journal of
thrombosis and haemostasis

Incidence of VTE, recurrence, and bleeding after isolated superficial vein thrombosis - findings from the TROLL registry.

Journal:	*Journal of Thrombosis and Haemostasis*
Manuscript ID	JTH-2023-00947.R1
Article Type:	Original Article
Date Submitted by the Author:	04-Oct-2023
Complete List of Authors:	Jørgensen, Camilla Tøvik; Sykehuset Ostfold HF, Department of Emergency Medicine; University of Oslo, Braekkan, Sigrid; UiT The Arctic University of Norway, TREC, Department of Clinical Medicine Førsund, Eli; Ostfold County Hospital, Department of research Pettersen, Heidi Hassel; Sykehuset Ostfold HF, Department of Research Tjønnfjord, Eirik; Østfold Hospital, Department of Emergency Medicine Ghanima, Waleed; Østfold Hospital, Departments of Medicine, Hematology and Research; University of Oslo Institute for Clinical Medicine, Department of Haematology Tavoly, Mazdak; Sahlgrenska universitetssjukhuset, Medicine
Key Words:	bleeding, direct oral anticoagulants, recurrence, registry, superficial vein thrombosis

Incidence of VTE, recurrence, and bleeding after isolated superficial vein thrombosis - findings from the TROLL registry.

Camilla Tøvik Jørgensen *, †, Sigrid Kufaas Brækkan ‡, §, Eli Førsund *, Heidi Hassel Pettersen ¶, Eirik Tjønnfjord *, Waleed Ghanima ¶, **, ††, Mazdak Tavoly ¶, §§

* Department of Emergency Medicine, Østfold Hospital, Sarpsborg, Norway
† Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
‡ Thrombosis Research Center (TREC), Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway
§ Thrombosis Research Group (TREC), Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway
¶ Department of Research, Østfold Hospital, Sarpsborg, Norway
** Clinic of Internal Medicine, Østfold Hospital Sarpsborg, Norway
†† Department of Hematology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
§§ Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

Corresponding author

Camilla Tøvik Jørgensen

Department of Emergency Medicine

Østfold Hospital

P.O. Box 300, Kalnesveien 300, 1714 Grålum

Norway

Camilla.tovik.jorgensen@gmail.com

+47 99719201

SUMMARY

Background: There is limited data on the long-term risk of venous thromboembolism (VTE) after high-risk isolated superficial vein thrombosis (iSVT) treated with anticoagulants.

Objectives: To determine the short- and long-term VTE and iSVT recurrence after cessation of anticoagulant treatment and to calculate 45-days cumulative bleeding incidence in patients with iSVT.

Methods: Between January 2014 and December 2021, 229 patients with high-risk iSVT (i.e., thrombus length ≥5cm), without active cancer, no history of VTE or iSVT, who had received anticoagulant treatment for the iSVT were identified through The Venous *T*hrombosis *R*egistry in Østf*OL*d Hospita*L* (TROLL), Norway. Cumulative incidences of VTE and iSVT recurrence as well as cumulative incidences of major- and clinically relevant non-major (CRNMB) bleedings were assessed.

Results: Median age was 60 years (IQR 48-71) and 125 (55%) were women. Most patients were treated with DOACs (74%), and of these, 79% received a dose of rivaroxaban 10 mg daily. Low-molecular weight heparin was given to 26% of the patients. The 1- and 5-year cumulative incidences of VTE after iSVT were 4.6% (95% CI 2.5-8.3) and 15.9% (95% CI 10.8-22.9), respectively. Further, the 1- and 5-year cumulative incidences of iSVT recurrence were 6.5% (95% CI 3.9-10.7) and 15.9% (95% CI 10.8-23.1), respectively. The overall 45 days cumulative incidence of major bleeding and CRNMB was 0.4% (95% CI 0.06-3.06) and 1.8% (0.7–4.6), respectively. No major bleedings were observed in patients treated with DOACs.

Conclusion: Despite anticoagulant treatment, the risk of VTE after high-risk iSVT was substantial, while bleeding complications were low.

