ORIGINAL ARTICLE

Impact of emergency department management of isolated superficial vein thrombosis of the lower limbs: a secondary analysis of data from the ALTAMIRA study

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Objectives. To describe the management of superficial vein thrombosis (SVT) of the lower limbs in patients treated in Spanish hospital emergency departments (EDs). To evaluate the impact of ED management of venous thromboembolic complications on outcomes and to determine the characteristics of patients who develop complications.

Methods. The retrospective multicenter ALTAMIRA study (Spanish acronym for risk factors, complications, and assessment of Spanish ED management of SVT) used recorded data for consecutive patients with a diagnosis of isolated SVT treated in 18 EDs. We gathered data on symptomatic venous thromboembolic disease (deep vein thrombosis, pulmonary embolism, or the extension or recurrence of SVT), clinically significant bleeding, and 180-day mortality. Cox regression analysis was used to explore variables associated with complications.

Results. A total of 703 patients were included. Anticoagulation was prescribed for 84.1% of the patients for a median of 30 days (interquartile range, 15-42 days); 81.3% were treated with low molecular weight heparin. A prophylactic dose was prescribed for 48% and an intermediate therapeutic dose for 52%. Sixty-four patients (9.2%) developed symptomatic thromboembolic disease within 180 days, 12 (1.7%) experienced clinically significant bleeding, and 4 (0.6%) died. Complications developed later in patients receiving anticoagulant therapy than in those not taking an anticoagulant (66 vs 11 days , *P*=.009), and 76.6% of those developing complications were not on anticoagulant when symptoms appeared. A history of thromboembolic disease was associated with developing complications (adjusted hazard ratio, 2.20; 95% confidence interval, 1.34-3.62).

Conclusions. ED treatment of SVT varies and is often suboptimal. The incidence of thromboembolic complications after SVT is high. Starting anticoagulation in the ED delays the development of complications. Patients with a history of thromboembolic disease are more at risk of complications.

Keywords: Venous thrombosis, superficial. Venous thromboembolic disease. Emergency department.

Impacto del manejo en urgencias en la evolución de los pacientes con trombosis venosa superficial aislada de miembros inferiores: subanálisis del estudio ALTAMIRA

Objetivos. Describir el manejo terapéutico de los pacientes con trombosis venosa superficial (TVS) aislada de miembros inferiores en servicios de urgencias hospitalarios (SUH) españoles. Evaluar el impacto del tratamiento instaurado en urgencias en la evolución, en términos de complicaciones de enfermedad tromboembólica venosa (ETV), y conocer las características de los pacientes que sufren complicaciones.

Método. El estudio multicéntrico (18 SUH) ALTAMIRA (fActores de riesgo, compLicaciones y evaluación del manejo de la TVS de Miembros Inferiores en hospitales españoles atendidos en los seRvicios de urgenciAs) creó un cohorte retrospectivo de pacientes consecutivos con diagnóstico objetivo de TVS aislada. Se recogieron las complicaciones de ETV sintomáticas (trombosis venosa profunda, tromboembolia pulmonar y extensión o recurrencia de TVS), sangrados clínicamente relevantes y defunciones a 180 días. Se evaluaron las variables asociadas a las complicaciones mediante una regresión de Cox.

Resultados. Se incluyeron 703 pacientes. El 84,1% recibieron anticoagulación durante 30 días (rango intercuartil 15-42), 81,3% con heparina de bajo peso molecular (48% dosis profilácticas, 52% intermedias-terapéuticas). En 180 días, 64 pacientes (9,1%) tuvieron complicación de ETV, 12 (1,7%) tuvieron sangrado clínicamente relevante, y 4 fallecieron (0,6%). Los pacientes en que se instauró anticoagulación en urgencias tardaron más tiempo en desarrollar complicaciones (66 *vs* 11 días, p = 0,009). El 76,6% de los que se complicaron no estaban anticoagulados en ese momento. La ETV previa se asoció de forma independiente con el desarrollo de complicaciones (*hazard ratio* ajustada 2,20; intervalo de confianza del 95%: 1,34-3,62).

