A systematic review and meta-analysis for the association between duration of anticoagulation therapy and the risk of venous thromboembolism in patients with lower limb superficial venous thrombosis

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ABSTRACT

Objective: The aim of this study was to determine the association between the duration of systemic anticoagulation therapy (ACT) and the risk of further venous thromboembolism (VTE) in patients with superficial venous thrombosis (SVT).

Methods: A systematic review and meta-analysis were performed using searches of Medline and Cochrane Library databases in September 2023. Papers that provided VTE incidence within mid-term follow-up of ≥45 days in patients who received any ACT were included. Patients were categorized into subgroups according to the course of treatment: (1) no ACT (0 days); (2) ACT of ≤14 days; (3) ACT of 15 to 30 days; (4) ACT of 31 to 45 days; and (5) ACT of >45 days. Reported events were transformed to events per 100 patient-years, and a random-effects model was used to calculate pooled rates for proportions. The primary outcome (VTE) was a combination of SVT progression or recurrence with the occurrence of deep vein thrombosis (DVT) and pulmonary embolism (PE). Secondary outcomes included major and clinically relevant non-major or minor bleeding.

Results: Twenty-four studies (10 randomized controlled trials and 14 cohort studies) combining outcomes in 12,341 patients were included in the quantitative synthesis. Minimum VTE and SVT recurrence or progression rates were observed with the ACT duration of 31 to 45 days of 16.2 (95% confidence interval [CI], 10.4-23.3) and 8.2 (95% CI, 3.1-15.8) events per 100 patient-years, respectively. Minimum DVT and PE rates observed with the treatment duration of 15 to 30 days were 5.5 (95% CI, 2.8-9.1) and 0.9 (95% CI, 0.5-1.3) events per 100 patient-years, respectively. Short-term treatment of ≤14 days was associated with the highest rates of VTE of 59.7 (95% CI, 37.7-86.4), DVT of 13.7 (95% CI, 9.6-18.4), and PE of 3.1 (95% CI, 1.4-5.6) events per 100 patient-years. Major bleeding rates were unrelated to the duration of ACT and did not exceed 0.5 events per 100 patient-years. The highest rate of clinically relevant non-major or minor bleeding was observed with ACT duration of 31 to 45 days of 14.2 (95% CI, 5.5-26.8) events per 100 patient-years. The most common risk factors for VTE included male sex, cancer, personal history of DVT, PE, or SVT, and thrombosis of non-varicose veins.

Conclusions: Prolonged systemic anticoagulation is associated with the tendency to decrease VTE rates in patients with lower limb SVT. (J Vasc Surg Venous Lymphat Disord 2024;12:101726.)

Keywords: Anticoagulation; Superficial vein thrombosis; Treatment; Venous thromboembolism

Superficial venous thrombosis (SVT) of lower limbs, also known as superficial thrombophlebitis, has been considered a self-limited benign disorder for a long time, with an incidence rate of 0.6 to 1.3 SVT events per 1000 patient-years.[1-3] However, emerging evidence suggests a high prevalence of concurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in 18% and 7% of all patients with SVT, respectively.[4] The cohort studies with a mid-term follow-up of 3 months showed an occurrence of further venous thromboembolism (VTE), including SVT progression or recurrence, new DVT, and/or PE in 3% to 10% of all patients.[5-7] In the long-term follow-up, a history of SVT has shown an association with a VTE risk increase of 5.4 to 8.6 times, and the risk of VTE recurrence after SVT is similar to proximal DVT.[8-10] All such findings suggest SVT should be combined with DVT and PE into the group of VTE and be treated with anticoagulation, as stated in the recent guidelines.[11,12] The previous meta-analysis included different SVT treatment approaches (nonsteroidal anti-inflammatory drugs [NSAIDs], unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, rivaroxaban, warfarin, surgery, and no therapy)

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and showed that anticoagulation is associated with minimal events rate of further VTE.[13] However, no standard anticoagulation type, dose, and duration were described. Although emerging evidence suggests a further increase of VTE rate by 50% to 70% after 45 days of anticoagulation in high-risk patients,[14] a knowledge gap has been found on the association of prolonged anticoagulation with VTE risk in individuals with SVT. This study aims to address this gap.

METHODS

The primary objective of this systematic review was to estimate the rate of VTE development during mid-term follow-up in patients with lower limb SVT without DVT and PE who received any systemic anticoagulation according to the treatment duration. Following the Patient, Intervention, Comparison, Outcome (PICO) rule, the main question was: "How does the duration of anticoagulation therapy impact the risk of venous thromboembolism in patients with superficial vein thrombosis of lower limbs within mid-term follow-up?" The systematic review protocol, including all planned analyses, was registered a priori through PROSPERO, an international database of prospectively registered systematic reviews in health and social care (CRD42021271486).

Search strategy. An electronic Medline and Cochrane Library search was done on September 1, 2023. It was performed according to the pre-specified strategy and keywords. Search terms for PubMed: ((("thrombophlebitis"[MeSH Terms]) OR (superficial vein thrombosis)) OR (superficial thrombophlebitis)) AND ("anticoagulants"[MeSH Terms]); search terms for Cochrane Library: ("superficial venous thrombosis"):ti,ab,kw OR ("thrombophlebitis"):ti,ab,kw AND ("anticoagulant therapy"):ti,ab,kw OR ("anticoagulation"):ti,ab,kw OR ("anticoagulant"):ti,ab,kw). Additionally, lists of references of the relevant publications and personal archives of the authors were screened for any complementary information. The search was restricted by language (English) but not publication date. No additional search was done for unpublished or preprint data, conference abstracts, and other papers not indexed.

References and titles were screened manually without any software. Two reviewers (I.S. and A.B.) independently screened the records for inclusion and exclusion criteria and selected eligible papers. Two reviewers (K.L. and E.D.) independently extracted data from the relevant articles, and the third (I.S.) checked accuracy. A collective discussion among all authors resolved any disagreements between the two reviewers. All relevant information was extracted according to the pre-specified plan through the Excel spreadsheet.

Full-text articles were chosen for the final analysis according to several criteria: (1) reports on unselected patients with symptomatic lower limb SVT without DVT and PE objectively confirmed by duplex ultrasound scan (DUS) in either a prospective cohort (PC), retrospective cohort (RC) study, or randomized controlled trial (RCT); (2) reported treatment with systemic anticoagulation of any type (UFH, LMWH, fondaparinux, vitamin K antagonist [VKA], direct oral anticoagulants), dose, and duration; (3) follow-ups of patients for no less than 45 days; and (4) objectively confirmed VTE event as an absolute number of patients or percentage during the follow-up period. Studies were excluded based on several criteria: (1) primary SVT was not confirmed; (2) known combination of patients with upper and lower limb SVT without providing separate outcomes for lower limb SVT; (3) did not identify the type, dose, and/or duration of anticoagulant therapy; (4) followed patients less than 45 days or did not report the duration of observation; (5) primary outcome was not confirmed; (6) primary outcome was not reported in relation with ACT duration; (7) not original research; (8) case report; and/or (9) not in English. The studies were also checked for data duplication and excluded if population overlap was identified. Among those, a more detailed paper was included.

The systematic review results were reported according to the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA).[15]

Outcome measures. The primary outcome was designed as any new VTE event that combined symptomatic or asymptomatic SVT progression or recurrence and development of new DVT or PE within a mid-term follow-up ≥45 days. The number of VTE events was calculated manually when individual outcomes were reported or used according to the definition of the original trial. The duration of follow-up was calculated from the diagnosis of SVT and the initiation of treatment, which usually does not match the time of symptom onset. Any of the appropriate imaging should have confirmed outcomes: (1) DUS for the symptomatic and asymptomatic SVT; (2) DUS or phlebography for symptomatic or asymptomatic DVT; and (3) pulmonary angiography or computed tomography pulmonary angiography or ventilation-perfusion scintigraphy for symptomatic PE. The diagnosis, codes, and/or prescription of anticoagulants were also suggested as a form of VTE confirmation in the individual retrospective cohort studies. Secondary outcomes included the components of the primary that were assessed separately: (1) SVT progression or recurrence; (2) new DVT; and (3) PE. The definition of every outcome was used according to the individual study. Also, (4) major bleeding and (5) clinically relevant non-major (CRNM) or minor bleeding, according to the criteria of original studies, were assessed as secondary outcomes.

As pre-specified, outcomes were measured in the different subgroups of patients according to the duration of anticoagulation: (1) ≤14 days; (2) 15 to 30 days; (3) 31 to

45 days; or (4) >45 days. These time intervals were suggested according to the most commonly used period of anticoagulation in the relevant papers. The duration was considered as an intention to treat in the randomized controlled trial and as treated in the cohort trials. If different courses of anticoagulation were reported separately, they were analyzed within the matched subgroups. Otherwise, the whole cohort was analyzed according to the mean or median duration. The use of a placebo in an RCT or absence of anticoagulation in most of the cohort (>90%) was considered as no treatment and was analyzed within a separate subgroup (0 days).

