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ORIGINAL ARTICLE

Clinical course of isolated distal deep vein thrombosis in patients with active cancer: a multicenter cohort study

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Essentials

- Isolated distal deep vein thrombosis (IDDVT) is frequently associated with cancer.
- No study has specifically evaluated the long-term clinical course of cancer-associated IDDVT.
- Patients with cancer-associated IDDVT are at very high risk of symptomatic recurrence and death.
- We observed low rates of major bleeding during anticoagulation.

Summary. *Background:* Although isolated distal deep vein thrombosis (IDDVT) is frequently associated with cancer, no study has specifically evaluated the long-term clinical course of IDDVT in this setting. *Aim:* To provide data on the rate of recurrent venous thromboembolism (VTE), major bleeding events and death in IDDVT patients with active cancer. *Patients and Methods:* Consecutive patients with active cancer and an objective IDDVT diagnosis (January 2011 to September 2014) were included from our files. We collected information on baseline characteristics, IDDVT location and extension, VTE risk factors, and type and duration of anticoagulant treatment. *Results:* A total of 308 patients (mean age 66.2 [standard deviation (SD), 13.2 years]; 57.1% female) with symptomatic IDDVT and a solid (n = 261) or hematologic (n = 47) cancer were included at 13 centers. Cancer was metastatic in 148 (48.1%) patients. All but three (99.0%) patients received anticoagulant therapy, which consisted of low-molecular-weight heparin in 288 (93.5%) patients. Vitamin K antagonists were used for the long-term treatment in 46 (14.9%) patients, whereas all others continued the initial parenteral agent for a mean treatment duration of 4.2 months (SD, 4.6 months). During a total follow-up of 355.8 patient-years (mean, 13.9 months), there were 47 recurrent objectively diagnosed VTEs for an incidence rate of 13.2 events per 100 patient-years. During anticoagulant treatment, the annual incidence of major bleeding was 2.0 per 100 patient-years. *Conclusions:* Cancer patients with IDDVT have a high risk of VTE recurrence. Additional studies are warranted to investigate the optimal intensity and duration of anticoagulant treatment for these patients.

Keywords: distal deep vein thrombosis; mortality; neoplasm; observational study; venous thromboembolism.

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Background

Isolated distal deep vein thrombosis (IDDVT) accounts for about half of all the diagnoses of deep vein thrombosis (DVT) [1]. The clinical relevance of IDDVT is controversial and, consequently, the suggested therapeutic approach remains highly heterogeneous, ranging from anticoagulant treatment to clinical and ultrasonographic follow-up [1,2]. In an early randomized study published in 1985, one of 23 (4%) patients with IDDVT receiving warfarin had a recurrent venous thromboembolic event (VTE) compared with 19 of 28 (68%) in the control group [3]. Despite some limitations, including the small sample size and the use of an outdated reference test to diagnose IDDVT, this study suggested that IDDVT confers a non-negligible risk of recurrence when left untreated. These findings were later supported by similar data from a number of cohort studies [4–6], whereas the randomized DOTAVK study [7] and two patient-level meta-analyses questioned the clinical relevance of IDDVT, showing a cumulative rate of recurrent VTE up to 5-fold lower than for proximal DVT [8,9]. These inconsistencies may be explained by differences in study populations and management patterns [10–12]. Although most IDDVT may be truly self-limiting without active treatment, the risk of progression or recurrence appears to be increased in high-risk patients, defined by the concomitance of major underlying risk factors [1,10–12]. In this context, several studies have shown an increased risk of recurrent VTE in IDDVT associated with cancer [4–7]. However, these studies included few patients with active cancer, and none evaluated the long-term risk of VTE recurrence in this specific population or assessed the potential benefits and risks of antithrombotic treatment. In the absence of solid evidence from large prospective studies, the American College of Chest Physicians (ACCP) guidelines suggest the same approach as for proximal DVT for patients with active cancer and IDDVT, with anticoagulant therapy continued for at least 3 months or longer [2]. However, whether anticoagulant treatment should be continued indefinitely in patients with active cancer and IDDVT remains uncertain and in clinical practice the duration of treatment in these patients is highly variable.

Given the paucity of data on the long-term clinical course of IDDVT in patients with cancer, we carried out a multicenter, retrospective cohort study with the aim of evaluating the long-term risk of VTE recurrence, major bleeding and mortality in cancer patients with acute, symptomatic IDDVT.

