

BRIEF REPORT

Survival and recurrent venous thromboembolism in patients with first proximal or isolated distal deep vein thrombosis and no pulmonary embolism

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Essentials

- The long-term risk of recurrence and death after distal deep vein thrombosis (DVT) is uncertain.
- We included subjects with first proximal or isolated distal DVT (IDDVT) and no pulmonary embolism.
- The risk of symptomatic and asymptomatic recurrence is lower after IDDVT (vs. proximal).
- IDDVT may be associated with a lower long-term risk of death, especially after unprovoked DVT.

Summary. *Background:* A few studies have focused on the risk of recurrence after first acute isolated distal deep vein thrombosis (IDDVT) compared with proximal DVT (PDVT), whereas the incremental risk of death has never been explored beyond the first 3 years after acute event. *Methods:* Our single-center cohort study included patients with first symptomatic acute PDVT or IDDVT. Patients were excluded if they had concomitant pulmonary embolism (PE) or prior venous thromboembolism. The primary outcomes were symptomatic objectively diagnosed recurrent PDVT or PE and all-cause death. *Results:* In total, 4759 records were screened and 831 subjects included: 202 had symptomatic IDDVT and 629 had PDVT. The median age was 66 years and

50.5% were women. A total of 125 patients had recurrent PDVT or PE during 3175 patient-years of follow-up: 109 events occurred after PDVT (17.3%) and 16 after IDDVT (7.9%). Annual recurrence rates were 4.5% (95% confidence interval [CI], 3.7–5.4%) and 2.0% (95% CI, 1.1–3.2%), respectively, for an adjusted hazard ratio (aHR) for IDDVT patients of 0.32 (95% CI, 0.19–0.55). Death occurred in 263 patients (31.6% [95% CI, 28.6–34.9%]) during 5469 patient-years of follow-up for an overall annual incidence rate of 4.8% (95% CI, 4.2–5.4%). The mortality rate was 33.5% ($n = 211$) in PDVT patients and 25.7% ($n = 52$) in IDDVT patients. The long-term hazard of death appeared lower for IDDVT patients (aHR, 0.75 [95% CI, 0.55–1.02]), especially after unprovoked events (aHR, 0.58 [95% CI, 0.26–1.31]). *Conclusions:* Compared with PDVT, IDDVT patients were at a lower risk of recurrent VTE. The risk of death appeared lower after IDDVT during a median follow-up of 7.6 years.

Keywords: anticoagulation; death; distal deep vein thrombosis; pulmonary embolism; venous thromboembolism.

Introduction

First venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep vein thrombosis (DVT), is associated with an overall high risk of recurrence and death [1–4]. Concomitant diseases, notably cancer, play a major role in determining these risks and international guidelines currently recommend a tailored length of anticoagulation based on the estimated individual probability of developing recurrence vs. bleeding [5,6].

Compared with PE and proximal DVT (PDVT), isolated distal DVT (IDDVT) seems to carry a lower but not

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negligible risk of symptomatic recurrence [7–12]. A standard length of anticoagulation is usually recommended in most patients after first IDVT, but serial imaging follow-up can be considered over anticoagulation in the absence of severe symptoms or risk factors for extension [5]. Although IDVT is not uncommon and represents up to half of all DVT cases, only a few cohort studies compared patients' outcomes after first IDVT vs. PDVT/PE and none studied the incremental risk of death beyond the first 3 years after the index event [13–16].

We investigated the risk of symptomatic recurrent PE or PDVT and death in a large cohort of subjects diagnosed with first acute symptomatic IDVT or PDVT and no concomitant PE.

Patients and methods

Our cohort study included consecutive adult subjects followed at the Thromboembolic Disease Unit-Coagulation Clinic of our academic institution between 2000 and 2012. Eligibility criteria were: objective diagnosis of PDVT or IDVT with compression ultrasound examination, no concomitant PE or prior VTE, presence of symptoms of DVT, complete chart data and at least one follow-up visit. The primary outcomes were: (i) symptomatic objectively diagnosed recurrent PDVT and/or PE and (ii) all-cause death. The secondary outcome was recurrent (a)symptomatic VTE, including PDVT and IDVT incidentally detected at control ultrasound, or PE.

