therapy. Thereby, anticoagulation therapy is the main stay of treatment for the majority of VTE patients. Patients, both with PE or proximal DVT, or with isolated distal DVT at high risk of recurrence should be anticoagulated for at least 3 months. Discontinuation of anticoagulation after 3 months should be mandated in patients with VTE secondary to a major transient/reversible risk factor, considering both PE and/or DVT alone. Extended anticoagulation should be based on the estimated individual risk for long-term VTE recurrence tailored against the anticoagulant-related bleeding risk. Anticoagulation extension in DVT patients should be considered in patients with intermediate or high risk of VTE recurrence (e.g. recurrent VTE, or active cancer) and low bleeding risk [16]. Indefinite anticoagulation is recommended in PE patients with recurrent VTE not related to a major reversible or transient risk factor and should be considered for patients with a first episode of PE and no identifiable, a persistent, or a minor transient/reversible risk factor as well as for patients with active cancer [12,14,15]. Although emerging from the same pathophysiological mechanism, PE and DVT differ vastly in their clinical manifestation, severity, and clinical outcome. However, guideline-based recommendations on treatment strategies including duration of anticoagulation are similar for both entities. Better understanding of real-world patterns assessing contemporary management strategies in PE and DVT alone may help to tailor future recommendations towards a more individualized patient care.

In the present analysis from the SWIss Venous ThromboEmbolism Registry, we compared demographic and clinical characteristics, VTE diagnosis and severity, anticoagulation treatment, reperfusion therapy, and 3-month clinical outcomes of patients with PE versus DVT alone.

2. Methods

2.1. Patients

Between November 2012 and February 2015, a total of 2062 patients with VTE from four academic and seven non-academic acute care hospitals in Switzerland were enrolled consecutively in the SWIss Venous ThromboEmbolism Registry (SWIVTER). Inclusion criteria were age $\geq$ 18 years, objectively confirmed VTE (symptomatic or incidentally diagnosed), and available 3-month follow-up data from clinical in- or out-patient visits. No exclusion criteria were applied. Eligible patients were enrolled between the day of diagnosis and 90 days after VTE diagnosis during clinical inpatient or outpatient visits. No recommendations on the VTE management were issued to the treating physicians by SWIVTER. The local ethics committees of all participating hospitals approved the study according to the local regulations.

2.2. Data and definitions

De-identified data on baseline demographics, comorbidities, duration of hospital stay, VTE diagnosis and severity, risk factors for VTE and bleeding, modalities and duration of initial, long-term, and prescription of extended anticoagulation treatment, modalities of reperfusion therapy, and clinical outcomes including mortality, recurrent VTE, and bleeding complications were collected up to 90 days after VTE diagnosis by study physicians or nurses, or by the physicians in charge and reported into a standardized electronic case report form.

According to the presence of PE, the enrolled patients were allocated into two groups: 1. PE $\pm$ DVT and 2. DVT alone. DVT had to be confirmed by compression ultrasound or venography, and PE by contrast-enhanced chest computed tomography, ventilation–perfusion scan, or conventional pulmonary angiography. In patients with confirmed PE, no mandatory search for concomitant DVT was required, and in patient with confirmed DVT without symptoms compatible with concomitant PE, no mandatory search for PE was required. Patients with DVT and concomitant PE were allocated to the PE group.

For the primary analysis, we did not exclude patients with isolated distal DVT of the leg or upper extremity DVT from the DVT alone group because according to the current consensus statement recommendations, patients with isolated distal DVT at high risk of recurrence should be anticoagulated as proximal DVT for at least 3 months and anticoagulation extension should be considered in all DVT patients with intermediate or high risk of VTE recurrence and low bleeding risk, independent of its localization [13,15]. Along the same lines, we did not exclude sub-segmental PE from the PE group for the purpose of our primary analysis. However, to account for differences in the risk of embolization from isolated distal or upper extremity DVT we also conducted the same analysis after exclusion of patients with isolated distal DVT of the leg and upper extremity DVT.

Provoked VTE was defined as thrombosis associated with surgery, estrogen therapy, pregnancy, bed rest for >3 days, or prolonged (>8 h) flight, all within 30 days prior to VTE diagnosis. Major VTE was defined as symptomatic PE or symptomatic proximal DVT of the leg (located in the popliteal, femoral, or iliac veins) or vena cava. Major bleeding was defined according to the ISTH criteria as previously published elsewhere [17,18].

