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Impact of Thrombus Sidedness on Presentation and Outcomes of Patients with Proximal Lower Extremity Deep Vein Thrombosis

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Abstract

Background—Small studies have suggested differences in demographics and outcomes between left and right-sided deep vein thrombosis (DVT), and also unilateral vs. bilateral DVT. We investigated the clinical presentation and outcomes of patients with DVT based on thrombus sidedness.

Methods—We used the data from the Registro Informatizado Enfermedad TromboEmbólica (RIETE) database (2001-2016) to identify patients with symptomatic proximal lower-extremity DVT. Main outcomes included cumulative 90-day symptomatic pulmonary embolism (PE) and 1-year mortality.

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Results—Overall, 30,445 patients were included. The majority of DVTs occurred in the left leg (16,421 left-sided, 12,643 right-sided, and 1,390 bilateral; P<0.001 for Chi-squared test comparing all 3 groups). Co-morbidities were relatively similar in those with left-sided and right-sided DVT. Compared with those with left-sided DVT, patients with right-sided DVT had higher relative frequency of PE (26% vs. 23%, P<0.001) and 1-year mortality (odds ratio [OR]: 1.08; 95% confidence interval [CI]: 1.00-1.18). This difference in mortality did not persist after multivariable adjustment (OR: 1.01; 95% CI: 0.93-1.1). Patients with bilateral DVT had a greater burden of co-morbidities such as heart failure, and recent surgery compared with those with unilateral DVT (P<0.001), and higher relative frequency of PE (48%), and 1-year mortality (24.1%). Worse outcomes in patients with bilateral DVT were attenuated but persisted after multivariable adjustment for demographics and risk factors (OR: 1.64; 95% CI: 1.43-1.87). Patients with bilateral DVT had worse outcomes during and after discontinuation of anticoagulation.

Conclusions—There is a left-sided preponderance for proximal lower-extremity DVT. Compared with those with left-sided DVT, patients with right-sided DVT have slightly higher rates of PE. Bilateral DVT is associated with markedly worse short-term and 1-year outcomes.

Keywords

Deep vein thrombosis; right; left; bilateral; pulmonary embolism

Introduction

Thrombosis is the leading global cause of death.[1] Venous thromboembolic disease (VTE) – including deep vein thrombosis (DVT) and its potentially fatal consequence, pulmonary embolism (PE) – is one of the major thrombotic diseases, occurring in almost 1 million new cases annually, and remains a major health problem with high prevalence, incidence, mortality, morbidity, and costs.[2–4]

Much investigation has been done on various aspects of DVT epidemiology, including clinical presentation, natural history, and factors indicating a higher risk for PE, such as thrombus location (proximal or distal),[5] co-morbidities,[5] residual edema,[6] and others. However, besides reports of more frequent occurrence of left-sided DVT in some prior studies,[7–9] the significance of thrombus sidedness (right-sided, left-sided or bilateral DVT) has been largely under-studied. A prior investigation in a small cohort of patients for the first time suggested differences in underlying factors, as well as clinical outcomes of patients with right-sided lower limb DVT compared with those who had left-sided DVT, including increased risk of PE in patients with right-sided DVT.[9] However, results of that small hypothesis-generating study have not yet been tested in a large patient population. Some studies have also suggested stronger association with cancer,[10] and unfavorable outcomes such as subsequent PE or development of cancer in patients with bilateral DVT.[9,11] However, such findings have not yet been verified in a large cohort of patients. We used the Registro Informatizado Enfermedad Tromboembólica (RIETE) registry to validate the presence and significance of differences in presentation and prognosis of left-sided, right-sided, and bilateral DVT in the lower limbs.

Methods

Data Source and Study Protocol

We used the data from RIETE, the largest existing prospective registry of patients with objectively-confirmed VTE. Details about methodology of RIETE have been detailed elsewhere (ClinicalTrials.gov identifier: NCT02832245).[12,13] In brief, RIETE is a multicenter registry of patients with diagnosed acute VTE. Initially started in Spain, RIETE currently has over 205 collaborating centers from 24 countries. The protocol for enrolling patients at RIETE for research purposes has been approved by the ethics committees at the participating sites. The study protocol for this manuscript was drafted by two authors (BB and MM) and reviewed by all coauthors.