KEY WORDS

Bleeding, direct oral anticoagulants, recurrence, registry, superficial vein thrombosis

INTRODUCTION

Superficial vein thrombosis (SVT) of the lower extremities is a relatively common condition with a reported incidence of 0.3-0.6 per 1000 person-years for younger individuals and 0.7-1.5 per 1000 person-years in the elderly [1, 2]. In most cases, the SVT is isolated and confined to the great saphenous vein [3], and thus referred to as isolated SVT (iSVT). Previously, iSVT was regarded a non-severe and self-limiting condition, which only required symptomatic treatment [4, 5]. However, during the last decade, growing evidence suggests that SVT is a potentially serious condition as it may coexist with or extend to deep vein thrombosis (DVT) and/or pulmonary embolism (PE) [6-8]. A 4- to 6-fold increase in the risk of DVT and PE have been reported in patients with iSVT compared to persons with no history of SVT [9-11], and incidence rates of venous thromboembolism (VTE; i.e., DVT and/or PE) after iSVT were found to be 1.8%-2.5% per person-years [11, 12].

Anticoagulant treatment of iSVT has been shown to prevent further extension to DVT and PE. A randomized trial comparing fondaparinux with placebo reported an 85% reduction in VTE in favor of fondaparinux, without increasing bleeding rates [13]. Based on these findings, the American College of Chest Physicians (ACCP) updated their guidelines to recommend fondaparinux or low-molecular weight heparin (LMWH) for 45 days as treatment of iSVT with thrombus length ≥ 5 centimeters [14]. In another trial, treatment with rivaroxaban 10 mg once daily (OD) was non-inferior to fondaparinux 2.5 mg OD for treatment of iSVT with regards to progression to VTE, recurrence of SVT, or major bleeding events [15]. Nevertheless, a Cochrane review from 2018 was unable to provide consensus on the optimal anticoagulant treatment in patients with iSVT [16]. Bleeding events have been

reported to be low, with cumulative incidences ranging from 0-0.5% [13, 15, 17, 18]. However, only one study included patients treated with DOACs (rivaroxaban) [15].

Most of the epidemiological studies reporting risk of VTE after iSVT were conducted in the period before anticoagulation was recommended as the choice of treatment. Based on the current uncertainties in optimal treatment strategies and limited data on long-term outcomes after iSVT in patients initially treated with anticoagulants according to ACCP guidelines, we conducted a study which aimed to determine long-term incidence of VTE in patients with a high-risk iSVT (i.e., ≥ 5 centimeters in length) objectively verified by compression ultrasonography (CUS) in a hospital setting and thus treated with anticoagulants. Secondary objectives were to explore the risk of iSVT recurrence, the 45 days cumulative incidence of major- and clinically relevant non-major bleedings and incidence of treatment failure for patients treated with rivaroxaban.

METHODS AND MATERIALS

Study population

The venous *T*hrombosis *R*egistry in Østf*OL*d Hospita*L* (TROLL) is an ongoing, prospective, single-center, quality control and research registry of consecutive and unselected patients with VTE who are diagnosed, treated and followed up at Østfold Hospital, Norway, since 2005. Østfold Hospital is the primary referral center in Østfold county and covers a population of 317 000 inhabitants. The details of the TROLL registry have been described previously [19]. According to hospital guidelines, all patients with VTE, including SVT who are treated at any of Østfold hospitals' departments, should be referred to the thrombosis outpatient clinic for further treatment and follow-up. Patients are subsequently included in

the TROLL registry when the first physical appointment occurs. The study population of the present study consisted of patients referred to the hospital and diagnosed with iSVT in the lower extremities who fulfilled the criteria for anticoagulant treatment according to the ACCP guidelines between January 2014 and December 2021 derived from TROLL. Inclusion criteria were: (i) age ≥ 18 years; (ii) first-time iSVT objectively confirmed by CUS (only the symptomatic leg was imaged); (iii) thrombus confined to superficial veins and ≥ 5 centimeters in length and thus treated with anticoagulant agents; (iv) consent to participate or deceased (consent was waived for diseased patients by the Regional Ethics Committee). The iSVT was further categorized based on its location, i.e., above or below the knee, or both. Participants were excluded if they: (i) had a history of VTE or SVT; (ii) were treated or diagnosed with cancer within six months prior to iSVT diagnosis; (iii) were diagnosed with cancer within three months after the iSVT event; (iv) not living in the catchment area for Østfold Hospital at inclusion; (v) did not receive anticoagulant treatment. To identify those patients who for various reasons were not referred to the thrombosis clinic, an additional search was performed in the hospital discharge registry using the International Classification of Diseases (ICD 10) superficial thrombosis code I80.0. For these patients, data was collected by reviewing medical records.