Assessment of study quality. The quality of the RCTs was evaluated using the Cochrane Risk of Bias assessment tool.[16] The quality of observational studies was evaluated using the Newcastle-Ottawa Assessment scale for cohort studies.[17] Two reviewers (K.L. and E.D.) assessed study quality independently, and a collective discussion of all authors resolved disagreements. A funnel plot analysis with Egger's test was performed to assess for publication bias.

Strategy of data synthesis. Individual study events were converted to rates per patient-month by estimating the total observation period as the number of patients multiplied by the duration of follow-up. This calculation allowed for a better comparison of studies with different observation periods. The unit of 1 month was chosen due to a low number of participants with short follow-ups reported in some studies, so the number of events exceeded the patient-years and made the analysis of proportions impossible. Event rates were pooled using a pooled proportion meta-analysis with a random-effects model. The final results were translated to patient-years by multiplying patient-months by 12 and were represented with a weighted mean proportion with 95% confidence intervals (CIs) as per 100 patient-years. All analyses were performed using MedCalc statistical software (MedCalc Software Ltd; 2021). Data were analyzed as intention-to-treat, per-protocol, or as-treated according to the original publication. The χ^2 test and I^2 statistic were used to estimate heterogeneity. Heterogeneity was considered high if the χ^2 value of $P < .05$ or $I^2 > 50\%$.

RESULTS

Search results. The initial search identified 20,499 records, and two additional papers were found by screening the reference lists of related articles. Only 24 were eligible and combined for the analysis (Supplementary Fig 1, online only). The quantitative synthesis included 10 randomized controlled trials,[14,18-26] and 14 cohort studies[3,5,27-38] containing data on 13,194 patients who received different treatments. The study by Karathanos et al was duplicated: the earlier paper represented a separate analysis of different outcomes (SVT progression or recurrence, DVT, and PE) according to the duration of anticoagulation, whereas the latest extended version allowed extraction of only combined results on VTE.[34,35] So, both versions were included in the analysis of different outcomes. The results of the INSIGHTS-SVT trial were also published in two papers, but the latest one with extended follow-up was included.[7,38]

The results of anticoagulation treatment were obtained from 12,341 patients who were followed for 63,015 patient-months or 5271 patient-years. The duration of anticoagulation varied from 3 to 200 days, and the follow-up time ranged between 74 and 1026 days, with a mean of 169 days. The mean age of patients was 59 years; varicose veins were reported in 66%, personal history of SVT in 19%, personal history of DVT and PE in 8%, family history of VTE in 6%, cancer in 4%, and thrombophilia in 2% of all participants. Detailed characteristics of the studies are presented in Tables I and II, and Supplementary Table I (online only).

Six studies included patients who did not use anticoagulants. They were placebo groups in the STENOX[19] and CALISTO trials[22] and an RCT by Kearon et al[26] that compared rivaroxaban (10 mg) with placebo. Two retrospective cohort studies with the assessment of medical records for diagnosis codes, disease-related free text, and anticoagulants that were prescribed in <10% of patients with established SVT without DVT and PE were also included. Geersing et al analyzed a database of general practitioners to identify patients seeking care for SVT.[3] Still, they could not extract any information on the thrombus localization, so the combined data was used for the synthesis. In contrast, Samuelson et al reported separate results for SVT of lower extremities, accounting for 61% of the cohort.[30] However, they presented only the total number of VTE events without clarification of DVT and PE. In the prospective cohort study INSIGHTS-SVT, 6.7% of patients did not receive anticoagulation, whereas separate outcomes of VTE were available for analysis.[38]

In four studies, patients received anticoagulation for ≤14 days. In two RCTs, treatment with LMWH was designed for 7 to 14 days and compared with NSAIDs and placebo.[19,23] In the STEFLUX randomized controlled trial, one of three groups received an intermediate dose of LMWH for only 10 days, followed by a placebo for additional 20 days.[24] In the prospective observational trial (POST), almost all patients received treatment with therapeutic (63%) or prophylactic (37%) doses of LWMH for a median of 11 days.[5] Therapy with VKA was continued for a mean of 81 days in a limited number of patients (17%). Thus, these participants were considered as having a short-term treatment of ≤14 days. The authors did not present the localization of asymptomatic VTE detected by DUS at 8 to 14 days follow-up, so the total number of VTE did not match their localization.

Table I. Summary of included studies

Author	Design	Total number of patients	Comparison	Anticoagulation duration, days	Follow-up duration, days	VTE imaging	Reporting of asymptomatic VTE
Marchiori A et al, 2002[18]	RCT	60	UFH high/ intermediate vs prophylactic dose	28	180	Serial DUS up to 90 days	SVT, DVT
STENOX, 2003[19]	RCT	427	Enoxaparin therapeutic or prophylactic dose vs tenoxicam vs placebo	8-12	97	Serial DUS and CTPA, V/Q, PA for symptomatic PE	SVT, DVT
Lozano FS et al, 2003[20]	RCT	60	Enoxaparin high/ intermediate dose vs high ligation	28	180	DUS	N/A
Prandoni P et al (VESALIO), 2005[21]	RCT	164	Nadroparin high/ intermediate vs prophylactic dose	30	90	Serial DUS	SVT, DVT
Decousus H et al (CALISTO), 2010[22]	RCT	3002	Fondaparinux prophylactic dose vs placebo	45	77	DUS, V/Q, CTPA, PA, autopsy if symptomatic patients	No
Rathbun SW et al, 2012[23]	RCT	72	Dalteparin high/ intermediate dose vs ibuprofen	7-14	90	DUS or V/Q or CTPA if symptomatic	No
Cosmi B et al (STEFLUX), 2012[24]	RCT	664	Parnaparin intermediate or prophylactic dose for different duration	10-30	93	Serial DUS at 30 days; at 90 days on physician's decision	SVT, DVT
Spirkoska A et al, 2015[25]	RCT	68	Dalteparin intermediate vs prophylactic dose	42	180	Serial DUS at 6 weeks, 3 and 6 months	SVT, DVT
Beyer-Westendorf J et al (SURPRISE), 2017[14]	RCT	472	Rivaroxaban prophylactic vs fondaparinux prophylactic doses	45	90	DUS, phlebography, V/Q, CTPA, PA if symptomatic	No
Kearon C et al, 2020[26]	RCT	85	Rivaroxaban prophylactic vs placebo	45	90	DUS at 7 das as recommended	SVT, DVT
Ascer E et al, 1995[27]	PC	20	IV UFH followed by warfarin	42	150	Serial DUS within 2-4 days, 2 weeks, and 8 months	SVT, DVT
Gorty S et al, 2004[28]	PC	60	LMWH switched to OAC	62	74	Serial DUS	SVT, DVT
Decousus H et al (POST), 2010[22]	PC	844	Anticoagulation in 91% of patients by predominantly therapeutic (63%) or prophylactic (37%) doses of LWMH	11	90	Serial DUS at 8-14 days	SVT, DVT
Sartori M et al, 2016[29]	PC	678	LMWH therapeutic followed by an intermediate dose	30	90	Objectively confirmed if symptomatic	No

Table I. Continued.

Author	Design	Total number of patients	Comparison	Anticoagulation duration, days	Follow-up duration, days	VTE imaging	Reporting of asymptomatic VTE
Samuelson B et al, 2016[30]	RC	329	LMWH or warfarin was provided in the minority of patients (4.3%)	0	365	Reported in the medical records	No
Blin P et al, 2017[31]	RC	978	Fondaparinux or LMWH in different doses and duration	34 ± 18 or 19 ± 27	90	DUS if symptomatic	No
Barco S et al (ICARO), 2017[32]	RC	411	LMWH predominantly in prophylactic or intermediate dose	30	1026	Objectively confirmed if symptomatic	No
Gouveia S et al, 2018[33]	RC	60	Enoxaparin prophylactic or intermediate dose in obese	42	84	Objectively confirmed if symptomatic	No
Geersing GJ et al, 2018[3]	RC	2008	LMWH was provided in the minority of patients (7.3%)	0	90	Reported in the medical records	No
Karathanos C et al (SeVEN), 2021[34]	PC	660	Tinzaparin intermediate dose	14-120 (30)	90	Serial DUS at 1 month	SVT, DVT
Karathanos C et al (SeVEN), 2023[35]	PC	956	Tinzaparin intermediate doses of different duration	3-200 (30)	90	Serial DUS at 1 month and phone call at 3 months	SVT, DVT
Clapham R et al, 2022[36]	RC	54	Rivaroxaban prophylactic dose	42	90	Symptomatic reported in the medical records, no information on imaging	No
Casian D et al, 2022[37]	RC	190	Open or endovascular surgery or anticoagulation of different types, doses, and duration	28	180	Serial DUS at 2 weeks and 1 month; DUS afterward if symptomatic	SVT and DVT
Rabe E et al (INSIGHTS-SVT), 2023[38]	PC	872	Fondaparinux, LMWH, and other anticoagulants in different doses and duration or no anticoagulation	34.9 ± 15.7 or 26.2 ± 23.2 or 35-43	374	DUS on physicians' decision	SVT

CTPA, Computed tomography pulmonary angiography; *DUS*, duplex ultrasound scan; *DVT*, deep vein thrombosis; *LMWH*, low-molecular-weight heparin; *N/A*, non-available; *OAC*, oral anticoagulant; *PA*, pulmonary angiography; *PC*, prospective cohort; *PE*, pulmonary embolism; *RC*, retrospective cohort; *RCT*, randomized controlled trial; *SVT*, superficial vein thrombosis; *UFH*, unfractionated heparin; *V/Q*, ventilation-perfusion scintigraphy; *VTE*, venous thromboembolism.