2.3. Statistical analyses

Continuous variables with normal distribution are denoted as mean values with standard deviations (SD), and compared using *t*-test; continuous variables with skewed distribution are displayed as medians with interquartile ranges (IQR), and group comparisons were conducted using the rank-sum test. Discrete variables are depicted as frequencies and percentages, and group comparisons were undertaken by use of the chi-square or Fisher's exact test. The cumulative risks of 90-day clinical outcomes were evaluated with the Kaplan-Meier method, and compared using a log-rank test.

Because patients with PE and DVT alone likely differ in the key baseline characteristics, and to allow for an unbiased comparison between the two groups, a propensity score matching was performed. The propensity scores were estimated using logistic regression with the dependent variable of VTE diagnosis and the independent variables selected from demographics as well as acute and chronic comorbidities of the study cohort. Variables used in the propensity score model included: age, sex, hypertension, prior VTE, cancer, severe renal impairment, congestive heart failure, hormone replacement, diabetes mellitus, chronic lung disease, alcohol or drug abuse, history of stroke or TIA, hepatic impairment, bed rest for >3 days, surgery, acute infection/sepsis, ICU admission, central venous catheter, acute inflammatory/rheumatic disease, bleeding requiring medical attention, ischemic stroke or palsy, pregnancy, acute heart failure, acute respiratory failure, and acute coronary syndrome. Matching was performed using the

'psmatch2' custom command in conjunction with STATA 13.0 software. Study cohorts were matched using nearest neighbor one-to-one matching without replacement.

Univariate logistic regression analysis reporting odds ratios (ORs) with 95 % confidence intervals (95 % CIs) was conducted to determine clinical factors associated with a prescription of anticoagulation for an indefinite duration. Subsequently, multivariate logistic regression analysis was performed to identify independent clinical predictors associated with the two dependent variables described above. Univariate predictors with a $p < 0.05$ were included in the regression model, and a backward elimination method was used to stepwise neglect variables without significance.

Univariate Cox regression analyses reporting hazard ratios (HRs) and 95 % CIs were performed to determine factors associated with 90-day clinical outcomes. In addition, multivariate Cox regression analysis was performed to identify independent predictors for the occurrence of clinical outcomes. Univariate predictors with a $p < 0.05$ were indicated as statically significant and included in the regression model. A backward elimination procedure was used to stepwise discard variables without significance.

All stated *p*-values are two tailed. The reported data were analysed using STATA 13 software (STATACorp LP, College Station, Texas, USA).

3. Results

3.1. Patient characteristics

Overall, 2062 patients with diagnosed VTE were enrolled; the mean age was 63 ± 17 years, 1246 (60.4 %) had PE (8.4 % incidental) with or without DVT and 816 (39.6 %) DVT alone (62.5 % proximal and 29.0 % isolated distal of the leg, and 8.5 % upper extremity). Major VTE was more often presented in patients with PE than those with DVT alone (91.6 vs. 68.8 %; $p < 0.001$). The VTE diagnosis was considered provoked in 33.8 % PE patients and 33.5 % DVT-only patients ($p = 0.88$). In total, 257 (21 %) patients with PE had confirmed concomitant DVT diagnosis.

PE patients were older, more frequently had chronic lung disease, congestive heart failure, history of stroke or TIA, diabetes mellitus, hypertension, alcohol or drug abuse, acute coronary syndrome, acute heart failure, acute respiratory failure, acute infection/sepsis, and bed rest for >3 days, and less often had prior VTE, hormone replacement, and were less often pregnant (Table 1). There was no difference in the rate of bleeding requiring medical attention upon VTE diagnosis between patients with PE and DVT alone. The characteristics of the propensity score adjusted population matched for demographics and the presence of acute and chronic comorbidities are displayed in Table 2.

3.2. Treatment of venous thromboembolism

Overall, inpatient therapy was more frequent in patients with PE compared to those with DVT alone (92 vs. 49 %; $p < 0.001$); the duration of hospital stay was similar in both groups (8 days; $p = 0.99$).

The initial anticoagulation of choice in PE versus DVT-alone patients was LMWH (63.7 vs 54.4 %; $p < 0.001$), UFH (33.9 vs. 14.6 %; $p < 0.001$), or DOAC (4.2 vs. 22.1 %; $p < 0.001$), respectively. Extended anticoagulation therapy was performed with VKA (67.6 vs. 50.9 %; $p < 0.001$), LMWH (21.1 vs. 16.8 %; $p = 0.017$), or DOAC (12.5 vs 31.6 %; $p < 0.001$), respectively.