Methods

Study population

This study was a multicenter, retrospective cohort study of adult patients (age 18 years or older) with a diagnosis of active cancer and symptomatic acute IDDVT referred to the anticoagulation clinics of 13 Italian centers between January 2011 and September 2014. Patients with concomitant proximal DVT or symptomatic pulmonary embolism (PE) and those who were currently receiving anticoagulant therapy for other indications were excluded. Asymptomatic PE was not systematically searched for. The diagnosis of IDDVT was objectively confirmed by means of whole leg compression ultrasound using high-resolution 5-MHz to 7.5-MHz linear transducers [13]. The proximal deep veins were examined with the patient in the supine position by applying gentle compression with the probe along the deep venous system from the common femoral vein at the groin to the trifurcation of the popliteal vein. The deep calf veins were examined down to the ankle with a similar ultrasound procedure, with the patient in the sitting position hanging the legs down. The calf veins examined were the posterior tibial, peroneal, gastrocnemius muscular and soleal veins. The criterion for diagnosing proximal and calf DVT was the non-compressibility of the vein in the transverse plane. Doppler evaluation of the iliac veins was used to aid the diagnosis in the case of suspected isolated iliac thrombosis.

Active cancer was defined by histologically or cytologically confirmed malignancy (with the exclusion of basal cell carcinoma or non-melanoma skin cancer) with any of the following: cancer diagnosis within the previous 6 months; recurrent, regionally advanced or metastatic disease; treatment for cancer during the previous 6 months; or not in complete remission from a hematological malignancy [14].

Data collection

Trained study personnel from each participating center recorded baseline patient characteristics in an electronic database. The following information was collected at the time of IDDVT diagnosis: clinical characteristics (age, sex, ethnicity and bodyweight); VTE risk factors (e.g. previous VTE, major trauma, surgery or hospitalization in the previous month, or immobilization for more than 3 days); cancer stage and treatments such as ongoing or recent chemotherapy, radiotherapy or hormonal therapy in the previous month; and placement of a central venous catheter.

All patients underwent regular follow-up visits or telephone contacts at intervals of about 6 months up to 24 months after IDDVT diagnosis. The last follow-up visit was performed in September 2016. During follow-up visits, the treating oncologist or general practitioner assessed vital status and verified the occurrence of thromboembolic and bleeding events.

Anticoagulant treatment

Because the study was non-interventional, no prespecified therapeutic protocols were used and treatment decisions

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were left at the discretion of the treating physician. Based on the findings from a recent study that suggested a similar efficacy and safety of a 6-week course of low-molecular-weight heparin (LMWH) and vitamin K antagonists for the treatment of IDDVT [15], most centers involved in the current study provided LMWH treatment for at least 6 weeks.

Study outcomes

The primary study outcome was the composite of objectively documented recurrent VTE, including symptomatic recurrent IDDVT, incidental or symptomatic proximal DVT of the lower limbs, incidental or symptomatic PE, or DVT in other sites (e.g. upper extremities, cerebral vein thrombosis and splanchnic vein thrombosis). Recurrent IDDVT was diagnosed in the presence of thrombosis of a previously normal vessel or in a previously completely recanalized distal venous segment. Proximal DVT was objectively confirmed using standard imaging techniques, including compression ultrasonography, computer tomography venography or magnetic resonance venography; non-fatal PE was diagnosed by computed tomography pulmonary angiography or ventilation-perfusion scintigraphy. The primary safety outcome was major bleeding, which was defined according to the International Society on Thrombosis and Haemostasis criteria [16]. Secondary outcomes were clinically relevant non-major bleeding and overall mortality. All study outcomes were locally adjudicated.