Eleven studies reported the use of anticoagulants for 15 to 30 days. Three RCTs were designed to use LMWH or UFH for 28 to 30 days while comparing different regimens or in comparison with surgical treatment.[18,20,21] In the STEFLUX study, two of three groups received either prophylactic or intermediate doses of parnaparin for 30 days, and these two groups were combined for the analysis.[24] One prospective and one retrospective cohort trial assessed outcomes of SVT treatment with different doses of LMWH for 30 days.[29,32] In the prospective cohort study by Casian et al, open or endovascular surgery was compared with administration of different

Table II. Risk profile of the included patients

Author	Mean age, years	Varicose veins, no. (%)	History of SVT, no. (%)	History of DVT/PE, no. (%)	Family history of VTE, no. (%)	Cancer, no. (%)	Thrombophilia, no. (%)
Marchiori et al, 2002[18]	62	37 (61.7%)	9 (15.0%)	7 (11.7%)	N/A	5 (8.3%)	N/A
STENOX, 2003[19]	62	N/A	N/A	62 (14.5%)	N/A	6 (1.4%)	N/A
Lozano et al, 2003[20]	59	49 (81.7%)	29 (48.3%)	N/A	N/A	N/A	N/A
Prandoni et al (VESALIO), 2005[21]	63	100 (61.0%)	N/A	N/A	N/A	N/A	N/A
Decousus et al (CALISTO), 2010[22]	57	2660 (88.6%)	356 (11.9%)	209 (7.0%)	N/A	61 (2.0%)	38 (1.3%)
Rathbun et al, 2012[23]	51	32 (44.4%)	7 (9.7%)	5 (6.9%)	N/A	7 (9.7%)	N/A
Cosmi et al (STEFLUX), 2012[24]	63	498 (75.0%)	191 (28.8%)	58 (8.7%)	78 (11.7%)	N/A	31 (4.7%)
Spirkoska et al, 2015[25]	60	0 (0%)	N/A	N/A	N/A	3 (5.0%)	N/A
Beyer-Westendorf et al (SURPRISE), 2017[39]	61	330 (69.9%)	229 (48.5%)		N/A	55 (11.7%)	N/A
Kearon C et al, 2020[26]	59	58 (68.2%)	25 (19.4%)	8 (9.4%)	N/A	2 (2.4%)	N/A
Ascer et al, 1995[27]	63	10 (50.0%)	4 (20.0%)	0 (0%)	N/A	N/A	N/A
Gorty et al, 2004[28]	52	48 (80.0%)	24 (40.0%)	10 (16.7%)	N/A	4 (6.7%)	12 (20.0%)
Decousus et al (POST), 2010[5]	65	690 (81.8%)	285 (33.8%)	120 (14.2%)	206 (24.4%)	93 (11.0%)	48 (5.7%)
Sartori et al, 2016[29]	65	430 (63.4%)	N/A	N/A	N/A	36 (5.3%)	N/A
Samuelson et al, 2016[30]	59	85 (23.7%)	N/A	12 (3.3%)	N/A	29 (8.1%)	N/A
Blin et al, 2017[31]	65	843 (86.2%)	400 (40.9%)	196 (20.0%)	N/A	95 (9.7%)	23 (2.4%)
Barco et al (ICARO), 2017[32]	54	140 (34.1%)	153 (37.2%)	68 (16.5%)	129 (31.4%)	29 (7.1%)	N/A
Gouveia et al, 2018[33]	51	43 (71.7%)	7 (11.7%)	21 (35.0%)	4 (6.7%)	0 (0%)	2 (3.3%)
Geersing et al, 2018[3]	56	782 (38.9%)	N/A	N/A	N/A	81 (94.0%)	N/A
Karathanos et al (SeVEN), 2021[34]	59	436 (66.1%)	187 (28.3%)	34 (5.2%)	91 (13.8%)	10 (1.5%)	N/A
Karathanos C et al (SeVEN), 2023[35]	59	601 (62.9%)	256 (26.8%)	48 (5.0%)	93 (9.7%)	3 (0,3%)	N/A
Clapham R et al, 2022[36]	61	41 (75.9%)	9 (16.7%)	16 (29.6%)	8 (14.8%)	1 (1.9%)	1 (1.9%)
Casian D et al, 2022[37]	60	104 (54.7%)	N/A	N/A	N/A	N/A	N/A
Rabe E et al (INSIGHTS-SVT), 2023[38]	61	698 (80.0%)	278 (31.9%)	148 (17.0%)	145 (16.6%)	63 (7.2%)	50 (5.7%)

DVT, Deep vein thrombosis; *N/A*, not available; *PE*, pulmonary embolism; *SVT*, superficial vein thrombosis; *VTE*, venous thromboembolism.

anticoagulants in prophylactic or therapeutic doses for a median duration of 28 days.[37] The last four cohort studies reported using anticoagulants separately according to the duration. In the study of Blin et al, fondaparinux was used for 34 ± 18 days and LMWH for 19 ± 27 days.[31] Therefore, patients who received LMWH were considered to be treated for 15 to 30 days. According to Karathanos et al, tinzaparin was used for 30 (14-120 or 3-200) days and analyzed separately in two subgroups: (1) ≤1 month and (2) >1 month.[34,35] The first subgroup was considered to have a duration of 15 to 30 days. In the INSIGHTS-SVT study, 25% of patients received LMWH for 26.2 ± 23.2 days (median, 21 days) and were considered to have treatment duration of 15 to 30 days.[38]

Ten studies assessed outcomes of anticoagulant therapy for 31 to 45 days. The CALISTO trial compared subcutaneous fondaparinux (2.5 mg) with placebo, and the SURPRISE trial compared oral rivaroxaban (10 mg) with the same dose of fondaparinux.[14,22] The duration of treatment was 45 days in both studies. Kearon et al preliminarily halted an RCT aimed to compare rivaroxaban (10 mg) and placebo with a treatment duration of 45 days.[26] A randomized controlled trial by Spirkoska et al compared intermediate and prophylactic doses of dalteparin in terms of thrombus regression.[25] The duration of treatment was designed to be 42 days. Two cohort studies assessed intravenous UFH followed by warfarin and prophylactic or intermediate doses of LMWH for 42 days.[27,33] The corresponding subgroups of patients from the above-mentioned cohort trials by Blin et al (fondaparinux with a mean duration of 34 ± 18 days) and Karathanos et al (a subgroup of >1 month)

were all considered as having a treatment duration of 31 to 45 days.[31,34,35] In the INSIGHTS-SVT trial, patients received fondaparinux for 34.9 ± 15.7 days (median, 39 days) and other anticoagulants for 35 to 43 days (figures are extracted from the table).[38] Clapham et al analyzed treatment results with a prophylactic dose of rivaroxaban (10 mg) for 42 days in the retrospective cohort trial.[36]

Only one prospective cohort study assessed the use of LMWH followed by non-specified oral anticoagulant (OAC) for a mean of 62 days in comparison with the absence of anticoagulation and surgical treatment.[28] These patients were matched with a subgroup of treatment duration of >45 days.

Assessment of quality. The quality assessment results are presented in Supplementary Fig 2 (online only) and Supplementary Table II (online only). In general, moderate-to-high quality was judged in the RCTs, and poor quality in the cohort trials due to the lack of comparability of cohorts based on the design and analysis controlled for confounders.

Assessment of publication bias. Funnel plots were generated by plotting the individual study-reported VTE event rate (proportion, x-axis) against the standard error (y-axis) for all pooled estimates obtained from studies. Publication bias was suggested by the asymmetry of the plot and confirmed by Egger's test ($P < .001$).

Primary and secondary outcomes. The VTE and bleeding rates according to the ACT duration, as extracted from the original trials, are represented in Supplementary Table III (online only). Table III and the Fig illustrate the pooled analysis results.

The analysis of all studies for the primary outcome showed a high heterogeneity of results ($P < .0001$; $I^2 = 94.14\%$). The pooled rate of VTE was estimated as 27.8 (95% CI, 21.4-34.9) per 100 patient-years with the incidence of SVT progression or recurrence, DVT, and PE as 23.3 (95% CI, 15.8-35.8), 7.9 (95% CI, 5.4-10.9), and 1.3 (95% CI, 0.8-2.0) per 100 patient-years, respectively. The rate of major bleeding was reported as 0.3 (95% CI, 0.2-0.6), and CRNM bleeding as 7.4 (95% CI, 4.0-11.7) per 100 patient-years.