Conclusiones. El tratamiento en urgencias de la TVS aislada es heterogéneo y con frecuencia subóptimo. La incidencia de complicaciones de ETV es elevada. El tratamiento anticoagulante iniciado en urgencias supone un retraso en el desarrollo de complicaciones. Los pacientes con ETV previa tienen más riesgo de complicaciones.

Palabras clave: Trombosis venosa superficial. Enfermedad tromboembólica venosa. Urgencias.

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Introduction

Lower limb superficial venous thrombosis (SVT) is one more manifestation of venous thromboembolism (VTE), along with the other main entities that comprise it: deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). They, therefore, share the same risk factors and are closely related.[1-4] 1 in 4 patients with lower limb DVT have concomitant DVT or PTE at diagnosis.[2]

Although isolated DVT without associated DVT is a common disease,[5] it has been less studied than DVT because it has been considered a benign disease and of little relevance.[6] Its management is controversial, and published studies yield information on a very heterogeneous treatment in real life.[7-9] There is little adherence to the recommendations of clinical practice guidelines in the diagnostic and therapeutic management of DVT.[7,10-12] Currently, the recommendations of scientific societies[13] and clinical practice guidelines[11] are to perform Doppler ultrasound in patients with DVT of the lower extremities, mainly to rule out concomitant DVT, but also to assess the involvement of the saphenous-femoral and saphenous-popliteal arch, as well as perforating veins. Patients with isolated DVT not involving the deep venous system recommend anticoagulation treatment for 45 days with fondaparinux at a prophylactic dose or, as alternative options, low-molecular-weight heparin (LMWH) at prophylactic or therapeutic doses or rivaroxaban at a prophylactic dose. The ALTAMIRA study (Risk Factors, Complications and Evaluation of the Management of Lower Limb DVT in Spanish Hospital Emergency Departments) evaluated the diagnostic and therapeutic management of patients diagnosed with DVT in Spanish hospital emergency departments (HED). A total of 1166 patients were enrolled in a retrospective cohort of routine clinical practice, of whom ultrasound was only performed to rule out DVT and confirm the diagnosis of DVT in 60.3% of patients, and anticoagulant treatment was not given in 23%.[10]

Previous observational studies in patients with isolated SVT showed a frequency of around 9-10% of symptomatic VTE complications despite a high anticoagulation initiation rate.[3,7,8,10] However, the anticoagulation therapeutic strategies in these studies were very heterogeneous in terms of intensity, duration, and molecule. The recommendations of the clinical practice guidelines are also controversial[6,11,11,14-16] and are sometimes opposed and variable, which partly explains the variability in the management of this entity.

There is little information on the therapeutic management and evolution of patients diagnosed with isolated DVT in the ED. The objectives of the study were: to obtain information on the therapeutic management in daily clinical practice and the evolution of patients who present to the ED and are diagnosed with isolated DVT, confirmed by ultrasound; to evaluate the influence of anticoagulant treatment initiated in the ED on the evolution of patients; and to determine the characteristics of patients who suffer complications of VTE during follow-up.

Methods

Patients

This study is a subanalysis of the ALTAMIRA registry. This registry recruited a retrospective, multicenter cohort with a 6-month follow-up. All patients ≥ 18 years, discharged with isolated lower limb SVT diagnosis in the 18 participating EDs between January 2016 and May 2017 were consecutively included. Patients who had or required anticoagulation therapy for any other history or pathology, including concomitant DVT or PTE diagnosis, were excluded.[10] Patients from the ALTAMIRA registry with diagnostic confirmation of isolated DVT by objective methods (compressive ultrasound performed during ED stay) were selected for this subanalysis.