As part of the routine clinical care, all subjects were instructed on how to contact the treating physicians in the presence of signs or symptoms of recurrence. Following the acute phase of DVT, annual controls were scheduled and patients contacted in case they missed the visit. A whole-leg compression ultrasound examination used to be performed at the time of DVT diagnosis, at anticoagulant discontinuation (to allow comparison in the case of suspected recurrence), at follow-up visits and if recurrence was suspected. All IDVT patients received routine anticoagulation at a dosage and duration consistent with recommendations provided by international guidelines available at the time of patients' management.

The database including demographics and personal data of all outpatients was accessed. Data were retrieved manually from the medical charts of the clinic and from the hospital electronic database, which includes information on admissions, consultancies, out-of-hospital visits and radiological data. The online registry of the local health authority served for the assessment of the patients' vital status (accessed on 12 May 2016). The following variables were recorded: age, sex, type and extension of DVT, risk factors for VTE, type, dosage and length of anticoagulant treatment, type and date of recurrent VTE, and presence of VTE-associated symptoms. The anatomical classification of IDVT includes paired distal deep veins (peroneal, posterior tibial and anterior tibial veins)

and calf muscle veins (soleal and gastrocnemius muscle veins) [16,17]. The study was conducted retrospectively and patients' data were anonymized. A study protocol had been developed and received formal approval by the institutional ethical committee. Patients provided standard written consent for the use of personal clinical data.

Descriptive analyses of baseline characteristics used counts and percentages for categorical data and mean/median (standard deviation/interquartile range) for continuous variables, where appropriate. Incidence rates ($n/100$ patient-years) were calculated by dividing the number of events by the time to event or right-censoring. For VTE rate calculation, the observation time started on the date of the index DVT and was censored at the latest available follow-up visit or death, whereas for the calculation of the fatality rate, the date on which the local health authority registry was accessed served for concluding the follow-up time. The 95% confidence intervals (CIs) of rates and proportions were based on the exact approximation of the Poisson's distribution and on the bivariate distribution (Wilson method), respectively. Kaplan–Meier curves described recurrence- and death-free survival. A multivariable Cox regression model and a logistical regression model (for survival over the first year after DVT) were fitted to estimate hazard ratios (HRs) or odds ratios (ORs), and corresponding 95% CI, for the risk of first recurrence or death after IDVT vs. PDVT. The duration of anticoagulation served for adjustment as a time-varying covariate; the other covariates were selected on the basis of clinical relevance and number of events (> 10 events per covariate). A separate analysis was performed for patients with unprovoked DVT [18]. In our study protocol, we estimated that a sample size of 780 subjects (n IDVT > 195) would have allowed us to detect a difference in symptomatic recurrence for an OR of 0.5 (5-year rate after PDVT = 20%, $1-\beta = 80\%$, $\alpha = 0.05$): screening and data collection were terminated once this target was reached. SPSS v.23.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis.

Results and discussion

We screened 4759 medical records of subjects referred to our center: 831 subjects fulfilled the inclusion criteria. The main reasons for exclusion were: a negative compression ultrasound examination, or the patient being referred for suspected disease other than VTE ($n = 2350$); concomitant PE or previous history of VTE ($n = 558$); death before discharge ($n = 276$, of whom $n = 38$ with IDVT); other thromboses (superficial [$n = 436$], neck or upper extremity [$n = 161$], cerebral [$n = 40$], splanchnic [$n = 55$] and other [$n = 29$]); and unspecified diagnosis or incomplete charts ($n = 23$).