Anticoagulation for an indefinite duration was more often prescribed in patients with PE than those with DVT alone (45.7 vs. 19.6 %; $p < 0.001$), and the same was true among patients with provoked (41.6 vs. 10.6 %; $p < 0.001$) and unprovoked (47.8 vs. 24.1 %; $p < 0.001$) VTE, among patients with first (40.1 vs. 13.8 %; $p < 0.001$) and recurrent (65.7 vs. 36.4 %; $p < 0.001$) episode of VTE, among patients with major (44.7 vs. 25.5 %; $p < 0.001$) and non-major (56.2 vs. 10.6 %; $p < 0.001$) VTE, and among patients with (58.3 vs. 27.9 %; $p < 0.001$) and without (41.4 vs. 17.3 %; $p < 0.001$) cancer-associated VTE, respectively. In both the univariate and multivariate analysis, the strongest factor associated with a prescription of anticoagulation for an indefinite duration was a diagnosis of PE, followed by prior VTE, cancer, congestive heart failure, major VTE, unprovoked VTE, and increasing age in the multivariate analysis (Table 3). In the propensity score adjusted population matched for demographics and the presence of acute and chronic comorbidities, anticoagulation for an indefinite duration was also more frequently prescribed to patients with PE than those with DVT alone (44.6 vs. 19.6 %; $p < 0.001$), and prior VTE together with a diagnosis of PE remained the two leading predictors associated with a prescription of anticoagulation for an indefinite duration (Table 4).

After exclusion of patients with isolated distal DVT of the leg and upper extremity DVT, anticoagulation for an indefinite duration was more often prescribed in patients with PE than those with proximal DVT of the leg alone (45.7 vs. 24.8 %; $p < 0.001$), and the same was true among patients with provoked (41.6 vs. 14.2 %; $p < 0.001$) and unprovoked (47.8 vs. 29.5 %; $p < 0.001$) VTE, among patients with first (40.1 vs. 16.8 %; $p < 0.001$) and recurrent (65.7 vs. 43.4 %; $p < 0.001$) episode of VTE, and among patients with (58.3 vs. 30.4 %; $p < 0.001$) and without (41.4 vs. 23.2 %; $p < 0.001$) cancer-associated VTE, respectively. In both the univariate and multivariate analysis, the two strongest factors associated with a prescription of anticoagulation for an indefinite duration were prior VTE and a diagnosis of PE (Table 5). In the propensity score adjusted population matched for demographics and the presence of acute and chronic comorbidities, anticoagulation for an indefinite duration was also more frequently prescribed to patients with PE than those with proximal DVT of the leg alone (45.4 vs. 24.8 %; $p < 0.001$), and prior VTE together with a diagnosis of PE remained the two leading predictors associated with a prescription of anticoagulation for an indefinite duration.

Table 1
Demographics, chronic and acute comorbidities in the overall population.

	DVT only N = 816		PE N = 1246		Total N = 2062	
Age, mean years ± SD	59	18	66	16	63	17
Elderly (age ≥65 years), n (%)	355	43.5	766	61.5	1121	54.4
Female sex, n (%)	399	48.9	579	46.5	978	47.4
Chronic comorbidities						
Hypertension, n (%)	250	30.6	534	42.9	784	38.0
Cancer, n (%)	179	21.9	314	25.2	493	23.9
Prior VTE, n (%)	209	25.6	271	21.7	480	23.3
Congestive heart failure, n (%)	81	9.9	244	19.6	325	15.8
Diabetes mellitus, n (%)	75	9.2	208	16.7	283	13.7
Chronic lung disease, n (%)	67	8.2	182	14.6	249	12.1
Severe renal impairment, n (%)	88	10.8	152	12.2	240	11.6
Hormone replacement, n (%)	84	10.3	70	5.6	154	7.5
Alcohol or drug abuse, n (%)	40	4.9	94	7.5	134	6.5
History of stroke or TIA, n (%)	36	4.4	87	7.0	123	6.0
Hepatic impairment, n (%)	19	2.3	40	3.2	59	2.9
Acute comorbidities within 30 days prior to VTE diagnosis						
Bed rest for >3 days, n (%)	117	14.3	260	20.9	377	18.3
Surgery, n (%)	124	15.2	184	14.8	308	14.9
Acute infection/sepsis, n (%)	72	8.8	217	17.4	289	14.0
Acute respiratory failure, n (%)	14	1.7	145	11.6	159	7.7
ICU admission, n (%)	41	5.0	82	6.6	123	6.0
Central venous catheter, n (%)	41	5.0	53	4.3	94	4.6
Acute inflammatory/rheumatic disease, n (%)	35	4.3	45	3.6	80	3.9
Bleeding requiring medical attention, n (%)	30	3.7	48	3.9	78	3.8
Ischemic stroke or palsy, n (%)	22	2.7	46	3.7	68	3.3
Acute heart failure, n (%)	13	1.6	54	4.3	67	3.2
Acute coronary syndrome, n (%)	9	1.1	57	4.6	66	3.2
Pregnancy, n (%)	17	2.1	9	0.7	26	1.3