The principal investigator of each center was responsible for patient inclusion based on ED discharge reports during the study period. Patient demographic characteristics (age and gender), comorbidities [arterial hypertension, diabetes mellitus, dyslipidemia, alcoholism, ischemic heart disease, stroke, peripheral artery disease, chronic obstructive pulmonary disease (COPD), sleep apnea syndrome, other pulmonary diseases (interstitial lung disease, restrictive pathology or others), rheumatologic disease], risk factors for VTE [history of VTE, thrombophilia, active cancer, major surgery in the previous 3 months, medical admission in the previous 3 months, medical admission in the previous 3 months, and risk factors for VTE [history of VTE, thrombophilia, active cancer, major surgery in the previous 3 months, medical admission in the previous 3 months, travel of more than 6 hours in the previous 2 months, hormonal treatment, pregnancy, childbirth in the previous 3 months, active smoking, immobility, history of varicose veins in lower limbs, central venous catheter carrier and obesity (body mass index-BMI > 30)] and usual medication, in the index episode of SVT (clinical symptoms and signs) and anticoagulant treatment (type, dose and duration).

Follow-up

Events during the 6 months following the diagnosis of SVT were obtained by telephone interview (after verbal consent by the patient) or consultation of the patient's medical history. The primary outcome variable was the incidence of symptomatic VTE complications, a combined variable including DVT, PTE, and extension or recurrence of SVT at the 6-month follow-up. Secondary outcome variables included the extent and recurrence of SVT, symptomatic PTE or DVT, overall mortality, and the composite of clinically relevant major or nonmajor bleeding. Bleeding complications were classified as "major" if they were overt and required transfusion of at least two units of blood; or were retroperitoneal, spinal, intracranial, or fatal. Clinically relevant nonmajor bleeding was defined as clinically evident acute or subacute bleeding that did not meet significant bleeding criteria and resulted in hospital ad-

mission for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in anticoagulation therapy due to bleeding.

Statistical analysis

Absolute and relative frequencies were used for qualitative variables. For quantitative variables, measures of central tendency and dispersion were used [mean and standard deviation (SD) or median and interquartile range (IQR), in the case of asymmetry, evaluated according to the Kolmogorov-Smirnov test]. For comparisons, the chi-square test or Fisher's exact test was used for qualitative variables, and the Student t-test or median test for quantitative variables. To investigate the influence of anticoagulant treatment on patient outcomes, the association of treatment with the development of VTE complications was evaluated by regression analysis, the median time to the complication was compared according to treatment, and survival curves to complication were constructed and compared using the log-rank statistic. A backward stepwise Cox proportional hazards model was fitted to evaluate the variables associated with the combined variable of VTE complications, which included the variables that, in the univariate analysis, obtained a $P < .10$. Differences were considered statistically significant when the p-value was less than .05. The analysis was performed with the SPSS version 25.0 statistical package.

The study was approved by the clinical research ethics committees of the participating hospitals, which granted an exemption from the requirement to obtain written informed consent from the participants. At all times, the current legislation on data protection was respected, and the national and international regulations for studies on human subjects included in the Declaration of Helsinki on Biomedical Research were complied with.

Results

Between January 2016 and May 2017, 1166 patients with a diagnosis of isolated lower limb DVT were recruited in 18 Spanish EDs. Of these, 703 had an objective diagnosis with ultrasound and were included in this analysis. The characteristics of the patients are shown in Table 1. The mean age was 61 years, 68.7% were women, 24% were obese, and 63% had varicose veins, 26.5% had a personal history of VTE, including SVT in 15.4% and DVT or PTE in 10.5%, 4.6% had active cancer. Arterial hypertension (43.7%) and diabetes mellitus (27.7%) were the most frequent comorbidities.

The median symptom duration was 4 days (IQR, 2-7), and most frequently presented as a painful leg (67.4%), painful cord (56.3%), and swollen cord (53.1%) (Table 1). Regarding the therapeutic management performed in the emergency department and during follow-up, 45.8% of the patients were indicated in the discharge report for non-pharmacological compressive treatment (stocking or bandage), and 44.8% were prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 1).

Most patients (84.1%) received anticoagulation at diagnosis of SVT in the ED (Table 2). LMWH was prescribed for initial and long-term treatment in most of them (81.3%). Almost half received prophylactic doses, and half received intermediate/therapeutic doses. Fondaparinux was administered to 6 patients (0.9%) and oral anticoagulants to 19 (2.7%). The median duration of anticoagulation treatment was 30 days (15-42). 503 patients (71.6%) received anticoagulation for more than 9 days and 126 (17.9%) for 45 days or more.