Outcomes

All patients were followed with regard to the incidence of VTE, iSVT recurrence and bleeding until October 31, 2022. The primary outcome measure was the incidence of VTE (i.e., lower proximal/distal or upper extremity DVT, all PE and/or splanchnic vein thrombosis) after discontinuation of anticoagulant treatment. Secondary outcomes were: 1) incidence of

recurrent iSVT after discontinuation of anticoagulant treatment (a recurrent iSVT is defined as iSVT in a new or same segment, diagnosed by CUS and anticoagulation was started); 2) incidence of treatment failure for patients treated with rivaroxaban, which was assessed only in patients receiving rivaroxaban and was defined as non-resolving symptoms or progression of symptoms, and in case of rivaroxaban increased dose from 10 to 20mg and/or treatment beyond 45 days; 3) major- and clinically relevant non-major bleeding (CRNMB). Bleeding was classified according to the criteria established by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) [20, 21]. Cumulative incidence of major bleeding and CRNMB was assessed during the first 45 days following the iSVT, since The Norwegian Guidelines from 2020 recommend treatment with LMWH or fondaparinux for 45 days [22]. After publication of the SURPRISE study (Superficial Phlebitis Treated for Forty-five Days with Rivaroxaban versus Fondaparinux), our hospital guidelines advocated rivaroxaban 10 mg OD as an additional treatment option [15]. Therefore, a subgroup analysis of bleeding rates restricted to patients treated with DOACs was also performed.

All bleeding events, VTEs, and iSVT recurrences were thoroughly reviewed and adjudicated by the investigators (mainly HHP and CTJ), and difficult cases were resolved by discussion between investigators to reach consensus.

Statistical analysis

Descriptive statistics were used to present baseline characteristics of the cohort. For continuous variables, means or medians with corresponding interquartile range (IQR) were reported, while frequencies and percentages were reported for categorical variables.

For VTE and iSVT recurrence, person-time of follow-up was counted from the date of discontinuation of anticoagulation until the date of VTE, iSVT recurrence, migration (out of the hospital's catchment area), death, or end of the study period (October 31, 2022). Patients with VTE or iSVT recurrence during anticoagulant treatment were excluded from the analysis. Incidence rates were calculated as the number of events divided by the total person-time at risk and expressed as events per 100 person-years with 95% confidence intervals (CI). The 1- and 5-year cumulative incidence of VTE and iSVT recurrence after discontinuation of anticoagulation were calculated using the 1-Kaplan-Meier (1-KM) function.

For bleedings events, follow-up was counted from the date of the iSVT diagnosis until the date of the bleeding event, migration, death, or 45 days after diagnosis. When analyzing CRNMB, patients who experienced major bleeding were censored from the date of the major bleeding event (as a major bleeding event would likely impact anticoagulant treatment and thereby alter the risk of CRNMB).

Statistical analysis was carried out using Stata version 17.0 (Stata corporation, College station, Texas, USA).

Ethics and approvals

The Regional Committee for Medical and Health Research Ethics (REK), reference number 200024, approved this study. Participants who provided signed informed written consent and deceased patients were included, as consent was waived for deceased patients by REK.

RESULTS

Between 2014 and 2021, 315 patients with iSVT in the lower extremities were identified in TROLL. In total, 86 patients were excluded according to the predefined exclusion criteria (24 patients lacked informed consent, 37 patients with previous VTE or SVT, 22 patients with either active cancer or cancer diagnosed within three months after the iSVT diagnosis, two patients did not receive any anticoagulant treatment, one patient was not living in the hospitals catchment area). Thus, the final study cohort consisted of 229 iSVT patients.

Median age was 60 years (IQR 48-71) and 125 (55%) were women. The iSVT was located in the saphenous veins in 141 patients (62%), while 88 (38%) had iSVT in other superficial veins. The iSVT was located below the knee in 124 patients (54%) and was observed both below and above the knee in 65 patients (28%). Median duration of treatment was 45 days (IQR 44.0-54.5). One hundred and seventy patients (74%) were treated with DOACs; of these 163 (96%) received rivaroxaban. In the rivaroxaban group, 135 patients (83%) were prescribed a dose of 10 mg OD. The remaining patients (n=59, 26%) were treated with LMWH (enoxaparin or dalteparin) (Table 1).