Statistical analysis

Continuous data are presented with mean and standard deviations (SD) or median and interquartile range according to their distribution, after applying the Kolmogorov-Smirnov test. The number of recurrent VTEs is expressed as percentage with 95% confidence intervals (CIs) with continuity correction, and incidence rate, calculated as the number of events per 100 patient-years of observation. A multivariate Cox-regression analysis was performed to estimate the hazard ratio (HR) and CI associated with potential predictors of recurrent VTE, which were associated with the outcome at univariate analysis ($P < 0.10$) [17]. The following variables were considered for the univariate analysis: age, sex, personal and family history of VTE, obesity (body mass index ≥ 30 kg m^{-2}), site of cancer, presence of metastases, ongoing cancer treatment and IDDVT extension. Incidence of major bleeding events and mortality rate during the follow-up period are expressed as percentage. The Fine and Gray model was used to assess the time to recurrence of VTE accounting for the competing risk of death, using the same strategy adopted for Cox-regression analysis. The incidence of recurrent VTE was analyzed according to the intensity and duration of anticoagulant treatment. The dose of parenteral treatment was classified as prophylactic or therapeutic according to drug labeling and prescription. All other doses were classified as intermediate doses. Vitamin K antagonists at a target international normalized ratio between 2.0 and 3.0 were considered within the therapeutic group. For the analysis on recurrent VTE by anticoagulant treatment duration, we considered patients receiving treatment (i) up to 6 weeks, which is the duration advised for IDDVT secondary to transient risk factors [1,15], (ii) up to 3 months, which is the duration suggested by the ACCP guidelines [2], or (iii) longer than 3 months. IBM SPSS Statistics software, version 19 (SPSS, Inc., IBM corporation, U.S., Armonk, NY, USA) was used for all the analyses. The Institutional Review Board of the Coordinating Institution in Varese approved the study and waived the need for written informed consent, with a verbal consent to gather data in a centralized database and contact patients on a regular basis for study purposes.

Results

Population characteristics

Between January 2011 and September 2014, we included 308 patients (mean age 66.2 [SD 13.2] years; 57.1% female) with acute symptomatic IDDVT and a solid ($n = 261$) or hematologic ($n = 47$) cancer. At the time of IDDVT diagnosis, the cancer was metastatic in 148 patients (48.1%). IDDVT involved the axial calf veins in 135 (43.8%) patients, the muscular veins in 200 (64.9%), and it was bilateral in 22 (7.1%). IDDVT extended up to the popliteal trifurcation in 39 (12.7%) patients. Clinical presentation of IDDVT included pain in 183 (59.4%) patients and edema in 176 (57.1%) patients, with a mean interval of 5 days (range 0–30) between symptoms onset and IDDVT diagnosis. Baseline characteristics are summarized in Table 1.

Anticoagulant treatment

Three-hundred and five (99.0%) patients received anticoagulant therapy, which consisted of LMWH in 288 (93.5%), fondaparinux in 15 (4.9%) and unfractionated heparin in one case (0.3%). Full therapeutic or intermediate dose of parenteral antithrombotic therapy was used in the vast majority of patients (93.5%). Vitamin K antagonists with a target international normalized ratio between 2.0 and 3.0 were used in 46 patients (14.9%) for long-term treatment, whereas all others continued the initial parenteral agent at prophylactic or half-therapeutic doses for an overall mean treatment duration of 4.2 months (SD, 4.6 months; median, 3 months; range, 0–24 months). Ninety-three (30%) patients received up to 6 weeks of treatment, 92 (30%) between 6 weeks and

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Table 1 Baseline characteristics of the study population

Number of patients	308
Age (years), mean (SD)	66.2 (13.2)
Women, n (%)	176 (57.1%)
Obesity*	25 (8.1%)
Concomitant risk factors for VTE	
Recent surgery or trauma	79 (25.6%)
In-patient/immobilization	45 (14.6%)
Prolonged bed rest	47 (15.3%)
Local or systemic infections	19 (6.2%)
Qualifying isolated distal deep venous thrombosis	
Axial calf veins	135 (43.8%)
Muscular calf veins	149 (48.4%)
Medial gastrocnemius veins	113 (36.7%)
Lateral gastrocnemius veins	45 (14.6%)
Soleal veins	73 (23.7%)
Bilateral venous thrombosis	22 (7.1%)
More than one vein involved	127 (41.2%)
Personal history of VTE	45 (14.6%)
Family history of VTE	16 (5.2%)
Primary cancer site	
Breast	54 (17.5%)
Gastrointestinal	51 (16.6%)
Pancreas	18 (5.8%)
Hepatic	9 (2.9%)
Lung	44 (14.3%)
Hematologic	47 (15.3%)
Prostate	17 (5.5%)
Brain	15 (4.9%)
Other	53 (17.2%)
Metastases	148 (48.1%)
Cancer therapy	
Systemic chemotherapy	174 (56.5%)
Radiotherapy	20 (6.5%)
Hormonal therapy	36 (11.7%)
Initial anticoagulant therapy	305 (99%)
Low-molecular-weight heparin	288 (93.5%)
Fondaparinux	16 (5.2%)
Unfractionated heparin	1 (0.3%)
Vitamin K antagonists	46 (14.9%)
Duration of anticoagulant therapy (months), mean (SD)	4.2 (4.6)

VTE, venous thromboembolism; SD, standard deviation. *Obesity was defined as body mass index > 30 kg m−2.