The results at 180 days are shown in Table 3. The primary variable of combined VTE complication occurred in 64 patients (9.1%), 43 (6.1%) in the first 90 days. The median time to the complication was 65 days (IQR 15-98). Recurrence of SVT was the most frequent complication and occurred in 34 (4.8%), the extension of SVT in 30 (4.3%), and DVT or PTE was diagnosed in 9 (1.3%) and 6 (0.9%) patients at 6 months, respectively. Clinically relevant bleeding occurred in 12 patients (1.7%) and major bleeding in 9 (1.3%). In total, 4 patients (0.6%) died, one due to PTE and none due to bleeding.

Variables independently associated with VTE complications are shown in Table 4. Anticoagulation therapy initiated in the emergency department was not associated with complications. However, patients who received anticoagulation at diagnosis (any type, dose, and duration) had a significantly longer median time to complication than those who were not anticoagulated [66 (IQR 21-108) vs. 11 (IQR 4.5-55.5), $P = .009$] (Table 3) and survival curves were significantly different ($P = .014$) (Figure 1). Furthermore, patients who became complicated did so while receiving anticoagulation therapy 23.4% (15 patients), whereas the majority became complicated without being anticoagulated at the time of complication [49 (76.6%) patients].

Discussion

This study shows the significant heterogeneity in treating patients with isolated lower limb DVT in Spanish EDs. Despite a high rate of initiation of anticoagulation at the time of DVT diagnosis in the ED, the development of VTE complications at the 6-month follow-up was high (9.1%). Moreover, patients who did not receive anticoagulation therapy at ED diagnosis developed complications earlier. The protective effect of anticoagulation was lost during follow-up. This result could be partially explained by poor adherence to the recommendations of international clinical practice guidelines[13,16-18] regarding the treatment received (dose, duration, and molecule).

Since 2010, five European observational studies in patients with isolated SVT have been published (Table 5).[3,7-10,11,19] In all of them, significant variability was ob-

Table 1. Patient characteristics according to the development of venous thromboembolic disease complications at 180 days