Patients

For this study, we included patients with confirmed symptomatic proximal lower-extremity DVT who had available information about thrombus sidedness (i.e. left-sided, right-sided, or bilateral). By design, every effort is made in RIETE to include consecutive patients at participating centers. We excluded patients with isolated distal DVT (below knee), patients with upper extremity DVT, and patients with isolated PE (either diagnosed PE and negative work-up for DVT, or diagnosed PE and no available work-up for DVT). All patients provided verbal and or written informed consent for participation in RIETE, in accordance with local ethics committee requirements.

Outcomes

We reported, according to thrombus sidedness, the relative frequency of DVT, co-morbidities, and major presenting symptoms and signs. The main outcomes of interest were the rate of cumulative 90-day symptomatic PE and its sub-components; concomitant PE at presentation with incident DVT event (i.e. PE diagnosed immediately before, along with, or immediately after DVT diagnosis), recurrent 90-day PE, and all-cause 1-year mortality rates. We also determined the rates of events during the course of anticoagulation, and after discontinuation of anticoagulation.

Statistical Analysis

We reported frequencies for categorical variables and mean with standard deviation for quantitative variables. We compared the frequencies of categorical variables using the Chi-square test across the three groups. We used Kaplan-Meier curves to present 1-year mortality rates in patients with left-sided, right-sided, and bilateral DVT. We used logistic regression analysis to determine whether thrombus sidedness (left-sided vs. right-sided) is a predictor of 1-year mortality, and if so, whether the association persists after adjustment for demographics and clinical risk factors. We used patients with left-sided DVT as the referent. We used a separate multivariable model to determine whether bilateral DVT (vs. unilateral DVT) is a predictor of 1-year mortality. We reported 1-year rates of new diagnosis of cancer based on thrombus sidedness in patients with new DVT and no prior diagnosis of cancer. To report the results during versus after use of anticoagulation, we reported the rate of adverse

events per 100 patient-years. All analyses were performed by SPSS (version 20, SPSS Inc. Chicago, IL).

Results

From January 2001 to September 2016, a total of 42,356 valid patients with DVT were enrolled in RIETE. After exclusions of those with upper extremity DVT or unclear information about thrombus sidedness (5,272), or isolated distal lower extremity DVT (6,639), a total of 30,445 patients entered the study (Figure 1). Among 30,445 with symptomatic proximal lower-extremity DVT, the majority were in the left lower extremity: 16,421 (53.9%) were left-sided, 12,634 (41.5%) were right-sided, and 1,390 (4.6%) were bilateral (P<0.001). Relative frequency of female gender was higher for left-sided DVT (51% vs. 45%, P<0.001). In patients with left-sided DVT versus right-sided DVT, co-morbidities were relatively similar, except for a difference in frequency of underlying malignancy (21% vs. 23%, P<0.001). Patients with bilateral DVT had an overall greater burden of co-morbidities and risk factors, including heart failure, prior myocardial infarction, recent surgery, or immobility compared with those with unilateral DVT. Co-existing cancer was reported in 40% of patients with bilateral DVT. Although use of anticoagulants was similar in the three groups, patients with bilateral DVT more frequently received thrombolytic therapy or inferior vena cava filters (P<0.001 for both comparisons, Table 1).

Rates of PE

Compared with patients with left-sided DVT, those with right-sided DVT more frequently had concomitant PE; while patients with bilateral DVT had markedly higher rates of concomitant PE than the two former groups (P<0.001 for all comparisons, Table 2). Similarly, compared with patients with left-sided DVT, the rate of subsequent 90-day new PE was higher in those with right-sided DVT, although the difference did not reach statistical significance (P=0.07). Patients with bilateral DVT had a significantly higher rate of subsequent new PE compared with those with unilateral DVT (P<0.001). Cumulative rates of 90-day symptomatic PE in those with left-sided, right-sided, and bilateral DVT were 23%, 26%, and 48% (P<0.001 for all comparisons).