Mean follow-up time was 3.3 years (maximum follow-up: 8.6 years). One patient was lost to follow-up due to migration out of the hospital's catchment area (censored from the date of migration), and 17 patients died (censored from the date of death). One patient experienced a proximal DVT during anticoagulant treatment (not included in the analysis). Incidence rate of VTE after discontinuation of anticoagulation was 3.5 (95% CI 2.4-5.2) per 100 person-years. The 1- and 5-year cumulative incidences of VTE were 4.6% (95% CI: 2.5-8.3) and 15.9% (95% CI: 10.8-22.9), respectively (Table 2 and Figure 1A). Of these thromboembolic events, 13 (50%) were pulmonary embolisms, 12 (40%) were deep vein

thrombosis and one (4%) splanchnic vein thrombosis (Table 3). In analyses restricting VTE to proximal DVT and PE only (i.e., isolated distal DVT not considered as an outcome), the 1- and 5-year cumulative incidences of VTE were 3.7% (95% CI 1.9-7.2) and 13.1% (95% CI 8.4-19.9), respectively (Table 2 and Figure 1B). Sex-specific analyses showed that the 1- and 5-year cumulative incidences of overall VTE after iSVT were 2.5% (95% CI 0.8-7.5) and 13.1% (95% CI 7.5-22.4) in women, and 7.1% (95% CI 3.5-14.4) and 19.3% (95% CI 11.4-31.7) in men, respectively (Figure 2).

In total, 28 patients experienced a recurrent iSVT in the lower extremities, yielding an iSVT recurrence rate of 4.4 (95% CI 3.1-6.4) per 100 person-years. The 1- and 5- year cumulative incidences of iSVT recurrence were 6.5% (95% CI 3.9-10.7) and 15.9% (95% CI 10.8-23.1), respectively (Table 2 and Figure 1C). The median time to VTE and iSVT recurrence was 1.5 and 1.1 years, respectively. Of patients treated with rivaroxaban, 32 (20%) were categorized as treatment failure. Of these, two patients experienced long-term iSVT recurrence and one patient a popliteal DVT.

The overall 45-day cumulative incidence of major bleeding was 0.4% (95% CI 0.1-3.1) and for CRNMB 1.8% (95% CI 0.7-4.6). The only major bleeding event was a woman receiving dalteparin with postoperative bleeding after a not-planned caesarean section. There were two cases of CRNMB in patients receiving enoxaparin; one rectal bleeding and one hematuria, and two CRNMB cases in patients receiving rivaroxaban; one vaginal bleeding and one bleeding in a Bakers cyst. Restricting the analyses to patients treated with DOAC revealed no major bleedings and a 45-day cumulative incidence of CRNMB of 1.2% (95% CI 0.3-4.6) (Table 4).

DISCUSSION

This study evaluated the long-term risk of VTE and recurrent iSVT in patients with high-risk iSVT treated with anticoagulants. Despite anticoagulant treatment according to current international guidelines, 4.6% of patients developed VTE and 6.5% had recurrent iSVT during the first year. These events continued to occur, reaching a similar cumulative incidence of VTE and of iSVT recurrence of 16% within 5 years. Major bleeding events were rare during the study period.

Limited data exists regarding long-term outcomes after iSVT. Galanaud et al. followed 285 patients with iSVT for three years and reported a recurrence rate of 5.4 per 100 person-years for the composite outcome of VTE and iSVT. However, when restricting the outcome to VTE only, the incidence rate was 2.5 per 100 person-years [12]. This is lower than the rate of 3.5 per 100 person-years observed in our study, which could possibly be explained by a difference in the severity of iSVT in the two study populations. In our study, a thrombus length of ≥5 centimeters and anticoagulant treatment were required for inclusion. In contrast, the study by Galanaud et al. did not list the thrombus length criterion, and only 75% of their patients were treated with anticoagulants, indicating inclusion of less severe cases [12]. Furthermore, outcomes were identified by telephone interviews, which could potentially have led to underreporting of events [12]. In agreement with our findings, Galanaud et al. found that recurrences were similarly distributed between VTE- and iSVT events (49% and 51% for VTE and iSVT, respectively) [12]. In a Danish registry study including 10973 iSVT patients followed for a median of seven years, the incidence rate of VTE was 1.8% per person-year [11]. However, this study was solely based on International Classification of diseases codes (ICD 8 and ICD 10), and consequently there could be some

degree of misclassification for both exposure (iSVT) and outcome (VTE) [11]. Furthermore, the Danish registry study included all iSVT patients, regardless of the size of the thrombus [11]. In this context, the patients included in our cohort may have been at a higher risk of VTE due to a more severe index iSVT.