	Total N = 703 n (%)	Complications N = 64 n (%)	No complications N = 639 n (%)	*P* value
Demographic data				
Age [mean (SD)]	61 (17)	58 (17)	62 (17)	.123
Sex (female)	483 (68.7)	40 (62.5)	443 (69.3)	.261
VTE risk factors				
Previous VTE	186 (26.5)	29 (45.3)	157 (24.6)	< **.001**
TVS	108 (15.4)	16 (25)	92 (14.4)	**.025**
DVT or PTE	74 (10.5)	13 (20.3)	61 (9.5)	**.007**
Known thrombophilia	20 (2.8)	5 (7.8)	15 (2.3)	**.028**
Cancer	32 (4.6)	3 (4.7)	29 (4.5)	.572
Major surgery (previous 3 months)	50 (7.1)	2 (3.1)	48 (7.5)	.304
BMI ≥ 30 Kg/m^2	170 (24.2)	16 (25)	154 (24.1)	.879
Medical hospital admission (3 previous months)	40 (5.7)	4 (6.2)	36 (5.6)	.777
Prolonged travel (> 6 hours)	8 (1.1)	4 (6.2)	4 (0.6)	**.003**
Hormone replacement therapy	35 (5)	3 (4.7)	32 (5)	.603
Pregnancy	16 (2.3)	0 (0)	16 (2.5)	.385
Puerperium	10 (1.4)	0 (0)	10 (1.6)	.611
Active smoker	100 (14.2)	12 (18.8)	88 (13.8)	.264
Immobility	84 (11.9)	9 (14.1)	75 (11.7)	.547
Varicose veins	444 (63.2)	41 (64.1)	403 (63.1)	.495
Central venous catheter	3 (0.4)	0 (0)	3 (0.5)	.751
Comorbidities				
Arterial hypertension	307 (43.7)	29 (45.3)	278 (43.5)	.830
Diabetes mellitus	195 (27.7)	25 (39.1)	170 (26.6)	**.040**
Dyslipidemia	80 (11.4)	7 (10.8)	73 (11.4)	1,000
Alcoholism	34 (4.8)	4 (6.2)	30 (4.7)	.540
Ischemic heart disease	26 (3.7)	0 (0)	26 (4.1)	.158
Stroke	17 (2.4)	2 (3.1)	15 (2.3)	.662
Peripheral arterial disease	16 (2.3)	2 (3.1)	14 (2.2)	.650
COPD	25 (3.6)	1 (1.6)	24 (3.8)	.719
OSA	29 (4.1)	0 (0)	29 (4.5)	.099
Other pulmonary diseases	35 (5)	9 (14.1)	26 (4.1)	**.003**
Rheumatologic disease	53 (7.5)	8 (12.5)	45 (7)	.132
Usual treatment				
Antiaggregation	109 (15.5)	10 (15.6)	99 (15.5)	1,000
Statins	139 (19.8)	14 (21.9)	125 (19.6)	.624
ACE inhibitors	113 (16.1)	14 (21.9)	99 (15.5)	.210
ARBs- II	99 (14.1)	10 (15.6)	89 (13.9)	.706
Beta-blockers	60 (8.5)	7 (10.9)	53 (8.3)	.479
Antidepressants	87 (12.4)	11 (17.2)	76 (11.9)	.231
Corticosteroids	28 (4)	2 (3.1)	26 (4.1)	1,000
NSAIDs	32 (4.6)	7 (10.9)	25 (3.9)	**.020**
Symptoms and complementary tests				
Swollen cord	373 (53.1)	27 (42.2)	346 (54.1)	.087
Erythematous cord	270 (38.4)	19 (29.7)	251 (39.3)	.140
Painful cord	396 (56.3)	33 (51.6)	363 (56.8)	.431
Bilateral SVT	17 (2.4)	2 (3.1)	15 (2.3)	.647
Diameter enlargement	226 (32.1)	22 (34.4)	204 (31.9)	.676
Limb swelling	133 (18.9)	9 (14.1)	124 (19.4)	.402
Cutaneous erythema	313 (44.5)	27 (42.2)	286 (44.8)	.398
Extremity pain	474 (67.4)	44 (68.8)	430 (67.3)	.467
Increase in Temperature	277 (39.3)	33 (51.6)	244 (38.2)	**.044**
Other treatments (alternative to anticoagulation)				
Compression therapy	322 (45.8)	36 (56.2)	286 (44.8)	.088
NSAIDs	315 (44.8)	27 (42.2)	288 (45.1)	.694
Antibiotic	105 (14.9)	13 (20.3)	92 (14.4)	.201
Anti-aggregation	12 (1.7)	3 (4.7)	9 (1.4)	.087
Analgesia	238 (33.9)	22 (34.4)	216 (33.8)	.514
Topical treatment	155 (22)	15 (23.4)	140 (21.9)	.753

SD: standard deviation; VTE: venous thromboembolic disease; SVT: superficial venous thrombosis; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; BMI: body mass index; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea syndrome; NSAIDs: nonsteroidal anti-inflammatory drugs; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs-II: aldosterone receptor antagonists and blockers.
Values in bold denote statistical significance ($P < .05$).

Table 2. Anticoagulant treatment according to the development of complications of venous thromboembolic disease at 180 days

	Total N = 703 n (%)	Complications N = 64 n (%)	No complications N = 639 n (%)	*P* value
Total anticoagulation	591 (84.1)	55 (85.9)	536 (83.9)	.858
LMWH	581 (82.6)	53 (82.8)	528 (82.6)	**.020**
Prophylactic dose	279 (48)	17 (32)	262 (49.6)	
Intermediate/therapeutic dose	302 (52)	36/53 (67.9)	266 (50.4)	
Oral anticoagulation (VKA/DOACs)	19 (2.7)	2 (3.1)	17 (2.7)	.689
Fondaparinux	6 (0.8)	0 (0)	6 (0.9)	–
Days of anticoagulation [median (IQR)]	30 (15-42)	30 (15-30)	30 (14-42)	.906
Duration of anticoagulation ≥ 10 days	503 (71.6)	49 (76.6)	454 (71)	.351
Anticoagulation at the time of the complication	15 (2.1)	15 (23.4)	–	–

VTE: venous thromboembolic disease; VKA: vitamin K antagonists; LMWH: low-molecular-weight heparin; VTE: venous thromboembolic disease; IQR: interquantile range; DOACs: direct-acting oral anticoagulant.
Bolded values denote statistical significance ($P < .05$).