Mortality Rates

In patients with left-sided, right-sided, and bilateral DVT, 30-day mortality rates were 2.9% (0.30% fatal PE), 3.3% (0.43% fatal PE), and 9.4% (1.2% fatal PE), respectively. At 90-day follow-up, corresponding rates were 5.8%, 6.3%, and 15.7%. At 1-year follow-up, cumulative mortality rates in the three groups were 10%, 10.7%, and 24.1% (Figure 2). Compared with patients with left-sided DVT, patients with right-sided DVT had a higher 1-year mortality rate (odds ratio [OR]: 1.08; 95% confidence interval [CI]: 1.00-1.18). However, the difference did not persist after multivariable adjustment (OR: 1.01; 95% CI: 0.93-1.1). Patients with bilateral DVT had a markedly higher risk of 1-year mortality (OR: 2.50; 95% CI: 2.19-2.86). By multivariable adjustment the association was partially attenuated but persisted (OR: 1.64; 95% CI: 1.43-1.87).

Major Bleeding

Major bleeding events (requiring transfusion ≥2 units of blood, or being retroperitoneal, spinal or intracranial, or fatal) during the first 30 days occurred in 213 (1.3%), 167 (1.3%), and 38 (2.7%) of patients with left-sided, right-sided, and bilateral DVT, respectively. The rates of non-major bleeding were comparable between the three groups (1.4%, 1.3%, and 1.5%).

Subsequent Cancer

There were no differences in 30-day or 1-year subsequent diagnosis of cancer in those with left-sided, right-sided, and bilateral DVT (Table 2).

Outcomes During versus After Completion of Anticoagulant Therapy

In analyses performed per 100-person years of each subgroup, rates of thrombotic events, hemorrhagic events, and mortality were consistently higher in those with bilateral DVT during the course of anticoagulation, as well as after cessation of anticoagulant therapy (Table 3).

Discussion

Our study showed higher relative frequency of left-sided DVT, but significantly higher rates of cumulative symptomatic 90-day PE and 1-year mortality in those with right-sided DVT compared with left-sided DVT, although the magnitude of the differences were small and the mortality difference was not present in adjusted analyses. More importantly, we demonstrated that bilateral DVT compared with unilateral DVT, frequently occurs in patients with a greater burden of co-morbidities, and is associated with higher rates of PE, short-term mortality and 1-year mortality. The difference in outcomes of those with bilateral versus unilateral DVT attenuated but persisted after multivariable adjustment for demographics, risk factors, and co-morbidities. Results were consistent across multiple analyses in short-term or longer term, and over the course of anticoagulation, as well as after cessation of anticoagulant therapy.

There are multiple potential explanations for the observed worse outcomes with bilateral DVT compared with unilateral DVT. Patients with bilateral DVT had a higher co-morbidity burden and their DVT might function as a risk marker, supported by our multivariable models which demonstrated an attenuation of the strength of effect for bilateral DVT. However, the association persisted and as such, it could be hypothesized that bilateral DVT is indicative of a higher thrombotic burden and thereby greater likelihood of subsequent PE events, which could be fatal. Further, we noted a higher risk of PE-related death in patients with bilateral DVT. Worse outcomes in patients with bilateral DVT have been also suggested in some prior investigations.[14] More frequent use of advanced therapies (such as thrombolytic therapy and also inferior vena cava filter placement) in our study among patients with bilateral DVT, are likely indicative of greater risk in those patients. To our knowledge, no prior comparative effectiveness study has evaluated distinct interventions, including more potent and or more prolonged antithrombotic therapy for bilateral DVT compared with unilateral DVT. Our findings suggest a potential need of such comparisons.

In our study, we did not find a significant difference in the rate of subsequent cancer diagnosis based on thrombus sidedness among those who had unprovoked DVT. Interestingly, a recent investigation also showed that occult cancer diagnosis is infrequent in patients with a first unprovoked DVT.[15] A prior RIETE investigation suggested bilateral DVT as a significant predictor of hidden cancer.[16] However, a subsequent dedicated investigation showed that bilateral DVT was not an independent predictor of ensuing diagnosis of hidden cancer.[17] Finally, we should reflect that in our study coexisting cancer was far more frequent in patients with bilateral DVT compared with unilateral DVT (40% vs. 22%).