Of 831 included subjects, 202 had symptomatic index IDVT and 629 PDVT. The median age was 66 years (IQR, 52–76) and 50.5% were women. IDVT was

located at the calf muscle veins in 120 patients (59.6%), at the paired distal deep veins in 55 (27.1%), and at both districts or bilaterally in 27 (13.4%). Patients with IDDVT received an anticoagulant treatment of shorter duration than those with PDVT (median 70 days [IQR, 41–157] vs. 238 days [IQR, 97–730]), more often consisting of parenteral anticoagulants as a stand-alone treatment (Table 1). The median duration of follow-up in survivors was 94 (IQR, 66–135) months after PDVT and 84 (IQR, 62–121) months after IDDVT; median time of follow-up for VTE recurrence (time to last visit, all patients) was 36 (IQR, 9–70) months after PDVT and 42 (IQR, 7–71) months after IDDVT.

One hundred and twenty-five (15.0%) recurrent symptomatic events of PDVT or PE were recorded during 3175 patient-years of follow-up, of which 109 were after PDVT (17.3%) and 16 after IDDVT (7.9%), corresponding to overall incidence rates of 4.5 events/100 patient-years (95% CI, 3.7–5.4%) and 2.0 events/100 patient-years (95% CI, 1.1–3.2%), respectively (Table 2, Fig. 1). IDDVT was associated with a lower risk of recurrent symptomatic PDVT or PE (adjusted hazard ratio [aHR], 0.32 [95% CI, 0.19–0.55]), especially for patients with unprovoked events (aHR 0.14 [95% CI: 0.04–0.46]; Table 3). First IDDVT was associated with a lower risk of (a)symptomatic PDVT, PE or IDDVT recurrence (aHR, 0.49 [95% CI, 0.32–0.74]).

Death from any cause was documented in 263 patients (31.6% [95% CI, 28.6–34.9%]) over a total follow-up of 5469 patient-years (Table 2, Fig. 1), corresponding to an incidence rate of 4.8 events/100 patient-years (95% CI, 4.2–5.4%). Of 263 subjects, 52 had IDDVT (25.7% of IDDVT patients) and 211 had PDVT (33.5% of PDVT patients) for an aHR of 0.75 (95% CI, 0.55–1.02; Table 3). For patients with unprovoked DVT, we also observed a tendency towards a lower risk of death after IDDVT (aHR, 0.58 [95% CI, 0.26–1.31], Table 3). The 12-month fatality rate was 12.3% ($n = 102$), with cancer representing the strongest risk factor (aOR, 12.74 [95% CI, 7.44–21.80]). The risk of death in the first year appeared lower for IDDVT patients when only unprovoked events were considered (aOR, 0.49 [95% CI, 0.05–4.31]).

The results of our cohort study indicate that patients with first IDDVT and no concomitant PE carry a significantly lower risk of recurrent symptomatic VTE, and possibly of death, compared with first PDVT. For recurrence, these findings confirm prior observations, although there is heterogeneity among previous studies in terms of study design and subjects' eligibility criteria (provoking factors, prior VTE, known thrombophilia or concomitant PE) [7, 8, 10–13, 19–21]. Of note, in our cohort a significant risk reduction of about 50% was present also when considering all recurrent VTE events, including (a) symptomatic IDDVT detected during routine ultrasonography at the time of anticoagulant discontinuation. Some authors suggested that different risk factors associated