Table 3. Complications of venous thromboembolic disease at 180 days according to anticoagulant therapy

	Total N = 703 n (%)	Anticoagulants N = 591 n (%)	Not anticoagulated N = 112 n (%)	*P* value
VTE complication at 90 days	43 (6.1)	36 (6.1)	7 (6.2)	.543
VTE complication at 180 days	64 (9.1)	55 (9.3)	9 (8)	.858
Days to complication Median (IQR)	58.5 (15.5-97.8)	66 (21-108)	11 (4.5- 55.5)	**.009**
SVT extension	30 (4.3)	23 (3.9)	7 (6.2)	.303
SVT recurrence	34 (4.8)	30 (5.1)	4 (3.6)	.635
DVT	9 (1.3)	9 (1.5)	0 (0)	.368
PTE	6 (0.9)	5 (0.8)	1 (0.9)	.648
Clinically relevant bleeding	12 (1.7)	9 (1.5)	3 (2.7)	.418
Major hemorrhage	9 (81.8)	7 (87.5)	2 (66.7)	.491
Mortality (any cause)	4 (0.6)	3 (0.5)	1 (0.9)	.501

VTE: venous thromboembolic disease; IQR: interquartile range; SVT: superficial venous thrombosis; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism.
Values in bold denote statistical significance ($P < .05$).

served in terms of anticoagulation therapy and with disparate results. The overall complication rates of symptomatic VTE (extension or recurrence of DVT, DVT, or PTE) at 3 months, despite most receiving anticoagulation therapy with an unstable molecule, dose, and duration, ranged from 3.0%[19] to 9.6%.[8] In the ICARO study, the annual incidence rate of DVT or PTE at 3-year follow-up was 3.9%, and for recurrence of DVT, 7.9%.[8]

Table 4. Variables independently associated with venous thromboembolic disease complications at 180 days*

Variable	HR (95% CI)	Adjusted HR (95% CI)	*P* value
Previous VTE	2.38 (1.46-3.89)	2.19 (1.33-3.61)	**.002**
Prolonged travel (> 6 hours)	8.01 (2.91-22.08)	8.73 (3.10-24.60)	< **.001**
Pulmonary pathology (non-COPD)	3.47 (1.71-7.02)	2.73 (1.34-5.59)	**.006**
NSAIDs previous treatment	2.77 (1.26-6.08)	2.63 (1.19-5.80)	**.016**
Raise in the extremity's skin temperature	1.67 (1.02-2.73)	1.64 (0.98-2.64)	.062
Swollen cord	0.64 (0.39-1.04)	0.65 (0.39-1.07)	.087

*Only those variables that remained in the final Cox model are included in the table.
COPD: chronic obstructive pulmonary disease; NSAIDs: nonsteroidal anti-inflammatory drugs; CI: confidence interval; VTE: venous thromboembolic disease; HR: hazard ratio.
Bolded values denote statistical significance ($P < .05$).