3 months, and 123 (40%) were anticoagulated for 3 months or longer.

Three patients did not receive any anticoagulant therapy because they were judged to be at high risk of bleeding by the treating physician. One patient with metastatic gastric carcinoma and severe anemia as a result of tumor infiltration of the intestinal wall underwent vena cava filter placement and died 2 days after the diagnosis of IDDVT. Another patient with metastatic gastric carcinoma was diagnosed with IDDVT during the course of hospitalization for neoplastic cachexia and severe anemia with concomitant antiplatelet therapy. The third patient had multiple myeloma-associated severe thrombocytopenia (17 000 mL^{-1}). None of these three patients left untreated developed recurrent VTE.

Table 2 Recurrent venous thromboembolic events, bleeding and death during follow-up

Recurrent VTE	47 (15.3%)
Symptomatic	40
Proximal DVT or PE	25 (81%)
Proximal DVT	12
PE with or without DVT	13
Recurrent IDDVT	15 (4.9%)
Incidental	7 (2.3%)
Proximal DVT	1
PE	3
Splanchnic DVT	3
Major bleeding	7 (2.3%)
Clinically relevant non-major bleeding	24 (7.8%)
Death	138 (44.8%)

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; IDDVT, isolated distal deep vein thrombosis.

Clinical outcomes

During a total follow-up of 355.8 patient-years (mean follow-up, 13.9 months), 47 patients had recurrent (a) symptomatic VTE for an incidence rate of 13.2 events per 100 patient-years (95% CI, 9.9–17.6%; Table 2). We did not consider recurrent incidental IDDVT as an outcome. The prognostic value of these events is unclear and their incidence would be inevitably influenced by the frequency and accuracy of diagnostic tests applied in each center. The overall recurrent-VTE-free survival after adjustment for death as competing risk factor is shown in Fig. 1. Thirty-three of the 47 recurrent VTEs were proximal DVT or PE with or without DVT, or splanchnic vein thrombosis. Forty VTE events were symptomatic, whereas seven VTEs (three PEs, one proximal DVT of the femoral vein and three splanchnic vein thrombosis) were incidentally diagnosed by computed tomography imaging performed for staging reevaluation after cancer treatment. In the three incidental PEs the most proximal pulmonary artery was the main pulmonary artery in two cases and the lobar artery in one patient. Incidental splanchnic vein thrombosis involved the portal vein in two cases and the mesenteric vein in one. The annual incidence of recurrent symptomatic VTE was of 11.2 per 100 patient-years (95% CI, 8.3–15.4%) and of proximal DVT or PE with or without DVT 9.0 per 100 patient-years (95% CI, 6.4–12.7%).

Sixteen (34%) recurrent VTEs occurred on treatment during a mean of 2.9 months (IQR, 1.9–4.1) for an annual incidence rate of 15.0 per 100 patient-years: four patients were on oral anticoagulant therapy with vitamin K antagonists, seven patients were receiving intermediate-dose LMWH and five patients were on therapeutic-dose LMWH. The remaining 31 (66%) events occurred after anticoagulant treatment withdrawal during a mean off-treatment period of 8.0 months (IQR, 3.0–14.0) for an incidence rate of 12.4 events per 100 patient-years.