In patients who did not receive anticoagulation (0 days), the event rate of VTE, SVT progression or recurrence, DVT, and PE was higher when compared with the pooled data from all studies. However, the rate of major bleeding did not differ, and the rate of CRNM bleeding was lower. The maximum incidence of VTE, DVT, and PE was observed in the studies with short-term anticoagulation of ≤14 days as 59.7 (95% CI, 37.7-86.4), 13.7 (95% CI, 9.6-18.4), and 3.1 (95% CI, 1.4-5.6) per 100 patient-years, respectively. These event rates were higher than the pooled data from all studies and compared with the absence of anticoagulation. However, short-term anticoagulation caused a reduction in the incidence of SVT progression or recurrence from 61.5 (95% CI, 11.5-147.6) to 41.3 (95% CI, 17.9-73.9) compared with no treatment. The rate of major bleeding was comparable to the absence of anticoagulation, whereas the rate of CRNM bleeding was the lowest (1.4; 95% CI, 0.1-4.3 per 100 patient-years).

The minimal VTE incidence was observed in prolonged anticoagulation of 31 to 45 days (16.2; 95% CI, 10.4-23.3 per 100 patient-years) followed by treatment of 15 to 30 days (25.4; 95% CI, 16.3-36.6 per 100 patient-years). The lowest rates of secondary outcomes were also observed in these groups with a minimum incidence of SVT progression and recurrence for the treatment of 31 to 45 days (8.2; 95% CI, 3.1-15.8 per 100 patient-years) and the lowest rate of DVT (5.5; 95% CI, 2.8-9.1 per 100 patient-years) and PE (0.9; 95% CI, 0.5-1.3 per 100 patient-years) for the treatment of 15 to 30 days. The rates of major bleeding were similar in both groups and did not differ from the pooled estimates of all studies, whereas the rate of CRNM or minor bleeding was the highest with anticoagulation of 31 to 45 days (14.2; 95% CI, 5.5-26.8 per 100 patient-years).

Only one study assessed treatment duration of more than 45 days with event rates of VTE, SVT, DVT, and PE of 141, 118, 24, and 0 per 100 patient-years, respectively, without any information on bleeding.[28] These figures appeared to be much higher compared with others due to a limited number of patients and a short follow-up period.

The risk factors for VTE development within the follow-up period were also extracted from the relevant studies and presented in Table IV. One additional trial from the full-text analysis that did not fulfill the inclusion criteria (did not clarify the duration of anticoagulation) reported the risk factors, and the data from the STEFLUX trial were published separately.[6,40] The most common (represented in ≥3 studies) factors that increased the VTE risk by 2 to 3 times were male sex, cancer, personal history of DVT, PE, and/or SVT, and thrombosis of non-varicose veins.

DISCUSSION

Different approaches have been suggested to treat lower limb SVT. Topical agents, NSAIDs, anticoagulants, heparinoids, elastic compression, and surgical intervention aim to reduce the symptoms of inflammation and prevent further VTE due to SVT extension into deep veins and to prevent the occurrence of new DVT and PE. Systemic anticoagulation appeared to be the most protective for VTE in thrombosis length of >5 cm.[11-13,41] In the case of smaller thrombus, local cold, topical agents, NSAIDs, and elastic compression are indicated without systemic anticoagulation.[11,12,39,42-44] VTE threat increases if thrombus length is more than 5 cm, predominantly if it is localized above the knee or near the connection

Table III. The pooled event rate per 100 patient-years of venous thromboembolism (*VTE*) and bleeding according to the duration of anticoagulation treatment

Duration of anticoagulation	VTE	SVT progression or recurrence	DVT	PE	Major bleeding	CRNM and minor bleeding
All studies	27.8 (21.4-34.9)	23.3 (15.8-35.8)	7.9 (5.4-10.9)	1.3 (0.8-2.0)	0.3 (0.2-0.6)[a]	7.4 (4.0-11.7)
0 days	28.8 (12.0-52.4)	61.5 (11.5-147.6)	8.3 (2.4-17.5)	1.9 (0.8-3.7)[a]	0.5 (0.1-1.4)[a]	4.8 (2.8-7.4)[a]
≤14 days	59.7 (37.7-86.4)	41.3 (17.9-73.9)	13.7 (9.6-18.4)[a]	3.1 (1.4-5.6)[a]	0.5 (0.0-2.7)[a]	1.4 (0.1-4.3)[a]
15-30 days	25.4 (16.3-36.6)	18.8 (9.7-30.9)	5.5 (2.8-9.1)	0.9 (0.5-1.3)[a]	0.3 (0.1-0.6)[a]	5.8 (1.6-12.6)
31-45 days	16.2 (10.4-23.3)	8.2 (3.1-15.8)	7.8 (3.0-14.9)	1.4 (0.2-3.8)	0.3 (0.1-0.7)[a]	14.2 (5.5-26.8)

CRNM, Clinically relevant non-major; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *SVT*, superficial vein thrombosis.
[a]Indicates low heterogeneity ($P > .05$ and $I^2 < 50\%$).

with deep veins. Studies on systemic anticoagulation included primarily patients with extensive SVT not reaching the junction. However, those with thrombus located within a 3 to 5 cm near junction were generally excluded, so the best treatment approach for them is not established (Supplementary Table I, online only). The current guidelines empirically equate such SVT with proximal DVT and suggest full-dose therapeutic anticoagulation for 6 to 12 weeks.[11,12] However, a recent analysis of the RIETE registry by Prandoni et al did not find any differences between full therapeutic and prophylactic anticoagulation that was administrated predominantly for 12 weeks in patients with SVT within 3 cm near a junction (the study was considered ineligible due to the absence of separate outcomes for different treatment durations).[45]

Thereby, systemic anticoagulation, as evaluated in the current systematic review, corresponds to extensive SVT with a length of >5 cm, not reaching the junction by 3 to 5 cm (Supplementary Table I, online only). The previous meta-analyses focused on the type and doses of anticoagulation but not on duration. The authors did not find

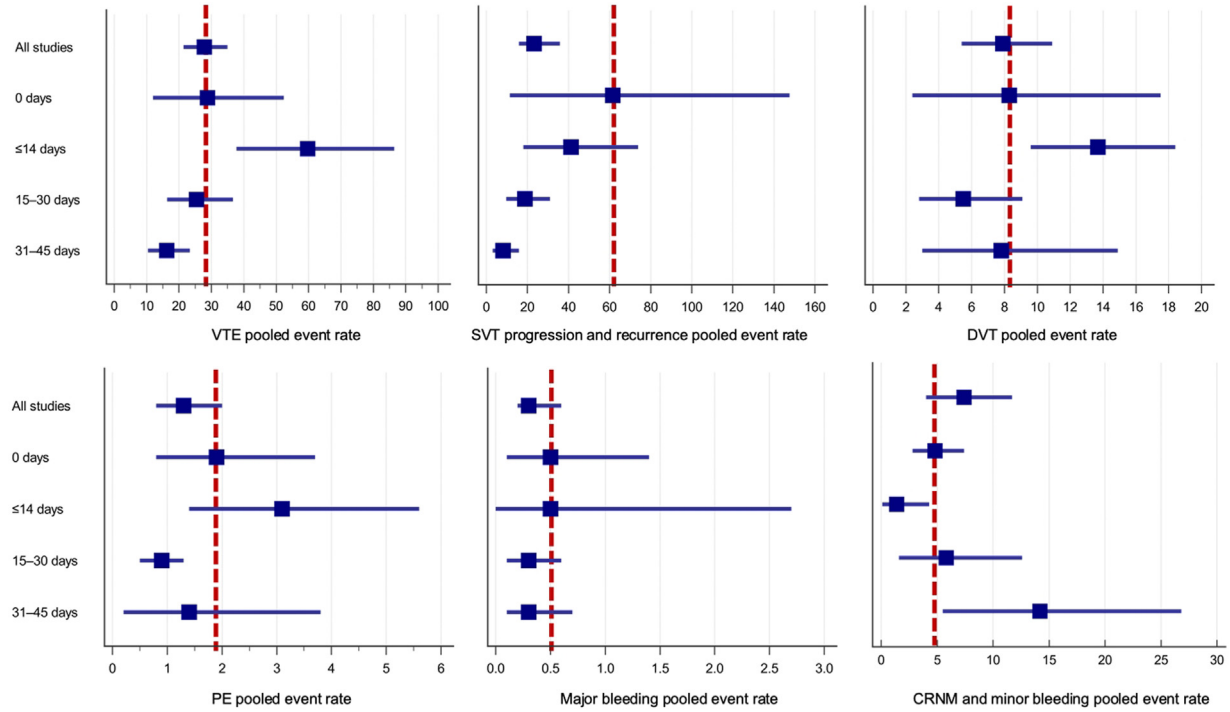

Fig. The pooled event rates of primary and secondary outcomes. Data are presented as per 100 patient-years. Boxes indicate polled event rates and whisker—lower and upper 95% confidence interval (CI). The vertical dashed line corresponds to the polled event rate in the group of no anticoagulation (0 days). *CRNM*, Clinically relevant non-major; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *SVT*, superficial venous thrombosis; *VTE*, venous thromboembolism.