In this prospective study, it was observed that the annual incidence rate of complication in the form of DVT or PTE significantly increased when patients stopped re-

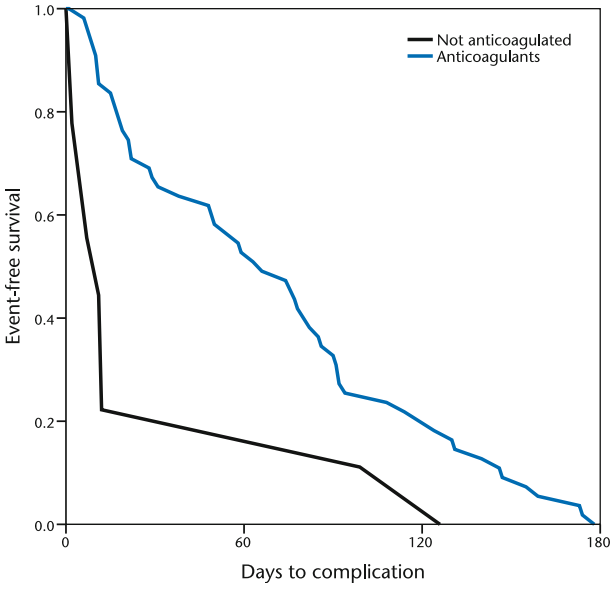

Figure 1. Complication of venous thromboembolic disease as a function of anticoagulant treatment in the emergency department for those patients who presented the complication.

Table 5. European observational studies of patients with isolated superficial venous thrombosis of the lower limbs

Study	Country	Publication year	Number of patients included	Type of study	Complication Incidence	Type of follow-up	Development of DVT	Development of PTE
POST[3]	France	2010	600	Prospective	8.3%	3 months	2.8%	0.5%
OPTIMEV[19]	France	2011	561	Prospective	3%	3 months	0.6%	0.6%
PERSEUS[9]	France	2017	978	Prospective	3.3% grupo fondaparinux 5.5% grupo LWMH/UFH	3 months	0.4% grupo fondaparinux 0.2% grupo LWMH/UFH	0%
ICARO[8]	Italy	2017	411	Prospective	31.9%	34.2 months	12.7%	2.9%
INSIGHTS-SVT[7]	Germany	2021	918	Prospective	5.8%	3 months	1.7%	0.8%
ALTAMIRA[10]	Spain	2022	703	Retrospective	9.1%	6 months	1.3%	0.9%

SVT: superficial venous thrombosis; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

ceiving anticoagulation: 1.3% vs. 4.4% in patients with and without anticoagulation therapy, respectively.8 In the present study, a similar effect of treatment was observed since most patients (76.6%) who suffered a VTE complication during follow-up did so without receiving anticoagulation treatment at that time.

Furthermore, patients who received anticoagulant treatment at ED diagnosis, regardless of type, dose, and duration, presented the complication later than those who never received anticoagulation (11 vs. 66 days). However, the development of complications after discontinuation of anticoagulation treatment had no effect on the overall incidence of complications. This effect, known as catch-up, is because patients who do not develop complications during treatment because they are protected with anticoagulation develop them upon withdrawal from such treatment. This phenomenon has been described in other settings, such as idiopathic VTE,[20] and observed in clinical trials evaluating different LMWH regimens for isolated SVT.[21-23] In all of them, an increase in the incidence of complications after discontinuation of anticoagulation was demonstrated.

In contrast, in the CALISTO trial, which evaluated prophylactic doses of fondaparinux versus placebo for 45 days in patients with isolated SVT, no such effect was observed after treatment discontinuation. However, the patients included were at low risk of complications, with an incidence of 5.9% at 90 days in the placebo group but 0.9% in the fondaparinux group ($P < .001$).[24] The SURPRISE trial was a randomized non-inferiority study that evaluated prophylactic doses of rivaroxaban vs. fondaparinux for 45 days and included patients with a high-risk profile for complications. In contrast to the CALISTO trial, a similar incidence of complications was found in both arms at 7% at 90 days, despite treatment. Again, this study observed an increased incidence of complications after discontinuing anticoagulation therapy at 45 days.[25]

The high incidence of complications despite establishing anticoagulant therapy in most patients at diagnosis raises different reflections.[3,8] On the one hand, the importance of adherence to treatment recommendations. Due to the results of the CALISTO trial, fondaparinux at a prophylactic dose for 45 days is the treatment suggested by the main clinical practice guidelines for treating isolated DVT of the lower extremities.[11,15,18]

In the present study, 15.9% of the patients did not receive anticoagulant treatment at any time, 37.9% of the patients who received anticoagulant treatment did so for less than 30 days, less than 1% were treated with fondaparinux, and the doses of LMWH were heterogeneous (48% prophylactic and 52% intermediate-therapeutic). On the other hand, given the high incidence of complications also observed in studies such as SURPRISE or INSIGHTS-SVT, in patients treated for 45 days with prophylactic doses of rivaroxaban or fondaparinux, optimal treatment for all patients with isolated SVT may not yet be available.