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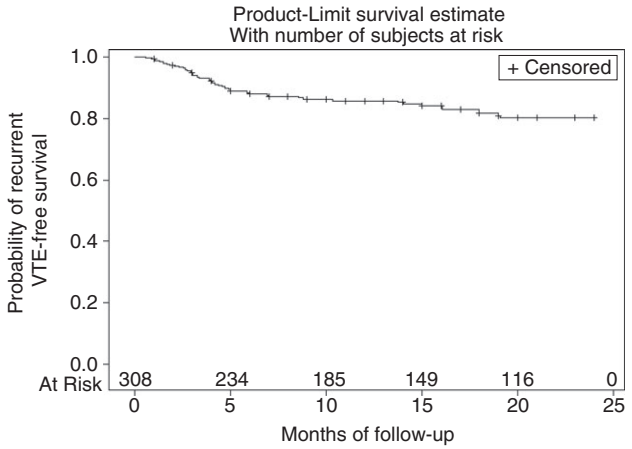

Fig. 1. Probability of survival without a VTE recurrence.

The rate of recurrent VTE both during anticoagulation and after treatment withdrawal was similar in patients who received prophylactic, intermediate or full therapeutic-dose anticoagulation ($P = 0.080$ and $P = 0.249$).The incidence of recurrent VTE after treatment withdrawal was significantly higher in patients with IDDVT treated for 6 weeks or less (15/92 patients, 16.3%) compared with patients who received anticoagulant therapy for up to 3 months (9/92 patients, 9.8%) or longer (7/123, 5.7%) ($P = 0.038$), and in particular, after adjustment for age and sex and for other possible confounders, patients treated for 6 weeks or less had a higher risk of recurrence (HR, 4.42; 95% CI, 1.75–11.15) compared to patients treated for more than 3 months. There were no case of heparin-induced thrombocytopenia during follow-up.

At univariate analysis, a personal history of VTE and metastatic disease were associated with an increased risk of VTE recurrence, whereas a diagnosis of gastrointestinal cancer was associated with a lower risk of recurrence than other cancer types. At multivariate analysis, only a personal history of VTE (HR, 2.15; 95% CI, 1.09–4.23) and gastrointestinal cancer (HR, 0.17; 95% CI, 0.04–0.70) remained as predictors. Multivariate analysis considering death as a competing risk for VTE recurrence gave similar results, with an association with previous VTE and an inverse relationship with gastrointestinal cancer (HR, 1.86; 95% CI, 0.95–3.63, and HR, 0.21; 95% CI, 0.05–0.84, respectively).

During a mean anticoagulant treatment duration of 4.2 months, seven patients (2.3%) had a major bleeding event for an incidence of 2.0 per 100 patient-years (95% CI, 1.0–5.0%). Major bleeding involved the upper or lower gastrointestinal tract in three patients, the urinary tract in two cases of gross hematuria, and the retroperitoneum in one patient. One patient with glioblastoma had intracranial bleeding during LMWH therapy. All but one of these patients had three or more bleeding risk factors, including previous major bleeding, thrombocytopenia and renal insufficiency. During the study, 138 patients died (44.8%) after a median time of 6 months (range, 1–24 months) since IDDVT diagnosis. Forty-one patients (29.7%) died within 3 months. One patient died one week after recurrent VTE and another patient had fatal major gastrointestinal bleeding. The mortality rate was higher in patients who had recurrent VTE than those who did not (93.5 per 100 patient-years vs. 34.7 per 100 patient-years, $P < 0.05$).

Discussion

The results of this study show that patients with acute symptomatic IDDVT and active cancer are usually treated for a limited period of time and are at a relatively high risk of recurrent VTE (13.2% per year), with about two-thirds of events occurring after anticoagulant treatment withdrawal. Anticoagulant treatment was well tolerated with a relatively low incidence of anticoagulant-related major bleeding events.

The clinical relevance of IDDVT remains uncertain [18], and most of these below-knee thrombi are supposed to be self-limited [1,2]. However, the risk of progression to proximal DVT or VTE recurrence may be increased in high-risk subgroups with persistent VTE risk factors [1,4–6]. Active cancer is a well-known major risk factor for first and recurrent VTE, accounting for about 20% of all VTEs [19]. Although a number of studies have suggested that active cancer may increase the risk of recurrent VTE in IDDVT, it should be realized that none of these studies specifically focused on cancer patients, and most had a relatively small size, lacked information on the type and duration of anticoagulant treatment, and presented significant methodological limitations [4–7,20–22]. To our knowledge, this is the largest cohort of IDDVT in patients with active cancer with long-term follow-up. The recent ACCP guidelines suggest for IDDVT the same therapeutic approach as for acute proximal DVT in the presence of active cancer, which translates into LMWH treatment for at least 3 to 6 months for most patients [2]. This study found an overall incidence rate of 13.2 recurrent VTEs per 100 patient-years and the rate of recurrence at 6 months (25.1 per 100 patient-years; 95% CI, 17.9–35.3%) is even higher than the recurrence rate observed in cancer patients with proximal DVT or PE [14]. Patients receiving 6 weeks of treatment were exposed to a significantly higher risk of developing recurrent VTE than patients treated for longer periods. Because of the observational design of the study, the lack of a control group and the possibility of an unbalanced distribution of VTE risk factors, these findings remain hypothesis generating. However, together with the observation of a high event rate after treatment discontinuation, these results strongly suggest that patients with active cancer and IDDVT benefit from long-term anticoagulation. As expected, patients with a previous VTE had