Table 1 Characteristics of the study population

	PDVT (<i>N</i> = 629)	IDDVT (<i>N</i> = 202)
Demographics and clinical characteristics		
Median age (IQR), years	67 (52–76)	66 (54–75)
Female sex, <i>n</i> (%)	306 (48.6)	114 (56.4)
Unprovoked DVT	227 (36.1)	61 (30.2)
DVT diagnosis during hospitalization	113 (18.0)	37 (18.3)
Oral contraception/HRT	33 (5.2)	10 (5.0)
Pregnancy or postpartum	11 (1.7)	1 (0.5)
Family history of VTE	31 (4.9)	6 (3.0)
Solid cancer	145 (23.1)	49 (24.3)
Hematological cancer	37 (5.9)	9 (4.5)
Recent surgery	102 (16.2)	43 (21.3)
Recent trauma	57 (9.1)	28 (13.9)
Prolonged immobilization	105 (16.7)	47 (23.3)
Long-distance travel	12 (1.9)	2 (1.0)
Known thrombophilia, <i>n</i> (%) of tested)	136 (54.0)	26 (37.1)
Severe thrombophilia, <i>n</i> (%) of tested)	34 (13.5)	8 (11.0)
Concomitant SVT	143 (22.7)	39 (19.3)
Prior SVT	55 (8.7)	24 (11.9)
Prior VTE unclear	14 (2.2)	1 (0.5)
Co-morbidities		
Arterial hypertension	229 (36.4)	82 (40.6)
Diabetes mellitus	77 (12.2)	26 (12.9)
Atrial fibrillation	60 (9.5)	14 (6.9)
Vascular disease	138 (21.9)	50 (24.8)
Long-term anticoagulant treatment		
Oral anticoagulants, <i>n</i> (%)	462 (73.4)	64 (31.7)
LMWH or fondaparinux	157 (25.0)	132 (65.3)
Unfractionated heparin	2 (0.3)	0 (0)
Missing data	8 (1.3)	6 (3.0)
Dose of anticoagulant treatment		
Prophylactic, <i>n</i> (%)	13 (2.1)	15 (7.4)
Intermediate or therapeutic	605 (96.2)	182 (90.1)
Missing data	11 (1.7)	5 (2.5)
Length of anticoagulant treatment		
≤ 3 months, <i>n</i> (%)	183 (29.0)	142 (70.3)
3–6 months	143 (22.7)	26 (12.9)
> 6 months	295 (46.9)	30 (14.9)
Missing data	8 (1.3)	4 (2.0)

PDVT, proximal deep venous thrombosis; IDDVT, isolated distal deep vein thrombosis; IQR, interquartile range; HRT, hormone replacement therapy; VTE, venous thromboembolism; SVT, superficial vein thrombosis; HIV, human immunodeficiency virus; LMWH, low-molecular-weight heparin. 'Cancer' defines patients with active cancer, receiving chemotherapy or radiation therapy, or with a cancer diagnosed in the prior 5 years. 'Severe thrombophilia' defines antithrombin, protein C or protein S deficiency, antiphospholipid antibodies, or the concomitance of more than one abnormality. 'Vascular disease' defines: prior myocardial infarction or ischemic stroke, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery, and peripheral artery disease. 'Long-distance travel', 'prolonged immobilization', 'hypertension' and 'autoimmune diseases' were considered present if reported by the treating physician. Prior VTE was defined as 'unclear' when clinical information was missing and the patient not able to describe the prior event and the treatment received.

with (especially unilateral) IDDVT and PDVT may explain such overall lower risk [7,21,22]. Although we could not perform any formal comparison between the

Table 2 Death and recurrent venous thromboembolism after first deep vein thrombosis

	Total (N = 831)	PDVT (n = 629)	IDDVT (n = 202)
Symptomatic recurrent PDVT or PE			
Number of events (%)	125 (15.0)	109 (17.3)	16 (7.9)
Annual incidence rate, % (95% CI)	3.6 (3.0–4.4)	4.5 (3.7–5.4)	2.0 (1.1–3.2)
New DVT, n	41	37	4
Extension, n	21	16	5
Contralateral leg, n	24	23	1
Bilateral, n	15	15	0
Site of index or recurrent DVT not detailed, n	2	2	0
PE ± DVT, n	22	16	6
Symptomatic recurrent IDDVT			
Number of events (%)	32 (2.4)	20 (3.2)	12 (6.4)
Annual incidence rate, % (95% CI)	1.0 (0.7–1.4)	0.8 (0.5–1.3)	1.6 (0.8–2.8)
New DVT, n	15	9	6
Extension, n	0	0	0
Contralateral leg, n	13	9	4
Bilateral, n	3	1	2
Site of index or recurrent DVT not detailed, n	1	1	0
Death			
Death from all causes, n (%)	263 (31.6)	211 (33.5)	52 (25.7)
Median time to death, months (IQR)	20 (7–53)	21 (8–55)	14 (7–47)