Similar to prior investigations, we noted a higher relative frequency for left-sided DVT.[7–9,18–20] Prior studies reporting mortality had small number of patients. In the study by Bikdeli et al there was no significant difference in 3-month mortality rates between those with right-sided and left-sided DVT (P=0.25).[9] The study by Lee et al did not clearly report the in-hospital mortality rates in the two groups.[21] The study by Narayan et al did not report on mortality, either.[22] The higher risk of PE observed in patients with right-sided DVT compared with left-sided DVT is consistent with prior studies in smaller cohorts.[9,21,22] Such differences might be the result of a larger vein diameter, and more vertical orientation of right-sided lower extremity veins towards the inferior vena cava, making it more likely to cause PE.[9] Further, in our study, we noted a higher relative frequency of left-sided DVT in women, and higher frequency of hormonal use or DVT in the setting of pregnancy/puerperal state in patients with left-sided DVT. While the absolute number of patients with such risk factors was small, younger age and lower co-morbidity burden of such patients may also play a role in the difference for outcomes of patients with left-sided and right-sided DVT. Such gender differences may also correlate with distinct anatomical abnormalities,[23] which we were not able to investigate. Based on our results it would be prudent to be more wary of right-sided DVTs. Yet, we must acknowledge that such differences are not clinically large and would likely not require a distinct management strategy based on thrombus sidedness.

To our knowledge, this study is the largest investigation to compare the presentation and outcomes bases on thrombus sidedness. Our study has some limitations. First, RIETE, by design, does not follow central outcome adjudication. However, periodic audits for quality control of the registry have not shown major errors in reported outcomes by site investigators. In addition, certain outcomes are evaluated by the RIETE steering committee. Although we cannot exclude the possibility of some outcomes getting recoded by adjudication, such a limitation is unlikely to fundamentally impact our findings. Second, we did not have available details, beyond thrombus sidedness, to explore anatomical differences in patients with left-sided and right-sided DVT, including further exploration about the May-Thurner syndrome. Third, our findings could not be extrapolated to those with asymptomatic or distal DVTs. RIETE, by design, does not ask the investigators to change the plan of care. For example, universal bilateral screening is not mandatory per RIETE for those with unilateral symptoms. As such, it is possible that for some of the patients with symptomatic right-sided or left-sided DVT, there was coexisting contralateral DVT that was undiagnosed by the site investigators. However, this limitation should have biased the results for comparison of outcomes between unilateral and bilateral DVT towards the null. Yet, we observed marked differences in outcomes. Our observed differences in outcomes of patients

with unilateral versus bilateral DVT might, in fact, underestimate the true differences. Finally, minimum required outcomes collection for RIETE extends to 3 months. Therefore, for 1-year analyses, inevitably, there were some dropouts. The consistent signal that we observed in various time intervals, however, confirms the robustness of our findings.

In conclusion, our study of a large cohort of patients showed preponderance of left-sided DVT, worse outcomes with right-sided DVT that attenuated in multivariable models, and also marked differences in co-morbidity burden and outcomes of patients with bilateral DVT versus unilateral DVT. Further studies are required to determine whether a specific management strategy could improve the outcomes for patients with bilateral DVT.