DVT deep vein thrombosis; ICU intensive care unit; PE pulmonary embolism; SD standard deviation; TIA transient ischemic attack; VTE venous thromboembolism.

Table 2
Demographics, chronic and acute comorbidities in the propensity score matched population.

	DVT only N = 816		PE N = 816		Total N = 1632	
Age, mean years ± SD	59	18	62	17	61	18
Elderly (age ≥ 65 years), n (%)	355	43.5	414	50.7	769	47.1
Female sex, n (%)	399	48.9	377	46.2	776	47.5
Chronic comorbidities						
Hypertension, n (%)	250	30.6	275	33.7	525	32.2
Prior VTE, n (%)	209	25.6	206	25.2	415	25.4
Cancer, n (%)	179	21.9	194	23.8	373	22.9
Severe renal impairment, n (%)	88	10.8	99	12.1	187	11.5
Congestive heart failure, n (%)	81	9.9	70	8.6	151	9.3
Hormone replacement, n (%)	84	10.3	64	7.8	148	9.1
Diabetes mellitus, n (%)	75	9.2	68	8.3	143	8.8
Chronic lung disease, n (%)	67	8.2	59	7.2	126	7.7
Alcohol or drug abuse, n (%)	40	4.9	37	4.5	77	4.7
History of stroke or TIA, n (%)	36	4.4	39	4.8	75	4.6
Hepatic impairment, n (%)	19	2.3	19	2.3	38	2.3
Acute comorbidities within 30 days prior to VTE diagnosis						
Bed rest >3 days, n (%)	117	14.3	125	15.3	242	14.8
Surgery, n (%)	99	12.1	95	11.6	194	11.9
Acute infection/sepsis, n (%)	72	8.8	73	8.9	145	8.9
ICU admission, n (%)	41	5.0	41	5.0	82	5.0
Central venous catheter, n (%)	41	5.0	30	3.7	71	4.4
Acute inflammatory/rheumatic disease, n (%)	35	4.3	33	4.0	68	4.2
Bleeding requiring medical attention, n (%)	30	3.7	34	4.2	64	3.9
Ischemic stroke or palsy, n (%)	22	2.7	18	2.2	40	2.5
Pregnancy, n (%)	17	2.1	9	1.1	26	1.6
Acute heart failure, n (%)	13	1.6	10	1.2	23	1.4
Acute respiratory failure, n (%)	14	1.7	1	0.1	15	0.9
Acute coronary syndrome, n (%)	9	1.1	1	0.1	10	0.6

DVT deep vein thrombosis; ICU intensive care unit; PE pulmonary embolism; SD standard deviation; TIA transient ischemic attack; VTE venous thromboembolism.

Table 3
Predictors associated with prescription of extended anticoagulation for an indefinite duration in the overall population (N = 2062).

Analysis	Univariate analysis			Multivariate analysis		
Factor	OR	95 % CI	*p*	OR	95 % CI	*p*
PE diagnosis	3.45	2.81–4.23	<0.001	3.21	2.55–4.06	<0.001
Prior VTE	2.62	2.13–3.23	<0.001	3.19	2.53–4.02	<0.001
Cancer	1.93	1.58–2.38	<0.001	2.05	1.63–2.57	<0.001
Congestive heart failure	2.02	1.59–2.57	<0.001	1.63	1.25–2.13	<0.001
Major VTE	2.28	1.77–2.93	<0.001	1.50	1.12–2.00	0.006
Unprovoked VTE	1.50	1.23–1.82	<0.001	1.28	1.03–1.59	0.025
Increasing age (per year)	1.02	1.02–1.03	<0.001	1.01	1.01–1.02	<0.001

CI confidence interval; OR odds ratio; PE pulmonary embolism; VTE venous thromboembolism.