In the present study, as in SURPRISE, ICARO, and other previous trials with LMWH,[21-23,26] there is an increased incidence of complications on discontinuing anticoagulation therapy, so prolonged anticoagulation may be necessary for some patients to maintain protection. Inflammation of the vessel wall plays an essential role in the pathophysiology of SVT, which may require more treatment time for its restoration or the need for other concomitant therapies.[12,13] In this regard, in the INSIGHTS-SVT study, the duration of anticoagulant therapy was significantly and independently associated with the development of complications (adjusted hazard ratio -HRa- 0.92 per week).[7] Finally, it is crucial to know the risk factors associated with the development of complications in patients with isolated SVT, as this could help to optimize the treatment (type, dose, and duration) appropriate for each patient.

In this regard, the patients who presented complications were somewhat younger and had a higher percentage of men, although this difference was not statistically significant. In the ICARO study, it was observed that male patients had a higher risk of complications (HRa 2.03) and active solid cancer (HRa 3.14).[8] In the present study, there was a similar overall frequency of cancer, but it was not associated with complications. In the INSIGHTS-SVT study, age was inversely associated with the risk of complications (HRa 0.97 per year) and the history of previous SVT (HRa 2.3), the duration of anticoagulant treatment and thrombus length (HRa 1.03).[7]

In the present study, a history of VTE was associated with the development of complications, similar to previ-

ous studies (HRa 2.20). Almost half of the patients with a complication had a previous VTE (25% DVT and 20.3% DVT and PTE). Other variables associated with complications were prolonged travel (> 6 hours), pulmonary pathology (non-COPD), previous treatment with NSAIDs, and increased extremity temperature. The inflammatory process associated with thrombosis in the pathogenesis of SVT may influence the evolution of the patients so that those who required NSAIDs and those who presented increased temperature as a symptomatological manifestation may be at greater risk of presenting complications during follow-up. Likewise, patients who present an episode of VTE, generally associated with prolonged travel, have baseline characteristics of a higher risk of thrombosis (unknown thrombophilia, obesity, chronic venous insufficiency, varicose veins) and, therefore, a higher risk of complications in the evolution.

This study has the following limitations. First, as this is a retrospective study, some baseline characteristics could be underestimated, such as the presence of chronic venous insufficiency-varicose veins (a variable collected from ED discharge reports) or other risk factors. Secondly, given that ALTAMIRA is an observational study, the treatment of SVT was not homogeneous but according to the usual clinical practice of each center. Third, only symptomatic VTE complications were recorded since no systematic ultrasound was performed on patients during follow-up. However, the results obtained were similar to other previous prospective observational studies. Fourth, in many cases, the ultrasound confirming the diagnosis of SVT did not provide information on the characteristics of the thrombus (distance to the arch, length, or involvement of perforating veins), although in all cases, concomitant DVT was ruled out. Finally, due to the study design, it should be considered only as hypothesis-generating. Nevertheless, this is the first multicenter study with a large number of patients with objectively confirmed isolated lower limb DVT from the perspective of the ED, a critical setting for the diagnostic and therapeutic management of this disease.[27-30]

In conclusion, emergency department management of patients with isolated SVT is heterogeneous and often suboptimal. The incidence of VTE complications is high, despite initiating anticoagulant therapy in most patients at diagnosis. Anticoagulant therapy initiated in the emergency department significantly delays the development of complications. Patients with a history of previous VTE are at higher risk of complications. There is room for improvement in adherence to the recommendations of clinical practice guidelines. Studies are needed to help identify those patients with a higher risk of complications and who may benefit from more intense anticoagulant therapy in terms of dose or duration.

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