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Disclosures

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APPENDIX

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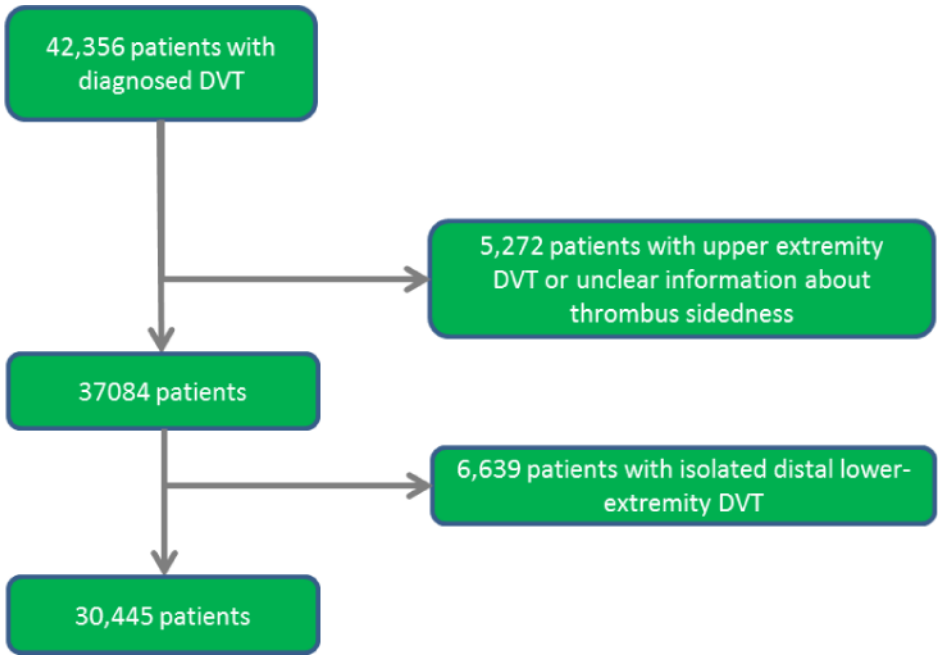