Table IV. Risk factors for venous thromboembolism (*VTE*) development during the follow-up period

	STENOX, 2003[19]	Decousus et al (POST), 2010[5]	Galanaud et al (Optimev), 2011[6]	Cosmi et al (STEFLUX), 2012[24,40]	Barco S et al (ICARO), 2017[32]	Blin et al, 2017[31]	Geersing et al, 2018[3]	Casian D et al, 2022[37]	Karathanos C et al (SeVEN), 2023[35]	Rabe E et al (INSIGHTS-SVT), 2023[28]
Male sex	2.2 (1.3-3.7)	2.6 (1.4-4.9)	3.5 (1.1-11.3)		2.0 (1.2-3.5)					
Cancer		3.1 (1.2-8.5)			3.1 (1.1-8.9)		2.2 (0.9-4.9)			
Inpatient treatment			4.5 (1.3-15.3)							
History of VTE	2.1 (1.1-4.0)	2.2 (1.2-4.1)		2.1 (1.3-3.2)		2.5 (1.1-6.1)				2.9 (1.5-5.6)
Non-varicose veins		2.1 (1.1-4.3)		2.6 (1.3-5.0)			1.8 (1.0-2.9)			
Symptoms <7 days	3.0 (1.4-6.3)									
Progressive stage of CVD	2.8 (1.1-6.9)									
Increased BMI				2.2 (1.3-3.2)						1.06 (1.02-1.11)
Thrombus <3 cm of junction						2.5 (1.1-6.1)				
Thrombus length								1.02 (1.0-1.05)		
Chronic- reduced mobility									4.6 (1.5-14.2)	
Severe systemic infection										7.6 (1.8-32.5)

BMI, Body mass index; *CVD*, chronic venous disease (progressive CVD means stage 3 by Porter);
BMI increased means more than 25 kg/m^2.
Cancer combines active and historical.
History of VTE combines personal and family history of superficial vein thrombosis, deep vein thrombosis, and pulmonary embolism.
Thrombus length reported as hazard ratio for every 1 cm.
Data are presented as the odds ratios or hazard ratios (with 95% confidence interval).

any significant differences between low (prophylactic) and high (intermediate or therapeutic) doses of LMWH while judging subcutaneous fondaparinux at 2.5 mg for 45 days as the best treatment associated with the lowest rate of VTE.[13,41] This conclusion was based on the results of the largest randomized controlled trial CALISTO and insights from a few cohort trials.[7,22,31,38] However, the comparison of fondaparinux with LMWH or other anticoagulants does not consider treatment duration. In most trials, LMWH was used for a short period of ≤14 or 15 to 30 days.

In the current meta-analysis, the treatment duration of ≤14 days was associated with the highest rate of VTE, which was even higher than that with no anticoagulation. These findings may be biased by large cohort trials, where patients without estimated risk did not develop VTE despite the absence of systemic anticoagulation.[3,30,38] It can be assumed that most of them had a limited SVT without additional VTE risk factors in contrast with other trials where individuals with higher VTE risk were treated with short-term anticoagulation. Like in DVT treatment, limited anticoagulation for SVT may be insufficient to control hypercoagulation and prevent VTE recurrence.[46]

Combining the results of the previous analyses based on type or dose indicates that the actual efficacy of the treatment with LMWH may be underestimated. Notably, in cohort trials by Rabe et al and Blin et al, fondaparinux showed superiority over LMWH.[31,38] However, the mean duration of therapy with fondaparinux was 35 ± 16 and 34 ± 8 days, respectively, compared with 26 ± 23 and 19 ± 27 days for LMWH, respectively.

In this study, we chose an alternative approach and combined different types and doses of anticoagulation according to the duration of treatment. An apparent tendency toward VTE risk reduction with prolonged therapy was observed. Treatment for 15 to 30 and 31 to 45 days was associated with the lowest rates of VTE. However, this rate was relatively high, particularly in terms of SVT progression or recurrence and DVT. Our findings are similar to the results of the previous meta-analysis by Duffet et al, who found that prolonged use of LMWH may reduce the event rate of DVT and PE from 18.3 (95% CI, 8.3-31.1) events per 100 patient-years with the treatment duration less than 30 days to 10.0 (95% CI, 5.3-16.1) events per 100 patient-years with the course of 30 to 42 days.[13] However, the results of the SURPRISE trial suggest that 45 days of anticoagulation may not be enough for patients at high risk of VTE.[14] Within 45 days after treatment cessation, the incidence of VTE increased from 3% to 7% and 2% to 7% in groups of rivaroxaban and fondaparinux, respectively. Unfortunately, we could not find any strong evidence of prolonged treatment lasting more than 45 days to be used in quantitative synthesis. Karathanos et al reported the use of LMWH up to 200 days with a mean duration of 30 days.[35] Actually, less than one-half of patients continued treatment after 30 days, and only 1.2% continued after 90 days. The authors did not find any difference in the outcomes between subgroups of

patients treated for less and more than 30 days. However, this study of real clinical practice was biased, and prolonged treatment was prescribed for patients at a higher risk, particularly those with a history of DVT and thrombus location above the knee.

Individual VTE risk factors may play a pivotal role in the development of new thrombosis after cessation of anticoagulation and may be used for treatment adjustment. Unfortunately, not all studies correctly reported the most common risk factors, which may lead to inadequate treatment and an increase in new thrombotic events. Male sex, cancer, personal history of DVT, PE, and/or SVT, and thrombosis of nonvaricose veins were identified as the most common risk factors that could be considered for individual treatment adjustment. Thus, treatment for more than 45 days may be beneficial in selected patients at high risk of VTE. However, such suggestions must be tested in randomized controlled trials to estimate the risk/benefit ratio.

Our review has limitations. The primary outcome was designed as any new VTE, combined SVT progression or recurrence, DVT, and PE. It was chosen due to strong evidence of SVT association with the development of clinically significant DVT and PE, and its progression or recurrence may indicate treatment failure. However, not all analyzed papers reported individual outcomes, and VTE could be defined as DVT and PE only according to the design of original trials. This fact introduced additional heterogeneity in the primary outcome analysis. The data from RCTs and cohort trials of varying quality and consistency were combined, and the statistical analysis of the difference between groups was unavailable. The reported pooled proportions are based on study-level data rather than individual patient data. Most studies did not present the follow-up as patient-years, so patient-months and patient-years were calculated based on the intended or median follow-up rather than on actual individual observation periods. The proportions estimated for relatively short observation periods may be valid for the assumption of an event rate that is consistent over time. Events that occurred within the follow-up period included both on- and off-anticoagulation. Mortality rates were not analyzed due to a low number of events in the previous reviews. Information on the further treatment after cessation of anticoagulation, particularly the surgical removal of varicose veins that may affect the risk of SVT recurrence and DVT or PE occurrence, was not available for analysis. Finally, most calculations were associated with high heterogeneity.

The systematic review and meta-analysis results suggest prolonged systemic anticoagulation is associated with decreased VTE rates in patients with lower limb SVT. The optimal duration of anticoagulant treatment needs to be established in future trials.

AUTHOR CONTRIBUTIONS

Conception and design: KL
Analysis and interpretation: KL, ED, IS, AB
Data collection: KL, ED, IS, AB
Writing the article: KL, ED
Critical revision of the article: KL, ED, IS, AB
Final approval of the article: KL, ED, IS, AB
Statistical analysis: KL
Obtained funding: Not applicable
Overall responsibility: KL

DISCLOSURES

None.