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an increased risk of recurrence, whereas gastrointestinal cancer appeared to have a lower risk. These associations should be interpreted with caution given the small number of patients.

The incidence of anticoagulant-related major bleeding in patients with IDDVT varied broadly from 0% to 6%, possibly as the consequence of differences in study populations, anticoagulant regimens and durations of follow-up [22]. We observed an overall low risk of anticoagulant-related major bleeding, in agreement with other studies of IDDVT [5] and with the results of a recent large randomized trial on the treatment of proximal DVT or PE in patients with cancer [14].

Our study has some limitations that deserve to be acknowledged. First, the study did not impose a specific treatment protocol for IDDVT. Over half (54%) of our patients were treated with LMWH at full therapeutic dose for 2–4 weeks followed by half-therapeutic doses according to the results of a previous study, which showed that this regimen was as effective and safe as vitamin K antagonists in patients with IDDVT [15]. However, the evidence on the efficacy and safety of this treatment regimen is limited and conflicting [23]. We were not able to confirm the efficacy of this regimen because of the significant heterogeneity of treatments in our population. Second, recurrent VTE events were not centrally adjudicated, which may have potentially resulted in an overestimation of their incidence. However, objective confirmation of all outcome events was mandatory for all centers, and this may have limited verification bias. Third, the accuracy of ultrasonography for IDDVT is significantly lower than for proximal DVT and some of the cases may represent, in fact, false positives. In addition, compression ultrasonography was not performed systematically in all centers at regular time intervals during follow-up. Although we cannot exclude that some asymptomatic IDDVT progressed to proximal DVT or PE, this risk may have been minimized by computed tomography scans ordered during follow-up by the treating oncologist to assess response to cancer treatment. Some of the recurrent events incidentally detected in the current study may in fact represent IDDVT progressions. Fourth, we restricted the number of VTE predictors by stepwise selection; however, the relatively low number of events may still be considered as a limitation of the multivariable analysis. We were not able to address the potential influence of confounders such as cancer stage or cancer progression as these data were not collected homogeneously or were not available in some centers. Fifth, our results were not adjusted for different chemotherapies because this was outside the objectives of our study. Finally, about half of the patients died during the study. Autopsy was not mandatory and it cannot be excluded that some deaths attributed to cancer progression were fatal PEs.

The strengths of this study include the large size of the population and duration of follow-up, which make this the largest cohort of active cancer patients with IDDVT. Finally, results were substantially unchanged when the potential competing risk of death was taken into account.

In conclusion, patients with cancer-associated IDDVT have a significant risk of recurrent VTE. The high incidence of recurrence both during anticoagulation and at treatment withdrawal strongly points to the need for additional studies to establish the optimal intensity and duration of treatment in these patients.

Addendum

F. Dentali and M. Di Nisio were responsible for study concept and design. F. Dentali, M. Di Nisio, S. Pegoraro, S. Barco, M. N. D. di Minno, D. Mastroiacovo, F. Pomero, C. Lodigiani, F. Bagna, M. Sartori, G. Barillari, N. Mumoli, M. Napolitano, S.M. Passamonti, R. Benedetti, and W. Ageno were responsible for acquisition of data. F. Dentali, N. Mumoli, M. Di Nisio, M. N. D. di Minno, and W. Ageno were responsible for database handling and updating. F. Dentali, M. Di Nisio, and W. Ageno were responsible for statistical analysis. F. Dentali, M. Di Nisio, and W. Ageno were responsible for drafting the manuscript. F. Dentali, M. Di Nisio and W. Ageno were responsible for interpretation of results. M. Di Nisio and F. Dentali were responsible for critical revision of the manuscript for important intellectual content. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References