In our study, we found a substantial incidence of VTE after iSVT despite that all patients were treated with anticoagulants. A large proportion of the VTE events were either a proximal DVT or PE (81%), and correspondingly, the cumulative incidences for proximal DVT and PE were high (1- and 5-year cumulative incidence: 3.7% and 13.1%, respectively). In comparison, Galanaud et al. found that 65% of the VTEs were either a proximal DVT or PE [12]. Since all patients in our study were treated with anticoagulants and a substantial portion of the patients developed VTE, it is important to establish more knowledge on treatment of iSVT to prevent VTE. Since our study was observational, we could not assess the impact of different dose regimens or treatment durations on the risk of recurrence. However, we found that 20% of the patients treated with rivaroxaban 10 mg OD were defined as treatment failures and needed prolonged anticoagulation and/or increased dose.

"In line with previous studies [6, 11, 23], we found that the risk of VTE was higher in men than in women. However, the wide and overlapping confidence intervals warrant cautious interpretation.

The cumulative incidence of major bleeding in this study was 0.4%, which is in line with findings reported by others [13, 15, 17, 18]. The one major bleeding observed in our study was a postoperative bleeding following acute caesarean section, i.e., not a spontaneous bleeding, in a woman treated with LMWH. Apart from the SURPRISE study [15], few studies have explored the safety of DOACs in patients with iSVT. The SURPRISE

study found no major bleeding events in the rivaroxaban group [15]. In the present study, most of the patients were treated with rivaroxaban. The absence of major bleedings in our study may support the safety of DOAC treatment in patients with iSVT.

The strengths of this study are the long and close follow-up of patients in the TROLL registry and the large number of iSVT patients treated with DOACs (rivaroxaban). We have a prospective design, with index-, recurrence- and bleeding events being validated. All patients included have been diagnosed by CUS and thereby DVT was ruled out. Furthermore, long-term data regarding high-risk iSVT patients are limited. This study also has some limitations that need consideration. Patients were followed from 2014 until October 2022 leading to some patients having less than five years of follow-up. Consequently, reduced statistical precision in the 5-year estimates is possible, as reflected by the wide 95% confidence intervals. Although most patients have been followed up at the thrombosis clinic and registered in TROLL, we cannot rule out the possibility of some patients being treated in other settings in case of a bleeding or recurrent event. However, patients still living in Østfold Hospital's catchment area would likely be followed up at the thrombosis clinic during anticoagulant treatment enabling the bleeding event to be registered at a later visit. Additionally, if a recurrent event occurs in another hospital the patient will be referred to the thrombosis clinic at our hospital or the event will be captured during medical records review for validation. Adjudication of recurrent iSVT might be difficult, particularly if it occurs in the same vascular segment as the first event. None of the participants were subjected to imaging after the anticoagulant treatment. However, a recurrence was defined as new onset of symptoms in combination with a CUS examination concluding that the iSVT was likely caused by a freshly formed thrombus (and not residual vein obstruction) requiring anticoagulant treatment. Our study population included patients referred to hospital with

iSVTs that required anticoagulant treatment. Therefore, our findings are not generalizable to all patients with iSVT, but represents a high-risk iSVT population. Finally, although, most general practitioners in Norway would refer patients with high-risk iSVT to an emergency department to rule out DVT, we cannot exclude the possibility that some patients could have been treated for their iSVT at their general practitioner, which could lead to a selection of patients with more severe clinical features in our study. However, most patient characteristics, such as age, BMI, VTE in first degree relatives, unprovoked iSVT, and localization of iSVT, were comparable to those of previous SVT studies [6, 24], while the proportion of females and patients with varicose veins were lower [6, 12, 24]. Moreover, we excluded patients with concomitant and previous VTE and patients with cancer, as these patient groups are known to have a high risk of VTE.

In conclusion, our findings indicate that the rates of VTE and recurrent iSVT are substantial in patients with a first high-risk iSVT treated with anticoagulants according to the ACCP guidelines, while bleeding rates are acceptably low. Further research is needed to establish the optimal dose and duration of anticoagulant treatment for secondary prevention in patients with high-risk iSVT.