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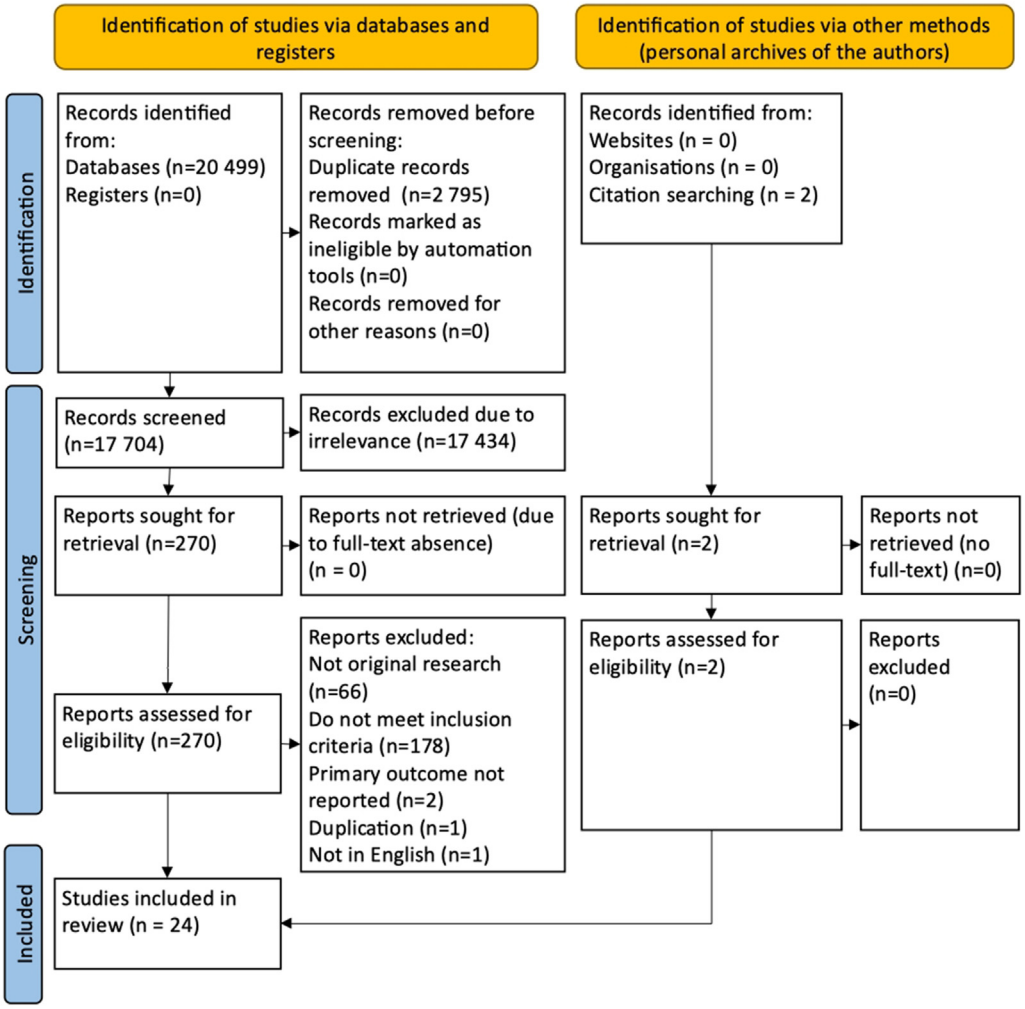
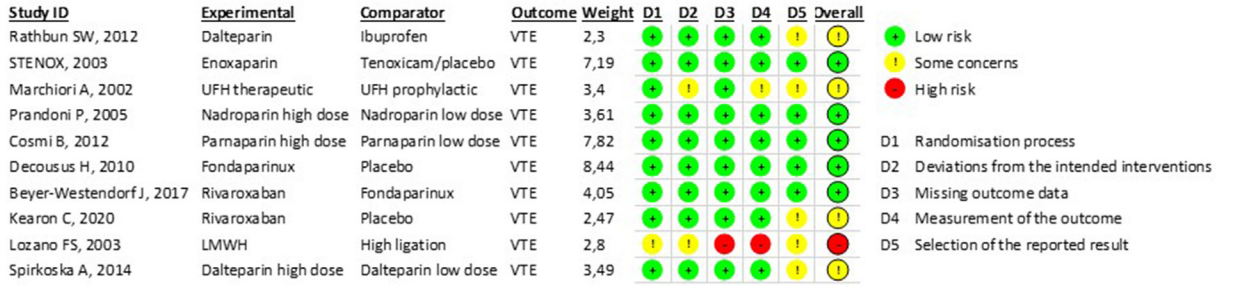
APPENDIX (online only).



Supplementary Fig 1 (online only). Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.



Supplementary Fig 2 (online only). The results of bias (RoB) risk assessment of randomized clinical trials with RoB 2 Tool. *VTE*, Venous thromboembolism.

Supplementary Table I (online only). Inclusion and exclusion criteria in the analyzed trials

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Marchiori A et al, 2002[18]	1) Symptomatic thrombophlebitis of the GSV, 2) confirmed by ultrasonography, 3) proximal (ie, above-knee) venous system.	1) Under 18 years, 2) thrombotic involvement of the SFJ (<1 cm from the junction), 3) concomitant DVT, 4) previous DVT not followed by complete, ultrasound-confirmed recanalization, 5) clinical suspicion of PE, 6) previous thigh SVT, 7) congenital or acquired bleeding disorders, 8) known hypersensitivity or contraindications to heparin, 9) anticoagulant therapy ongoing or required for concomitant diseases, 10) body weight <50 kg, 11) pregnancy.	SVT within 1 cm of the SFJ excluded
STENOX, 2003[19]	1) Older than 18 2) weighing 45 to 110 kg 3) acute SVT of lower limbs 4) confirmed by ultrasound 5) at least 5 cm long	1) 2 or more SVT, 2) SVT following sclerotherapy, 3) DVT on initial DUS, 4) documented PE, 5) pregnant, breastfeeding, or not using contraception (if women of childbearing age), 6) known thrombophilia, 7) uncontrolled arterial hypertension (systolic blood pressure >180 mm Hg, diastolic blood pressure >110 mm Hg, or both), 8) previous or active peptic ulcer, 9) bacterial endocarditis, stroke within the previous 3 months, 10) other conditions favoring hemorrhage, 11) history of hypersensitivity to heparins, 12) heparin-induced thrombocytopenia, 13) hypersensitivity to paracetamol or NSAIDs, 14) serum creatinine concentration above 1.81 mg/dL (>160 μmol/L), 15) platelet count below $100\times10^3/\mu L$, 16) prothrombin ratio below 60%, 17) contraindication to elastic bandages or support stockings, 18) patients who required anticoagulant therapy, 19) patients who required ligation of the SFJ, 20) patients who required thrombectomy 21) received any type of anticoagulant therapy or NSAIDs for more than 48 hours	Those who required ligation or full therapeutic anticoagulation excluded
Lozano FS et al, 2003[20]	1) Internal saphenous thrombophlebitis above the knee close to its junction with the femoral vein 2) met the basic selection requirements for patients eligible for outpatient treatment of DVT. 3) underwent echo-Doppler (to determine the extension of SVT and the condition of the deep venous system lower limbs)	1) Associated DVT, 2) treatment with oral anticoagulants, 3) known systemic disorders (neoplasm or thrombophilia).	SVT with thrombus close to the junction included

Supplementary Table I (online only). Continued.

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Prandoni P et al (VESALIO), 2005[21]	1) Recent (<10 days) clinical symptoms suggestive of acute SVT of the legs 2) a thrombus involving the GSV and extending up to 3 cm from the SFJ confirmed by ultrasonography, 3) the contemporary presence of DVT excluded by ultrasonography	1) Younger than 18 years, 2) pregnant, 3) received saphenectomy, 4) a history of previous (<1 year) SVT in the affected leg, 5) concurrent or previous VTE, 6) congenital or acquired bleeding disorders contraindicating heparin treatment, 7) thrombocytopenia (platelet count $<100\times10^9$/L), 8) ongoing anticoagulant or antiplatelet therapy for other indications, 9) received full-dose anticoagulants for more than 48 h, 10) known thrombophilia, 11) known hypersensitivity to heparin or derivatives, 12) active gastro-duodenal ulcer, 13) active cancer, 14) severe renal insufficiency (serum creatinine level >180 mmol/L), 15) severe hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >90 mmHg), 16) previous hemorrhagic stroke or a recent (<1 month) ischemic stroke.	SVT within 3 cm of the SFJ excluded
Decousus H et al (CALISTO), 2010[22]	1) 18 years of age or older, 2) acute, symptomatic lower-limb SVT. 3) at least 5 cm long confirmed by ultrasonography	1) More than 3 weeks between the onset of symptoms and randomization, 2) treated for cancer within the previous 6 months, 3) symptomatic or asymptomatic DVT, symptomatic documented PE, 4) SVT associated with sclerotherapy or placement of an intravenous catheter, 5) within 3 cm of the SFJ, 6) history of SVT within the previous 3 months, 7) DVT or PE within the previous 6 months, 8) received an antithrombotic agent for more than 48 hours (other than aspirin at a dose ≤325 mg per day), 9) received NSAID for more than 72 hours as treatment for the current episode of SVT, 10) if, in the investigator's opinion, required ligation of the SPJ or stripping of varicose veins, 11) major surgery within the previous 3 months, 12) conditions that could confer a predisposition to bleeding, including severe hepatic impairment, a creatinine clearance of less than 30 ml per minute, and a platelet count of less than 100,000 per cubic millimeter, 13) pregnant or not using a reliable contraceptive method.	SVT within 3 cm of the SFJ excluded

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Supplementary Table I (online only). Continued.

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Rathbun SW et al, 2012[23]	1) SVT of the lower or upper extremities, objectively confirmed by ultrasound, 2) absence of a current intravenous catheter	1) Receiving anticoagulant therapy, including warfarin, heparin or LMWH for > 24 hour duration 2) concurrent DVT, 3) active, clinically significant bleeding, 4) known hypersensitivity to NSAIDs, heparin or derivatives, 5) currently pregnant or <1 week postpartum, 6) a history of a bleeding gastric or duodenal ulcer in the past year, 7) a history of a hemorrhagic cerebrovascular event in past year, 8) platelet count <100000, 9) known inherited or an acquired bleeding disorder, 10) serum creatinine >2 mg/dL, 11) blood pressure >180/110 at the time of enrollment, 12) weight <40 kg or >135 kg, 13) unable to return for repeat diagnostic testing or follow-up visits.	Not reported
Cosmi B et al (STEFLUX), 2012[24]	1) Age >18 years, 2) weight above 50 kg and <130 kg, 3) SVT of the GSV or short saphenous vein or their collaterals at least 4 cm in length, 4) an ability to provide informed consent	1) SVT within 3 cm of the SFJ or SPJ, 2) documented proximal or distal DVT or PE, 3) SVT secondary to sclerotherapy, 4) pregnancy or puerperium, 5) uncontrolled arterial hypertension (systolic pressure >180 mmHg and diastolic pressure >110 mmHg), 6) active peptic ulcer, 7) bacterial endocarditis, stroke in the previous 3 months, 8) hemorrhagic diathesis, thrombocytopenia (platelets <100000/μL), 9) hypersensitivity to heparin or a history of heparin-induced thrombocytopenia, 10) creatinine >2 mg/dL (>180 μmol/L), 11) heparin therapy (any dose) or anticoagulant therapy for more than 72 hours, 12) in-hospital development of SVT, 13) previous saphenectomy, 14) surgery in the previous 30 days, 15) serious liver disease, 16) use of dextran, mannitol, thrombolytic treatment, 17) chronic use of NSAIDs, 18) active cancer or undergoing chemotherapy or radiotherapy (except adjuvant hormonal therapy), 19) thrombectomy of superficial vein involved, 20) refusal to give informed consent.	SVT within 3 cm of SFJ or SPJ excluded

Supplementary Table I (online only). Continued.