Figure 1.
Study Cohort Selection

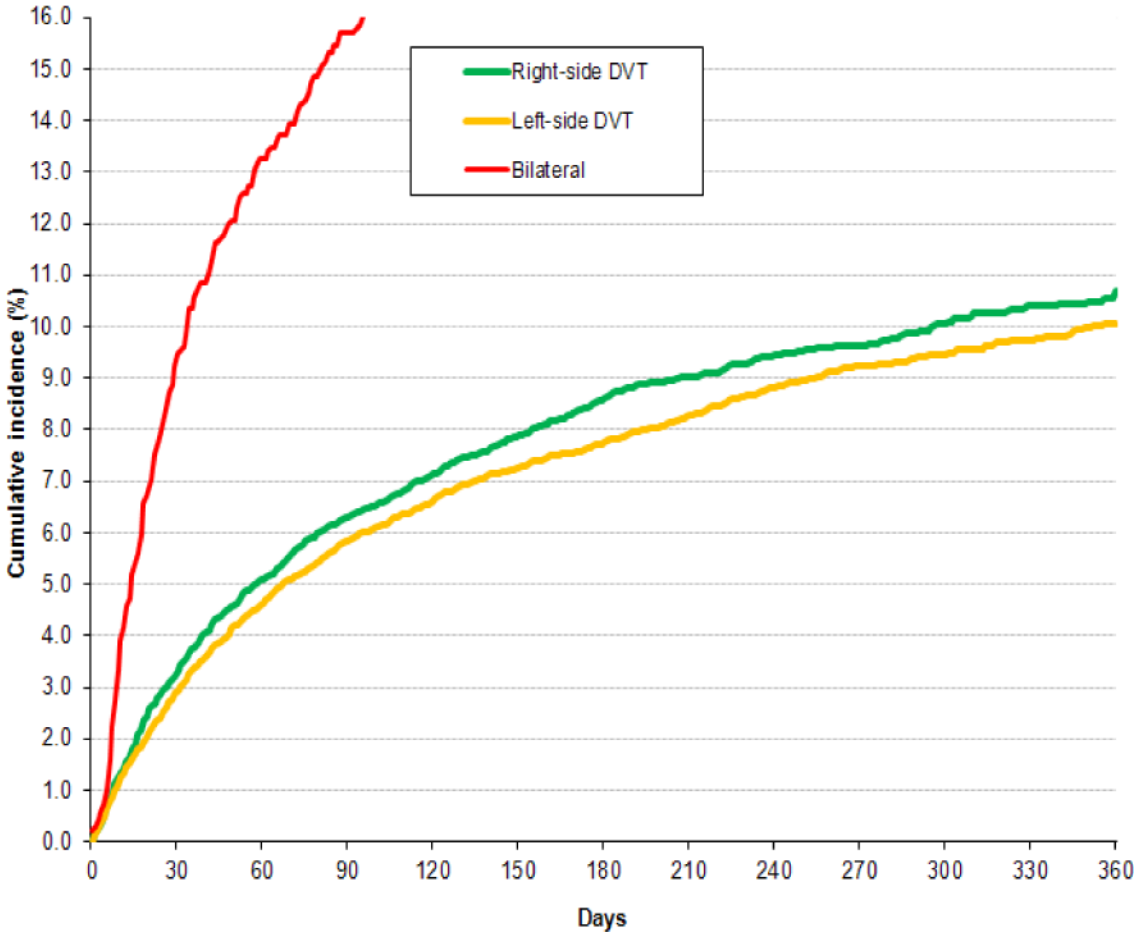

Figure 2.
Cumulative mortality rate within the first 12 months.

Table 1

Basic Characteristics of Patients (N=30,445)

	Left-sided DVT	Right-sided DVT	Bilateral DVT
Patients (%)	16,421	12,634	1,390
Demographics			
Male (%)	8,020 (49%)	6,906 (55%)‡	702 (51%)†
Age (years ± SD)	64.8±18.1	65.8±16.8‡	65.9±17.3
Body mass index (kg/m2)	27.7±5.2	28±5.3‡	26.9±5.2‡
Inpatient status	4,019 (25%)	3,126 (25%)	475 (35%)‡
Underlying conditions			
Chronic lung disease	1,647 (10%)	1,318 (10%)	170 (12%)*
Chronic heart failure	777 (4.7%)	688 (5.4%)†	128 (9.2%)‡
Diabetes **(N=16,982)**	1,319 (14%)	1,115 (16%)†	154 (19%)*
Hypertension **(N=17,042)**	4,134 (45%)	3,275 (47%)*	402 (49%)
Prior myocardial infarction **(N=16,973)**	574 (6.3%)	460 (6.6%)	78 (9.5%)†
Prior ischemic stroke **(N=16,962)**	589 (6.4%)	447 (6.4%)	72 (8.8%)*
Recent major bleeding	306 (1.9%)	251 (2.0%)	56 (4.0%)‡
Anemia	5,650 (34%)	4,290 (34%)	691 (50%)‡
Abnormal platelet count	3,286 (20%)	2,593 (21%)	340 (24%)‡
Recent Surgery	1,490 (9.1%)	1,117 (8.8%)	175 (13%)‡
Recent immobility	3,917 (24%)	2,964 (23%)	399 (29%)‡
Active cancer	3,457 (21%)	2,882 (23%)‡	556 (40%)‡
Prior VTE	2,726 (17%)	2,217 (18%)*	271 (19%)
Pregnancy/puerperium	381 (2.3%)	110 (0.87%)‡	12 (0.86%)
Hormonal use	940 (5.7%)	554 (4.4%)‡	46 (3.3%)
Initial therapy			
Low-molecular-weight heparin	15,086 (92%)	11,525 (91%)*	1,147 (83%)‡
Unfractionated heparin	639 (3.9%)	556 (4.4%)*	150 (11%)‡
Fondaparinux	286 (1.7%)	216 (1.7%)	34 (2.4%)*
NOACs	218 (1.3%)	171 (1.4%)	17 (1.2%)
Thrombolytic therapy	104 (0.63%)	73 (0.58%)	26 (1.9%)‡
Vena cava filter	455 (2.8%)	329 (2.6%)	114 (8.2%)‡

Comparisons are made using patients with left-sided DVT as the referent.

*P<0.05;

†P<0.01,

$^{\neq}$P<0.001.

COPD: chronic obstructive lung disease, DVT: deep vein thrombosis, IU: international units, LMWH: low-molecular-weight heparin, NOACs: Non-vitamin K oral anticoagulants, PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