PDVT, proximal deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; PE, pulmonary embolism; 95% CI, 95% confidence interval; IQR, interquartile range. New DVT was defined as (i) a non-compressible venous segment of a site previously not involved, (ii) with ultrasonographic documentation of DVT resolution at the time of anticoagulant discontinuation, and (iii) with a significant increase in the thrombus diameter compared with baseline echography. Extension was defined as a significant involvement of a new non-compressible venous segment in direct proximity to the index DVT, including extension from IDDVT to trifurcation or the popliteal vein, as judged by the treating physician. Bilateral events were defined in the presence of bilateral ultrasonographic signs of recurrence or extension associated with unilateral or bilateral symptoms.

patients' baseline characteristics of the two groups because of the small sample size of our cohort, female subjects appeared over-represented among IDDVT subjects (56.4% vs. 48.6% in PDVT) as well as some temporary provoking risk factors like recent surgery or trauma.

The main novelty of our study is represented by survival data. We suggest that not only the severity of concomitant diseases, but IDDVT itself might be associated with a lower risk of death (aHR, 0.75 [95% CI, 0.55–1.02]). Such a risk seems lower beyond the first years of follow-up (Fig. 1) and particularly among subjects with unprovoked DVT (aHR, 0.58 [95% CI, 0.26–1.31]). In fact, one may appreciate that the Kaplan–Meier curves for survival are superimposed for the first 2 years of follow-up: this seems to be linked to the adverse prognosis of patients with active

cancer, who constituted approximately one-quarter of both PDVT and IDDVT groups. Thus far, only the OPTIMEV study evaluated the long-term risk of death in non-cancer patients after IDDVT (7.8%) and PDVT (12.2%) over 3 follow-up years, suggesting similar relative risk reduction, but lower absolute figures [13]. In a recent Italian multicenter study of more than 300 patients with cancer-associated IDDVT, 15.2% of patients developed recurrence despite initial anticoagulant treatment and 44.5% died during a mean follow-up of 15 months [23]. This observation indicates that cancer is the main risk factor to be considered for the development of adverse events after IDDVT. Consistently, the results of the two OPTIMEV sub-studies focusing on the 3-year rate of recurrence and death after cancer-associated DVT [24] and on subsequent cancer diagnosis after unprovoked DVT [13] suggested no differences between IDDVT and PDVT patients. It remains to be confirmed whether a more aggressive or diffused cancer is associated with a more proximal site of presenting DVT.

The strengths of our study include the large sample size and inclusion of both IDDVT and PDVT patients, who received a diagnostic approach, follow-up schedule and anticoagulant treatment based on recommendations from international guidelines. Major limitations are represented by the *post hoc* nature of the analysis and lack of independent adjudication of outcomes, possibly affecting the evaluation of VTE recurrence rates. A bias for indication was also likely to be present, because (i) IDDVT patients received shorter (and more often at lower dosage) anticoagulation, (ii) patients of both groups used to receive extended anticoagulant treatment in the presence of a strong risk factor for recurrence, notably cancer, and (iii) treatment strategies for PDVT and IDDVT changed over the years. Indeed, the presence of such bias, which is intrinsic to the observational study design, would have more likely biased our estimates towards underestimation of the lower risk of VTE recurrence after IDDVT, not vice versa, providing reassurance about the validity of our data. The data on mortality were directly extracted from the registry of the local health authority and thus can be considered free of bias. Finally, we could not provide data regarding bleeding events or evaluate covariates previously included in cohort studies, such as body mass index and use of acetylsalicylic acid.