1 Palareti G. How I treat isolated distal deep vein thrombosis (IDDVT). *Blood* 2014; **123**: 1802–9.
2 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE Disease: CHEST guideline and expert panel report. *Chest* 2016; **149**: 315–52.
3 Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet* 1985; **2**: 515–8.
4 Astermark J, Björgell O, Lindén E, Lethagen S, Nilsson P, Berntorp E. Low recurrence rate after deep calf-vein thrombosis with 6 weeks of oral anticoagulation. *J Intern Med* 1998; **244**: 79–82.
5 Galanaud JP, Quenet S, Rivron-Guillot K, Quere I, Sanchez Muñoz-Torrero JF, Tolosa C, Monreal M; The RIETE INVESTIGATORS. Comparison of the clinical history of symptomatic isolated distal deep-vein thrombosis vs. proximal deep vein thrombosis in 11 086 patients. *J Thromb Haemost* 2009; **7**: 2028–34.
6 Spencer FA, Kroll A, Lessard D, Emery C, Glushchenko AV, Pacifico L, Reed G, Gore JM, Goldberg RJ. Isolated calf deep vein thrombosis in the community setting: the Worcester Venous Thromboembolism study. *J Thromb Thrombolysis* 2012; **33**: 211–7.

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7 Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP; Investigators of the "Dur´ee Optimale du Traitement AntiVitamines K" (DOTAVK) Study. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; **103**: 2453–60.

8 Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, Hirsh J, Kearon C. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ* 2011; **342**: d3036.

9 Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost* 2012; **10**: 698–702.

10 Schwarz T, Buschmann L, Beyer J, Halbritter K, Rastan A, Schellong S. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. *J Vasc Surg* 2010; **52**: 1246–50.

11 Schwarz T, Schmidt B, Beyer J, Schellong SM. Therapy of isolated calf muscle vein thrombosis with low-molecular-weight heparin. *Blood Coagul Fibrinolysis* 2001; **12**: 597–59.

12 MacDonald PS, Kahn SR, Miller N, Obrand D. Short-term natural history of isolated gastrocnemius and soleal vein thrombosis. *J Vasc Surg* 2003; **37**: 523–7.

13 Schellong SM, Schwarz T, Halbritter K, Beyer J, Siegert G, Oettler W, Schmidt B, Schroeder HE. Complete compression ultrasonography of the leg veins as a single test for the diagnosis of deep vein thrombosis. *Thromb Haemost* 2003; **89**: 228–34.

14 Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA. Tinzaparin vs Warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015; **314**: 677–86.

15 Ghirarduzzi A, Camporese G, Siragusa S. A randomized, prospective, open-label study on distal vein thrombosis (low molecular weight heparin vs. warfarin for 6 weeks): the Todi study. *J Thromb Haemost* 2009;**7**(Suppl. 2; Abstr: PP-WE-403): 761.

16 Schulman S, Kearon C, on behalf of the subcommittee on control of anticoagulation of the Scientific and Standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Scientific and Standardization Committee Communication. *J Thromb Haemost* 2005; **3**: 692–4.

17 Hosmer D, Lemeshow S. *Applied Logistic Regression*, 2nd edn. New York: John Wiley & Sons, 2000.

18 Righini M, Paris S, Le Gal G, Laroche JP, Perrier A, Bounameaux H. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost* 2006; **95**: 56–64.

19 Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015; **12**: 464–74.

20 Gillet JL, Perrin MR, Allaert FA. Short-term and mid-term outcome of isolated symptomatic muscular calf vein thrombosis. *J Vasc Surg* 2007; **46**: 513–9.

21 Sartori M, Migliaccio L, Favaretto E, Palareti G, Cosmi B. Two years outcome of isolated distal deep vein thrombosis. *Thromb Res* 2014; **134**: 36–40.

22 Seinturier C, Bosson JL, Colonna M, Imbert B, Carpentier PH. Site and clinical outcome of deep vein thrombosis of the lower limbs: an epidemiological study. *J Thromb Haemost* 2005; **3**: 1362–7.

23 Masuda EM, Kistner RL, Musikasinthorn C, Liquido F, Geling O, He Q. The controversy of managing calf vein thrombosis. *J Vasc Surg* 2012; **55**: 550–6.

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