Table 2

Main Outcomes According to Thrombus Sidedness

	Left-side DVT (N=*16,421*)	**Right-side DVT (N=*12,634*)**	**Bilateral DVT (*N=1,390*)**
Cumulative 90-day PEs	3,752 (23%)	3,252 (26%)‡	672 (48%)‡
Concomitant symptomatic PE (%)	3,634 (22%)	3,137 (25%)‡	648 (47%)‡
Subsequent symptomatic 90-day PE	118 (0.72%)	115 (0.91%)	24 (1.7%)†
Mortality			
30-day all-cause mortality (%)	479 (2.9%)	417 (3.3%)	130 (9.4%)‡
30-day PE-specific mortality (%)	49 (0.30%)	54 (0.43%)	17 (1.2%)‡
Subsequent cancer in patients with unprovoked VTE	**7,893**	**6,304**	**440**
Day 90	73 (0.92%)	45 (0.71%)	5 (1.14%)
Day 365	134 (1.70%)	98 (1.55%)	6 (1.36%)
over Day 365	187 (2.37%)	145 (2.30%)	8 (1.82%)

Comparisons are made using patients with left-side DVT as the referent.

*p <0.05;

†p <0.01;

‡p <0.001

DVT: deep vein thrombosis, PE: pulmonary embolism.

Table 3

Clinical Outcomes During and After Anticoagulant Therapy

	Left-sided DVT		**Right-sided DVT**		**Bilateral DVT**	
Median duration of anticoagulation (d) (IQR)	181 (103-282)		182 (103-296)		144 (91-256)‡	
Median follow-up post-discontinuation (d) (IQR)	171 (57-446)		164 (57-450)		106 (35-353)†	
	N	*Events per 100 person-years* (95% CI)	*N*	*Events per 100 person-years* (95% CI)	*N*	*Events per 100 person-years* (95% CI)
During Anticoagulation						
	16,421		**12,634**		**1,390**	
Recurrent DVT	309	2.59 (2.32-2.90)	238	2.51 (2.20-2.84)	42	4.58 (3.34-6.13) ‡
Recurrent PE	165	1.38 (1.18-1.60)	149	1.57 (1.33-1.83)	24	2.61 (1.71-3.83) *
Recurrent VTE	465	3.98 (3.63-4.35)	385	4.15 (3.75-4.58)	66	7.38 (5.76-9.33) ‡
Major bleeding	429	3.58 (3.25-3.93)	344	3.62 (3.25-4.01)	62	6.78 (5.25-8.64) ‡
Death	1,379	11.41 (10.82-12.02) †	1,140	11.87 (11.20-12.58)	283	30.43 (27.03-34.13) ‡
Causes of death						
Pulmonary embolism	68	0.56 (0.44-0.71)	69	0.72 (0.56-0.90)	19	2.04 (1.27-3.13) ‡
Bleeding	79	0.65 (0.52-0.81)	63	0.66 (0.51-0.83)	18	1.94 (1.18-3.00) ‡
Disseminated cancer	523	4.33 (3.97-4.71)	426	4.44 (4.03-4.87)	12	13.0 (10.8-15.5) ‡
After Cessation of Anticoagulation						
	5,642		***4,287***		***346***	
Recurrent DVT	416	7.58 (6.88-8.33)	318	7.52 (6.73-8.38)	26	9.17 (6.12-13.2)
Recurrent PE	168	3.05 (2.62-3.54)	126	2.97 (2.49-3.53)	16	5.62 (3.32-8.93) *
Recurrent VTE	583	10.7 (9.86-11.6)	444	10.6 (9.64-11.6)	42	15.1 (11.0-20.1) *
Major bleeding	25	0.45 (0.30-0.66)	24	0.56 (0.37-0.83)	0	-
Death	510	9.24 (8.46-10.1)	381	8.95 (8.08-9.88)	64	22.4 (17.4-28.5) ‡
Causes of death,						
Pulmonary embolism	11	0.20 (0.10-0.35)	3	0.07 (0.02-0.19)	4	1.40 (0.45-3.38) ‡

	Left-sided DVT		Right-sided DVT		Bilateral DVT	
Bleeding	30	0.54 (0.37-0.77)	22	0.52 (0.33-0.77)	2	0.70 (0.12-2.32)
Disseminated cancer	195	3.53 (3.06-4.05)	145	3.41 (2.88-4.00)	28	9.81 (6.65-14.0) ≠

Comparisons are made using patients with left-sided DVT as referent:

* p <0.05;

† p <0.01;

≠ p <0.001.

CI: confidence interval; IQR: Interquartile range