Because data from interventional studies are still inconclusive [9,14,20,25,26], it appears clear that the clinical gestalt, and not firm evidence, influences the management of patients with first symptomatic IDDVT. Our study indicates that IDDVT patients are at a lower risk of recurrent symptomatic VTE, and possibly long-term death, compared with those with first symptomatic PDVT, especially if only first unprovoked events are considered.

Addendum

S. Barco contributed to the concept and design of the study, clinical follow-up of patients, collection of data,

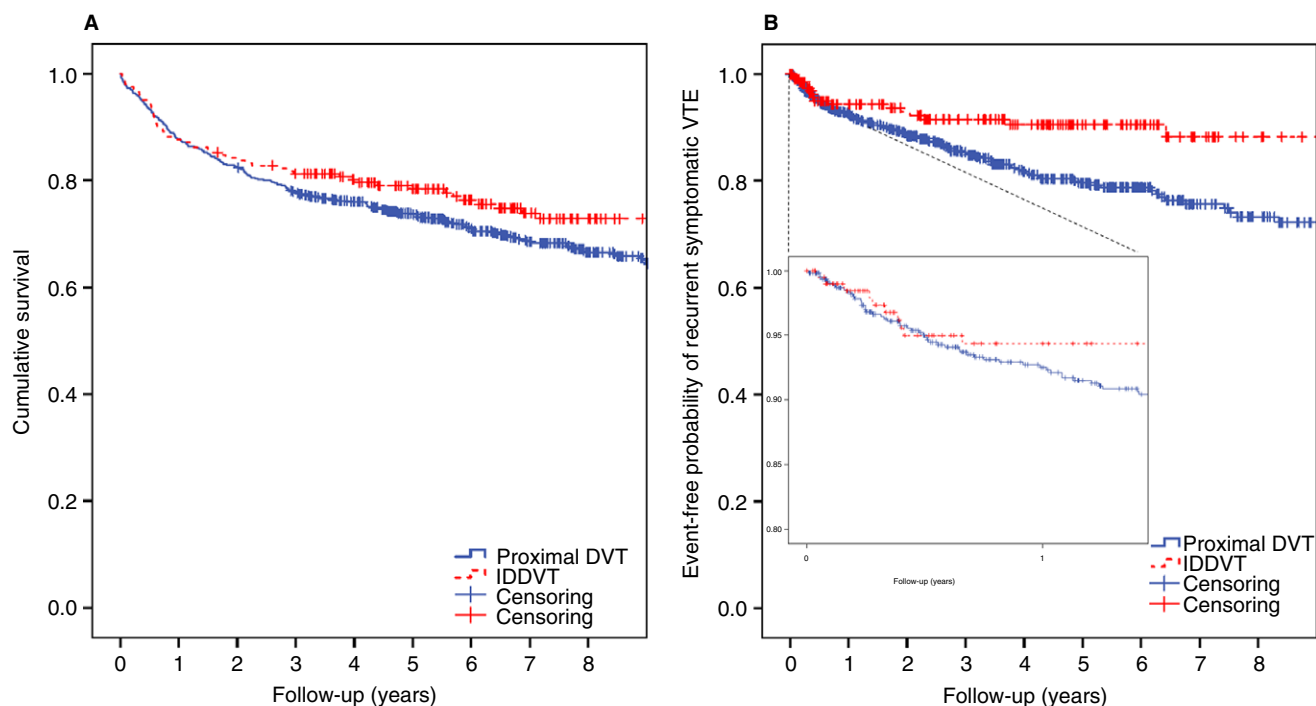


Fig. 1. Kaplan–Meier curves showing cumulative survival rate (left panel) and recurrent symptomatic venous thromboembolism-free cumulative rate (right panel) after first proximal or isolated distal deep vein thrombosis. The curves depicted in the left panel describe the survival rate of patients with first proximal DVT or first IDDVT over time. The curves in the right panel describe the cumulative rate of patients free from symptomatic objectively diagnosed VTE (proximal DVT or pulmonary embolism) recurrence over time. DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Risk factors for long-term recurrence or death after first deep vein thrombosis and no pulmonary embolism