In total, reperfusion therapy was used in 152 (12.2 %) patients with PE and 115 (14.1 %; $p = 0.21$) with DVT alone. Thereby, catheter-directed thrombolysis (CDT) was the most frequently performed procedure in both patients with PE and DVT alone (81.6 vs. 89.6 %; $p = 0.07$). Systemic thrombolysis (11.8 vs. 3.5 %; $p = 0.014$), and surgical thrombectomy (8.6 vs. 1.7 %; $p = 0.017$) was performed more frequently, and catheter thrombectomy (4.6 vs. 15.7 %; $p = 0.002$) less frequently in PE patients compared to DVT-only patients.

3.3. Clinical outcomes up to 90 days

The diagnosis of PE was associated with an increased risk of cumulative 90-day all-cause mortality both in the univariate analysis (6.1 vs. 2.7 %; HR 2.31, 95 % CI 1.44–3.71; $p = 0.001$) and in the multivariate analysis (HR 1.90, 95 % CI 1.17–3.07; $p = 0.009$) after adjustment for other independent predictors of death such as cancer, acute coronary syndrome, acute heart failure, and severe renal impairment. The Kaplan-Meier curves for the risk of cumulative 90-day mortality are displayed in Fig. 1. The all-cause death rates at 90 days were higher in both PE patients with (4.6 vs. 0 %; $p = 0.020$) and without (6.3 vs. 3.1 %; $p = 0.003$) reperfusion therapy than in DVT-only patients, respectively. There was a trend towards a lower mortality in patients with versus without reperfusion therapy (2.6 % vs. 5.1 %, $p = 0.08$). However, reperfusion therapy was not a predictor of 90-day mortality.

Furthermore, patients with PE had an increased risk of cumulative 90-day major bleeding both unadjusted (2.8 vs. 0.7 %; HR 3.88, 95 % CI 1.63–9.22; $p = 0.002$) and adjusted (HR 3.66, 95 % CI 1.53–8.75; $p = 0.004$) for other independent factors of major bleeding including central venous catheter and acute coronary syndrome. The Kaplan-Meier curves for the risk of cumulative 90-day major bleeding are displayed in Fig. 2. The rates of major bleeding complications were 4.0 % for initial anticoagulation with UFH and 1.4 % for LMWH, and 2.1 % for extended anticoagulation with VKA, and 0.5 % for DOAC. Major bleeding was more frequent in PE than DVT alone in patients anticoagulated with LMWH (2.0 % vs. 0.5 %; $p = 0.036$) and VKA (2.8 % vs. 0.5 %; $p = 0.007$). The rates of major bleeding complications were similar in patients with versus without reperfusion therapy (3.0 % vs. 1.8 %, $p = 0.21$). In addition, there was a trend towards higher rate of recurrent VTE at 90 days in patients with PE versus DVT alone (3.4 vs 2.1 %; $p = 0.09$).

Table 4
Predictors associated with prescription of extended anticoagulation for an indefinite duration in the propensity score matched population (N = 1632).

Analysis	Univariate analysis			Multivariate analysis		
Factor	OR	95 % CI	*p*	OR	95 % CI	*p*
Prior VTE	3.29	2.61–4.16	<0.001	3.60	2.79–4.65	<0.001
PE diagnosis	3.30	2.65–4.12	<0.001	3.19	2.48–4.10	<0.001
Cancer	1.82	1.43–2.31	<0.001	1.95	1.49–2.55	<0.001
Major VTE	2.63	1.98–3.50	<0.001	1.66	1.20–2.29	0.002
Unprovoked VTE	1.92	1.52–2.43	<0.001	1.49	1.14–1.93	0.003
Increasing age (per year)	1.02	1.02–1.03	<0.001	1.02	1.01–1.02	<0.001

CI confidence interval; OR odds ratio; PE pulmonary embolism; VTE venous thromboembolism.

Table 5
Predictors associated with prescription of extended anticoagulation for an indefinite duration in patients with PE versus proximal DVT of the leg only (N = 1750).

Analysis	Univariate analysis			Multivariate analysis		
Factor	OR	95 % CI	*p*	OR	95 % CI	*p*
Prior VTE	2.66	2.12–3.32	<0.001	3.23	2.53–4.11	<0.001
PE diagnosis	2.55	2.02–3.21	<0.001	2.76	2.15–3.54	<0.001
Cancer	1.84	1.48–2.30	<0.001	1.87	1.47–2.36	<0.001
Congestive heart failure	1.87	1.45–2.40	<0.001	1.59	1.20–2.09	0.001
Unprovoked VTE	1.41	1.14–1.74	0.001	1.23	0.98–1.54	0.069
Increasing age (per year)	1.02	1.01–1.03	<0.001	1.01	1.00–1.02	0.001

CI confidence interval; DVT deep vein thrombosis; OR odds ratio; PE pulmonary embolism; VTE venous thromboembolism.