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Spirkoska A et al, 2015[25]	1) Ultrasonographically confirmed first symptomatic presentation, 2) acute SVT of lower extremities (<5 days after the onset of the symptoms), 3) ultrasonographically confirmed thrombus length of at least 10 cm in the GSV, SSV, or major tributaries of the GSV, 4) body weight 65 to 90 kg, 5) age 18 to 85 years.	1) Concomitant DVT and/or PE, 2) thrombosis extending closer than 5 cm to the SFJ or 3 cm to the SPJ, 3) inability to objectively confirm the diagnosis,4) history of previous venous thromboembolism (DVT, PE, or SVT), 5) secondary vein thrombosis as a consequence of previous trauma or intravenous access, 6) contraindications for anticoagulant treatment, 7) thrombocytopenia ($<100 \times 10^9$/l), 8) previous or recent malignancy, sepsis, autoimmune disorders, pregnancy, hormone therapy, 9) hepatic or renal insufficiency (glomerular filtration rate <50 ml/min/1.73 m^2), 10) receiving anti-inflammatory treatment (except aspirin ≤100 mg/ day).	SVT within 5 cm of the SFJ or 3 cm of SPJ excluded
Beyer-Westendorf J et al (SURPRISE), 2017[14]	1) Symptomatic SVT involving a 5 cm or longer segment, 2) confirmed by ultrasound 3) superficial vein above the knee, With at least one of the following risk factors for VTE: - older than 65 years, - male sex, - previous SVT or DVT or PE, - active cancer or history of cancer, - autoimmune disease, - involvement of non-varicose veins.	1) Symptoms for >3 weeks, 2) SVT within 3 cm of the SFJ, 3) treated for the index event for more than 3 days with therapeutic doses of anticoagulants or for >5 days with prophylactic doses, 4) concomitant DVT or another indication for full-dose anticoagulation, 5) severe hepatic disease associated with a coagulopathy, 6) creatinine clearance <30 mL per min, 7) contraindications to anticoagulant treatment.	SVT within 3 cm of SFJ excluded
Kearon C et al, 2020[26]	1) Symptomatic SVT of the leg, 2) at least 5 cm length diagnosed on clinical grounds, with or without, confirmatory findings on an ultrasound examination.	1) <18 years, 2) symptoms present for more than 42 days, 3) receiving or needs to receive an anticoagulant for another indication, 4) SVT has already been treated with >3 days of anticoagulant therapy, 5) SVT judged to require a course of anticoagulant therapy or surgical management, 6) proximal DVT or PE within the past 12 months, 7) SVT associated with sclerotherapy or an intravenous cannula, 8) high risk for bleeding, 9) creatinine clearance less than 30 mL/min, 10) on a medication that is expected to interact importantly with rivaroxaban.	Those who required surgical management or full therapeutic anticoagulation excluded
Ascer E et al, 1995[27]	1) SVT involving the GSV up to within 1 cm of SFJ, 2) confirmed by DUS	1) Absence of trauma or malignancy, 2) no contraindication to anticoagulation.	SVT with thrombus close to the junction included
Gorty S et al, 2004[28]	1) DUS-documented new-onset SVT of leg, 2) a history and physical examination at out office.	1) Incomplete records, 2) lack of follow-up, 3) chronic SVT.	Not reported

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Supplementary Table I (online only). Continued.

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Decousus H et al (POST), 2010[5]	1) 18 years or older, 2) symptomatic lower-limb SVT, 3) confirmed by ultrasonography, 4) more than 5 cm in length on ultrasonography.	1) Surgery in the previous 10 days, 2) sclerotherapy in the previous 30 days, 3) follow-up not considered feasible.	Not reported
Sartori M et al, 2016[29]	1) Objectively confirmed SVT diagnosis	1) Younger than 18 years, 2) pregnant or in puerperium, 3) with established diagnosis of concomitant DVT or symptoms attributable to PE, 4) with life expectancy of <3 months, 5) undergoing radiotherapy or chemotherapy, 6) clinical or laboratory findings compatible with disseminated intravascular coagulation, sepsis, 7) clinical or laboratory findings compatible with liver cirrhosis, 8) chronic renal failure with creatinine clearance <30 ml/min, 9) treated with anticoagulant agents other than LMWH, 10) SVT located within 3 cm of the SFJ.	SVT within 3 cm of the SFJ excluded
Samuelson B et al, 2016[30]	1) ICD-9-CM diagnosis code of venous thrombosis, 2) between January 1, 2004 and December 31, 2010, 3) isolated SVT: no evidence of a DVT or PE, 4) medical chart documentation of either ultrasound evidence of a superficial vein clot or a clinical description of SVT, 5) review by second physician reviewer to confirm the diagnosis of SVT.	Not indicated	Not reported
Blin P et al, 2017[31]	1) Acute symptomatic spontaneous isolated SVT of the lower limbs, 2) confirmed by compression ultrasonography	1) SVT secondary to sclerotherapy or a venous catheter, 2) concomitant DVT or PE, 3) anticoagulant use for another reason than SVT, 4) clinical trial inclusion.	Not reported
Barco S et al (ICARO), 2017[32]	1) Acute symptomatic isolated SVT diagnosed on compression B-mode ultrasound or echo-color Doppler, 2) previously included in the cross-sectional ICARO study, 3) with available follow-up of a minimum of 30 days.	1) Presence of signs or symptoms of PE and/or an established diagnosis of PE, 2) detection of concomitant DVT, 3) follow-up duration of <30 days.	Not reported
Gouveia S et al, 2018[33]	1) Confirmed on compression ultrasonography; 2) leg SVT, 3) absence of co-existent DVT.	1) Active cancer, 2) a thrombus ≤3 cm from SFJ, 3) treatment with other anticoagulant regimens or NSAIDs.	SVT within 3 cm of the SFJ excluded
Geersing GJ et al, 2018[3]	1) ICPC code of SVT in addition to automated 'free text searching' in all patient contacts using a variety of synonyms for SVT, 2) the GP clearly described signs and symptoms related to a new SVT diagnosis,	1) Findings were not clearly reported; 2) SVT was only considered in differential diagnosis but finally 'ruled-out' (not managed accordingly) by the general practitioner, 3) SVT was part of a patient's medical history rather than related to current and new complaints.	Not reported

Supplementary Table I (online only). Continued.

Author	Inclusion criteria	Exclusion criteria	Patient selection according to thrombus location close to the junction
Karathanos C et al (SeVEN), 2021[34]	1) Aged 18 years 2) symptomatic SVT of the legs, 3) thrombus length 5 cm confirmed by DUS, 4) duration of symptoms less than 10 days.	1) Proximal extension of the SVT <3 cm from the SFJ or SPJ, 2) history of DVT or PE within the last 6 months, 3) SVT after sclerotherapy, 4) placement of an intravenous catheter within the past 1 month, 5) body mass index >35 kg/m^2 , 6) receiving medication that affects blood coagulation (acetylsalicylic acid, vitamin K antagonists, dextrane), 7) subjected to spinal or epidural anesthesia within 48 hours prior to study inclusion, 8) history of major surgery within last 3 months, 9) history of cerebral surgery, trauma and/or bleeding within last 1 month.	SVT within 3 cm of the SFJ or SPJ excluded
Karathanos C et al (SeVEN), 2023[35]	1) Aged 18 years2) symptomatic SVT of the legs, 3) thrombus length 5 cm confirmed by DUS, 4) duration of symptoms less than 10 days.	1) Proximal extension of the SVT <3 cm from the saphenofemoral or saphenopoplitelal junction, 2) history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within the last 6 months, 3) SVT after sclerotherapy, 4) placement of an intravenous catheter within the past 1 month, 5) body mass index >35 kg/m^2, 6) receiving medication that affect blood coagulation (acetylsalicylic acid, vitamin K antagonists, dextrane), 7) subjected to spinal or epidural anaesthesia within 48 hours prior to study inclusion, 8) history of major surgery within last 3 months, 9) history of cerebral surgery, trauma and/or bleeding within last 1 month.	SVT within 3 cm of the SFJ or SPJ excluded
Clapham R et al, 2022[36]	1) Isolated SVT confirmed by compression ultrasonography.	1) Thrombus within 3 cm of SFJ, 2) conservative management, 3) treatment with alternative antiocoagulant, 4) treatment interrupted due to other conditions.	SVT within 3 cm of the SFJ excluded
Casian D et al., 2022[37]	1) Clinical manifestations of SVT and varicose veins of lower limbs, 2) age 18 years or more, 3) first episode of SVT confirmed by DUS, 4) duration of SVT symptoms ≤14 days.	1) Ipsilateral or contralateral lower limb DVT, 2) SVT of non-varicose veins, 3) SVT associated to treatment of varicose veins (thermal ablation, sclerotherapy), 4) administration of any anticoagulants for more than 48 hours.	Not reported
Rabe E et al (INSIGHTS-SVT), 2023[38]	1) Objectively confirmed acute isolated SVT of the lower extremities, 2) concomitant DVT excluded by compression ultrasound or duplex sonography, 3) no symptoms of PE.	1) Proximal extension of SVT located ≤3 cm from the SFJ, 2) unlikely to comply with the study's protocol due to cognitive or language limitations, 3) unlikely to be available for 12-month follow-up.	SVT within 3 cm of the SFJ excluded