	Total DVT (<i>N</i> = 831)		Unprovoked DVT (<i>n</i> = 288)
	Crude HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Recurrent PDVT or PE			
IDDVT	0.48 (0.28–0.82)	0.32 (0.19–0.55)	0.14 (0.04–0.46)
Age (per unit increase)	1.00 (0.99–1.02)	1.01 (0.99–1.02)	1.01 (0.99–1.04)
Female sex	0.66 (0.46–0.94)	0.61 (0.42–0.87)	0.51 (0.27–0.95)
Cancer	1.43 (0.94–2.15)	1.66 (1.03–2.67)	NA
Unprovoked DVT	1.00 (0.70–1.44)	1.60 (1.02–2.52)	NA
Recent hospitalization	1.62 (1.05–2.51)	1.75 (1.10–2.83)	NA
Anticoagulation off	4.11 (2.57–6.57)	5.97 (3.70–9.63)	13.36 (5.53–32.24)
Death			
IDDVT	0.79 (0.59–1.08)	0.75 (0.55–1.02)	0.58 (0.26–1.31)
Age (per unit increase)	1.06 (1.04–1.07)	1.05 (1.04–1.07)	1.09 (1.06–1.12)
Female sex	0.92 (0.72–1.17)	0.99 (0.77–1.28)	0.70 (0.39–1.25)
Cancer	4.99 (3.90–6.38)	4.79 (3.69–6.22)	NA
Recent hospitalization	2.03 (1.55–2.66)	1.29 (0.97–1.70)	NA
Vascular disease	1.67 (1.29–2.16)	1.46 (1.08–1.97)	2.21 (1.23–3.96)
Diabetes mellitus	1.84 (1.35–2.50)	1.24 (0.89–1.71)	1.32 (0.68–2.55)
Atrial fibrillation	1.78 (1.26–2.51)	1.36 (0.94–1.98)	0.69 (0.36–1.36)
Arterial hypertension	1.49 (1.17–1.89)	0.72 (0.55–0.95)	0.90 (0.50–1.62)

DVT, deep vein thrombosis; HR, hazard ratio; OR, odds ratio; 95% CI, 95% confidence interval; IDDVT, isolated distal deep vein thrombosis; NA, not applicable. The multivariable regression models have been fitted with covariates entered in one step (shown in the table).

adjudication of recurrent events, statistical analysis, interpretation of the results and writing of the manuscript. M. Corti and A. Trincherò contributed to the collection of data, interpretation of the results and critical revision of

the manuscript, and gave final approval. C. Picchi contributed to the clinical follow-up of patients, collection of data, interpretation of the results, critical revision of the manuscript, and gave final approval. C. Ambaglio

contributed to the clinical follow-up of patients, adjudication of recurrent events, interpretation of the results, critical revision of the manuscript, and gave final approval. S. V. Konstantinides and F. Dentali contributed to the interpretation of the results, methodological supervision, critical revision of the manuscript, and gave final approval. M. Barone contributed to the concept of the study, clinical follow-up of patients, interpretation of the results, critical revision of the manuscript, and gave final approval.

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Disclosure of Conflicts of Interests

S. Barco has received payment for travel accommodation from Daiichi Sankyo and financial support for the production costs of his PhD thesis from Pfizer bv, CSL Behring bv, Sanquin Plasma Products, Boehringer Ingelheim bv, Aspen Netherlands bv, Bayer bv, and the Academic Medical Center (Amsterdam, the Netherlands). S. V. Konstantinides reports having received lecture fees and advisory board honoraria from Bayer Health Care, Boehringer Ingelheim, Pfizer-Bristol-Myers Squibb, Daiichi-Sankyo and Actelion, and research grants to his institution from Bayer Health Care, Boehringer Ingelheim, and Actelion. The other authors state that they have no conflict of interest.

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