4. Discussion

In this large multicentre observational study of patients with VTE, PE

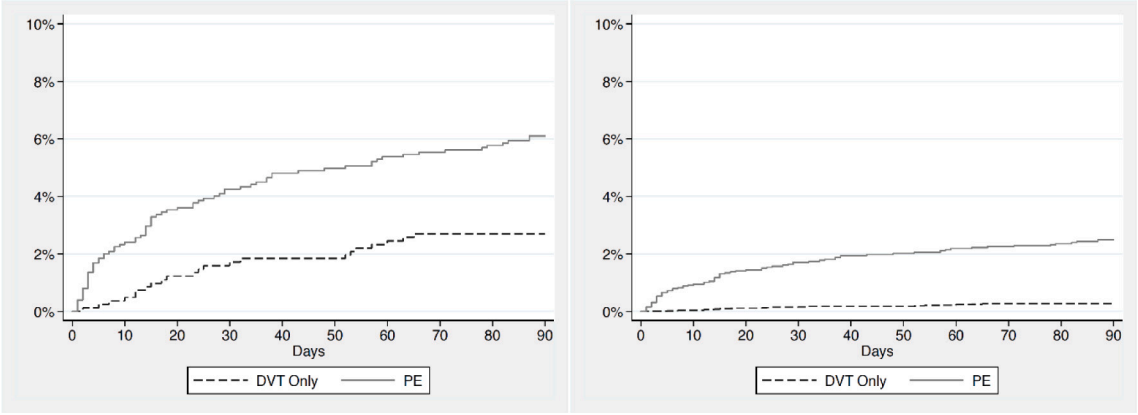

Fig. 1. Kaplan-Meier cumulative 90-day rates of all-cause mortality according to the VTE diagnosis.
VTE venous thromboembolism; *for other independent predictors of all-cause mortality.

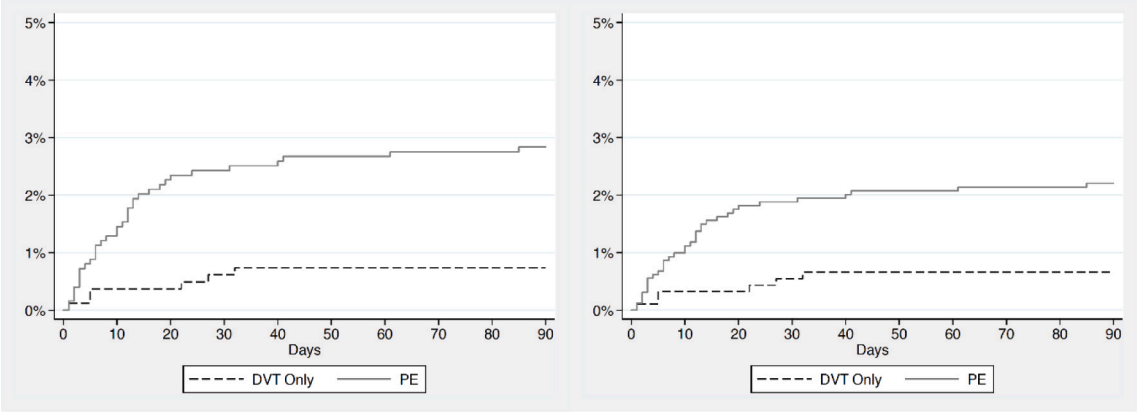

Fig. 2. Kaplan-Meier cumulative 90-day rates of major bleeding according to the VTE diagnosis.
VTE venous thromboembolism; *for other independent predictors of major bleeding.

was more frequently associated with acute and chronic comorbidities than DVT alone. As expected, both mortality and major bleeding rates were higher in PE patients owing to the higher proportion of risk factors for both VTE recurrence and bleeding complications in these patients. Anticoagulation for an indefinite duration was more often prescribed to patients with PE than those with DVT alone in overall cohort and in all of the following patient subgroups: provoked and unprovoked VTE, first and recurrent VTE, cancer and non-cancer related VTE. Moreover, PE diagnosis was the strongest predictor of indefinite anticoagulation in both univariate and multivariate analyses, the latter after adjustment for other guideline-recommended factors of indefinite anticoagulation such as unprovoked, recurrent, or cancer-associated VTE. These results remained similar in the propensity score adjusted population matched for demographics as well as acute and chronic comorbidities.