DUS, Duplex ultrasound scan; *DVT*, deep vein thrombosis; *GP*, general practitioner; *GSV*, great saphenous vein; *ICD-CM*, International Classification of Diseases, Clinical Modification; *ICPC*, International Classification of Primary Care; *LMWH*, low-molecular weight heparin; *NSAID*, non-steroidal anti-inflammatory drug; *PE*, pulmonary embolism; *SFJ*, sapheno-femoral junction; *SPJ*, sapheno-popliteal junction; *SSV*, small saphenous vein; *SVT*, superficial vein thrombosis; *VTE*, venous thromboembolism.

Supplementary Table II (online only). Risk of bias Newcastle-Ottawa for cohort studies

Author	Summary: Selection (max. four stars)	Summary: Comparability (max. two stars)	Summary: Outcome (max. three stars)	Quality
Ascer E et al, 1995[27]	☆☆☆	–	☆☆	Poor
Gorty S et al, 2004[28]	☆☆☆☆	–	☆☆☆	Poor
Decousus H et al (POST), 2010[5]	☆☆☆	–	☆☆☆	Poor
Sartori M et al, 2016[29]	☆☆☆	–	☆☆	Poor
Samuelson B et al, 2016[30]	☆☆	–	☆☆	Poor
Blin P et al, 2017[31]	☆☆☆☆	–	☆☆	Poor
Barco S et al (ICARO), 2017[32]	☆☆☆	–	☆☆☆	Poor
Gouveia S et al, 2018[33]	☆☆☆	–	☆☆	Poor
Geersing GJ et al, 2018[3]	☆☆	–	☆☆	Poor
Karathanos C et al, 2021[34]	☆☆☆☆	–	☆☆☆	Poor
Karathanos C et al, 2023[35]	☆☆☆☆	☆☆	☆☆☆	Good
Clapham R,et al, 2022[36]	☆☆☆	–	☆☆☆	Poor
Rabe E et al, 2023[38]	☆☆☆☆	–	☆☆	Poor
Casian D et al, 2022[37]	☆☆☆☆	☆	☆☆☆	Good

Thresholds for converting the Newcastle-Ottawa scales to the Agency for Healthcare Research and Quality standards (good, fair, and poor):
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain;
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain;
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Supplementary Table III (online only). The main results of the trials used for quantitative synthesis

Author	Anticoagulation duration, days	No. patients in the group	Total VTE, n (%)	SVT progression or recurrence, n (%)	DVT, n (%)	PE, n (%)	Major bleeding, n (%)	CRNM and minor bleeding, n (%)
Marchiori A et al, 2002[18]	28	60	26 (43.3)	19 (31.7)	6 (10.0)	1 (1.7)	0 (0)	N/A
STENOX, 2003[19]	18-21	216	36 (16.7)	32 (14.8)	9 (4.2)	2 (0.9)	0 (0)	1 (0.5)
	0	112	38 (33.9)	37 (33.0)	5 (4.5)	0 (0)	0 (0)	1 (0.9)
Lozano FS et al, 2003[20]	28	30	3 (10.0)	3 (10.0)	0 (0)	0 (0)	0 (0)	2 (6.7)
Prandoni P et al (VESALIO), 2005[21]	30	164	13 (7.9)	7 (4.3)	5 (3.0)	1 (0.6)	0 (0)	N/A
Decousus H et al (CALISTO), 2010[22]	45	1502	17 (1.1)	13 (0.9)	4 (0.3)	0 (0)	1 (0.1)	16 (1.1)
	0	1500	102 (6.8)	80 (5.3)	19 (1.3)	6 (0.4)	1 (0.1)	15 (1.0)
Rathbun SW et al, 2012[23]	7-14	37	4 (10.8)	2 (5.4)	1 (2.7)	1 (2.7)	0 (0)	0 (0)
Cosmi B et al (STEFLUX), 2012[24]	10	217	48 (22.1)	37 (17.1)	10 (4.6)	1 (0.5)	0 (0)	0 (0)
	30	446	50 (11.2)	39 (8.7)	10 (2.2)	1 (0.2)	0 (0)	2 (0.4)
Spirkoska A et al, 2015[25]	42	68	3 (4.4)	0 (0)	2 (2.9)	1 (1.5)	0 (0)	4 (5.9)
Beyer-Westendorf J et al (SURPRISE), 2017[14]	45	472	30 (6.4)	23 (4.9)	8 (1.7)	0 (0)	0 (0)	40 (8.5)
Kearon C et al, 2020[26]	45	43	1 (2.3)	1 (2.3)	0 (0)	0 (0)	0 (0)	1 (2.3)
	0	42	5 (11.9)	5 (11.9)	0 (0)	0 (0)	0 (0)	0 (0)
Ascer E et al, 1995[27]	42	12	2 (16.7)	0 (0)	2 (16.7)	0 (0)	N/A	N/A
Gorty S et al, 2004[28]	62	21	6 (28.6)	5 (23.8)	1 (4.8)	0 (0)	N/A	N/A
Decousus H et al (POST), 2010[5]	11	586	58 (9.9)	28 (4.8)	15 (2.6)	3 (0.5)	N/A	N/A
Sartori M et al, 2016[29]	30	678	36 (5.3)	29 (4.3)	6 (0.9)	1 (0.1)	0 (0)	N/A
Samuelson B et al, 2016[30]	0	200	15 (7.5)	N/A	N/A	N/A	N/A	N/A
Blin P et al, 2017[31]	34±18	735	24 (3.3)	N/A	N/A	N/A	0 (0)	N/A
	19±27	127	7 (5.5)	N/A	N/A	N/A	0 (0)	N/A
Barco S et al (ICARO), 2017[32]	30	411	152 (37.0)	100 (24.3)	37 (9.0)	12 (2.9)	3 (0.7)	N/A
Gouveia S et al, 2018[33]	42	60	11 (18.3)	4 (6.7)	5 (8.3)	2 (3.3)	0 (0)	3 (5.0)
Geersing GJ et al, 2018[3]	0	1957	32 (1.6)	N/A	N/A	N/A	N/A	N/A
Karathanos C et al (SeVEN), 2021[34]	≤30	347	6 (1.7)	4 (1.2)	2 (0.6)	0(0)	1 (0.3)	2 (0.6)
	>30	313	9 (2.9)	5 (1.6)	3 (1.0)	1 (0.3)	0 (0)	2 (0.6)
Karathanos C et al (SeVEN), 2023[35]	≤30	552	17 (3.1%)	N/A	N/A	N/A	N/A	N/A
	>30	404	16 (4.0%)	N/A	N/A	N/A	N/A	N/A
Clapham R et al, 2022[36]	42	52	1 (1.9)	0 (0)	1 (1.9)	0 (0)	0 (0)	1 (1.9)
Casian D et al, 2022[37]	28	105	6 (5.7)	5 (4.8)	1 (1.0)	0 (0)	0 (0)	6 (5.7)

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Supplementary Table III (online only). Continued.

Author	Anticoagulation duration, days	No. patients in the group	Total VTE, n (%)	SVT progression or recurrence, n (%)	DVT, n (%)	PE, n (%)	Major bleeding, n (%)	CRNM and minor bleeding, n (%)
Rabe E et al (INSIGHTS-SVT), 2023[38]	35-43	596	65 (10.9)	N/A	N/A	N/A	1 (0.2)	N/A
	21	218	49 (22.5)	N/A	N/A	N/A	2 (0.9)	N/A
	0	58	7 (12.1)	N/A	N/A	N/A	0 (0)	N/A

CRNM, Clinically relevant non-major; *DVT*, deep vein thrombosis; *N/A*, non-available; *PE*, pulmonary embolism; *SVT*, superficial vein thrombosis; *VTE*, venous thromboembolism.
VTE is represented as a combination of SVT progression or recurrence, DVT, and PE when available or according to the definitions of the original trials; does not always match the sum of individual events due to reporting issues.