In a study from the *Registro Informatizado de Enfermedad TromboEmbólica* (RIETE) registry including 7664 patients with DVT-only signs, 3968 patients with PE-only signs, and 2287 with signs of both DVT and PE, Monreal et al. reported that PE patients with or without DVT, compared to those with DVT-only signs, were older, more often females, had more frequently chronic lung disease, chronic heart failure, and renal insufficiency [19]. Although in SWIVTER we did not observe more female or renal insufficient patients in the PE-patients group, we reproduced the other differences in risk factors and chronic comorbidities between the PE and DVT-only groups. In addition, we report further acute and chronic comorbidities that were more frequent in PE patients, such as diabetes mellitus, alcohol or drug abuse, or acute infection/sepsis. Prior VTE, pregnancy, and hormone replacement was more frequent in DVT-only patients. The latter finding contrasts with the study of Palareti et al., where higher numbers of patients using hormonal contraception presenting as isolated PE were reported [4]. However, in that study, the authors differentiated between PE with DVT and PE without DVT, and limited the analysis to hormonal contraception and therefore considered only women younger than 50 years, which may explain these differences.

Similarly to the RIETE and COMMAND VTE registry, we observed a remarkably higher rate of all-cause mortality at 3 months in PE patients compared to those with DVT alone in our study [19,20]. This observation may at least partially be explained by the higher rate of recurrent (and possibly fatal) PE, as well as higher prevalence of acute and chronic comorbidities, the older age, and the more drastic clinical manifestation in patients with PE [20–22]. Previous studies showed that although the incidence rate of VTE recurrence tends to be higher in patients with DVT alone (15–29 per 100,000 person-years) compared to PE patients ± DVT (4–13 per 100,000 person-years), patients with initial PE are 3 times

more likely to develop a recurrent PE and thus are at higher risk of having a more severe recurrent event compared to patients with initial DVT [7,23]. We reported a mortality rate of 6.1 % and 2.7 % for PE and DVT-only patients up to 90 days after diagnosis. Interestingly, RIETE reported a much higher mortality rate of 14 %, 11 %, and 6.3 % in PE + DVT, PE, and DVT-only patients within the same follow-up period, respectively [19]. Heit et al. stated an even higher rate of death after 3 months with 47.9 % for PE and 8.1 % for DVT, respectively [24]. These differences may be explained by the various periods of patient enrolment (Heit: 1966–1990, RIETE: 2001–2006, SWIVTER: 2012–2015) and temporary advances in the general medical management and VTE specific treatments such as introduction of new anticoagulant agents or reperfusion therapies, as well as differences between the healthcare systems. In addition, we reported a significantly higher rate of major bleeding episodes at 3 months in PE than DVT-only patients. In fact, a diagnosis of PE was the second strongest independent predictor of major bleeding. These findings are similar to the reports of the RIETE registry and contrary to findings in the COMMAND VTE registry, which had a longer follow-up period [19,20]. Similarly to higher mortality, the higher frequency of major bleeding in PE patients may be explained by the older age and higher prevalence of comorbidities.

Interestingly, 1 out of 3 PE and 1 out of every 7 DVT events were treated with UFH, at least partially due to the high proportion of patients undergoing reperfusion treatment in our cohort. Indeed, the use of UFH was more than twice higher in patients with vs. without reperfusion therapy.

Anticoagulation for an indefinite duration was strikingly more often prescribed to patients with PE than those with DVT alone, overall in almost half of the PE patients. This is in contrast with recommendations of the current consensus statement guidelines on the management of VTE [10,12–15,25]. These guidelines recommend virtually the same strategy for the duration of therapeutic anticoagulation in both patients with PE and DVT alone. The recommended duration of extended anticoagulation is solely dependent on the presence of provoking factors, VTE episode, and the presence of cancer. In our study, anticoagulation for an indefinite duration was more often prescribed in the presence of PE among each of the following patient subgroups: provoked and unprovoked VTE, first and recurrent VTE, cancer and non-cancer related VTE. Actually, PE diagnosis was the strongest predictor of indefinite anticoagulation in both univariate and multivariate analyses, the latter after adjustment for other guideline-recommended factors of indefinite anticoagulation such as unprovoked, recurrent, or cancer-associated VTE. Moreover, these results remained remarkably similar in the propensity score adjusted population matched for demographics and the presence of acute and chronic comorbidities. In addition, the validity of our findings is further strengthened by the fact that the observed results remained consistent even after exclusion of patients with isolated distal DVT of the leg and upper extremity DVT, thus those who may receive anticoagulation for a limited duration (e.g. 3 months) according to the guidelines, particularly if the risk of recurrence is low [10,12–15,25]. Taken together, our results imply that in a real-world setting, physicians perceive PE as the more severe disease with potentially worse adverse outcomes than DVT alone and ultimately, do not treat PE and DVT alone as the same disease.

According to the guidelines, an individual assessment of the risk-to-benefit ratio based on factors like sex, index event, D-dimer, residual venous obstruction, or age should be performed and re-evaluated over time in patients with extended duration of anticoagulation therapy [26]. In our study, PE patients were older which may partially explain the more frequently prescribed extended therapy in PE patients over DVT-alone patients. On the other hand, bleeding events are more frequent in PE patients, as also observed in our study, thus making the decision on appropriate treatment duration based on the benefit-to-risk evaluation more complex. Despite this, our results reproduce the supposition of Barnes et al. that many practitioners chose to treat PE patients for longer durations than DVT patients, although the guidelines do not recommend different lengths of therapy [27]. Similar findings in a study from Ageno et al. suggest that clinicians frequently make the decision on the duration of anticoagulation based on factors, including the site of VTE (DVT vs. PE), that are in part different from those recommended in the current consensus guidelines [28]. Although the authors did not specify differences between PE and DVT-alone, Yamashita et al. also concluded that the duration of anticoagulation in real-world VTE patients vary widely, often in discordance to the current guideline recommendations [29]. Clinical trials of extended DOAC therapy have shown no significant difference in recurrence or efficacy between DVT-only and PE patients [30–32]. As the consensus guidelines recommend to tailor the extended anticoagulation individually against the bleeding risk, the observed tendency for a continuation of anticoagulation beyond 3 months in PE patients may present a potentially unnecessary hazard. Indeed, neither bleeding upon VTE diagnosis nor major bleeding at 90 days was associated with refraining from prescription of extended anticoagulation for an indefinite duration in our study.

The current analysis has several limitations. First, the populations of PE and DVT alone patients differ substantially. Thereby, direct comparison of management strategies and clinical outcomes need to be adjusted for confounders by the means of multivariate analyses or propensity score matching. In our analysis, we present results for both of these methods to reduce the typical bias derived within the scope of observational studies. Second, we could not fully distinguish between PE patients with and without DVT as DVT was not systematically confirmed or excluded in patients with PE. Third, the treatment patterns have further evolved since the stopping date of our data collection, e.g. the use of DOAC for treatment of both DVT and PE has steadily increased over the last years. Fourth, almost half of the patients with DVT were admitted to hospital for a median duration of eight days, many of those having proximal manifestation of the disease in iliac or common femoral veins or vena cava and undergoing reperfusion therapy. Indeed, the use of reperfusion therapy in both PE and DVT was rather frequent in our cohort. This likely represents contemporary local practice in Switzerland and may not be applicable to most other countries. Fifth, no conclusions regarding long-term differences in clinical outcomes were incorporated as the follow-up data was solely collected up-to 90 days after diagnosis. Sixth, missing of several VTEs during the follow-up period cannot be excluded because standardized diagnostic workup was not mandated, and autopsy was not performed routinely. Finally, the findings may not be generalizable to other regions as SWIVTER was conducted in Switzerland only. However, we believe that this study cohort is representative for comparison of patients with PE and DVT only, due to the multicentre enrolment of consecutive patients with VTE and the systematic collection of detailed data on VTE diagnosis, demographics, acute and chronic comorbidities, VTE treatment, and clinical outcomes.

In conclusion, our data confirm that PE and DVT alone, the two manifestations of VTE, display differences in demographics, risk factors and comorbidities, and early clinical outcomes. In contrast to recommendations of several current consensus guidelines for the management of VTE, duration of therapeutic anticoagulation after PE and DVT alone is not being managed similarly in routine practice. Apparently, physicians have more respect from potential thrombotic adverse clinical outcomes of PE than DVT alone, including the risk of potentially fatal recurrence outweighing the risk of bleeding. These observations may support tailoring future guideline recommendations towards more individualized patient care.

Conflict of interest

JHB reports grants from the Swiss National Science Foundation and the Swiss Heart Foundation, grants, and personal fees from Boehringer Ingelheim, Pfizer, Bayer, and Daiichi-Sankyo, outside the submitted work. RPE reports personal fees from Bayer, Daiichi-Sankyo and Sanofi-Aventis, outside the submitted work. WK reports personal fees and non-financial support from Bayer, Pfizer, Shire/Takeda, Roche, Daiichi-

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