ADDENDUM

C.T.Jørgensen participated in patient inclusion, data collection, study conception and design, statistical analysis, interpretation of results and drafted the manuscript. W.Ghanima established the registry and was responsible for study conception and design, and interpretation of results. M.Tavoly and S.K.Brækkan participated in study conception and design, choice of statistical analysis, and interpretation of results. H.H.Pettersen, E.Førsund

and E.Tjønnfjord participated in patient inclusion, updating of registry, and data collection. All authors participated in critical revision of the manuscript and approved the final version of the manuscript.

DISCLOSURES

C.T.Jørgensen reports lecture honoraria from Bayer. W.Ghanima reports fees for participation in Advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc- a Sanofi Company, Sanofi, SOBI, Griffols, UCB, Argenx. Lecture honoraria from Bayer, Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Griffols, Sanofi. Research grants from Bayer, and BMS/Pfizer. E.Tjønnfjord reports fees from Novartis, SOBI, Alexion, Janssen, BiGene, Abbvie, Grifols, Jazz, Takeda and Incyte. H.H.Pettersen reports fees from Novartis and Sanofi. Authors M.Tavoly, E.Førsund and S.K.Brækkan disclose no conflict of interest.

REFERENCES

[1] Frappé P, Buchmuller-Cordier A, Bertoletti L, Bonithon-Kopp C, Couzan S, Lafond P, et al. Annual diagnosis rate of superficial vein thrombosis of the lower limbs: the STEPH community-based study. Journal of thrombosis and haemostasis : JTH. 2014;12(6):831-8;10.1111/jth.12575.
[2] Coon WW, Willis PW, 3rd, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation. 1973;48(4):839-46;10.1161/01.cir.48.4.839.
[3] Decousus H, Frappé P, Accassat S, Bertoletti L, Buchmuller A, Seffert B, et al. Epidemiology, diagnosis, treatment and management of superficial-vein thrombosis of the legs. Best Pract Res Clin Haematol. 2012;25(3):275-84;10.1016/j.beha.2012.07.005.
[4] Décousus H, Bertoletti L, Frappé P. Spontaneous acute superficial vein thrombosis of the legs: do we really need to treat? Journal of thrombosis and haemostasis : JTH. 2015;13 Suppl 1:S230-7;10.1111/jth.12925.
[5] Kitchens CS. How I treat superficial venous thrombosis. Blood. 2011;117(1):39-44;10.1182/blood-2010-05-286690.
[6] Decousus H, Quéré I, Presles E, Becker F, Barrellier MT, Chanut M, et al. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med. 2010;152(4):218-24;10.7326/0003-4819-152-4-201002160-00006.
[7] Galanaud JP, Genty C, Sevestre MA, Brisot D, Lausecker M, Gillet JL, et al. Predictive factors for concurrent deep-vein thrombosis and symptomatic venous thromboembolic recurrence in case of

superficial venous thrombosis. The OPTIMEV study. Thromb Haemost. 2011;105(1):31-9;10.1160/th10-06-0406.

[8] Quéré I, Leizorovicz A, Galanaud JP, Presles E, Barrellier MT, Becker F, et al. Superficial venous thrombosis and compression ultrasound imaging. J Vasc Surg. 2012;56(4):1032-8.e1;10.1016/j.jvs.2012.03.014.

[9] van Langevelde K, Lijfering WM, Rosendaal FR, Cannegieter SC. Increased risk of venous thrombosis in persons with clinically diagnosed superficial vein thrombosis: results from the MEGA study. Blood. 2011;118(15):4239-41;10.1182/blood-2011-05-356071.

[10] Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160(6):809-15;10.1001/archinte.160.6.809.

[11] Cannegieter SC, Horváth-Puhó E, Schmidt M, Dekkers OM, Pedersen L, Vandenbroucke JP, et al. Risk of venous and arterial thrombotic events in patients diagnosed with superficial vein thrombosis: a nationwide cohort study. Blood. 2015;125(2):229-35;10.1182/blood-2014-06-577783.

[12] Galanaud JP, Sevestre MA, Pernod G, Kahn SR, Genty C, Terrisse H, et al. Long-term risk of venous thromboembolism recurrence after isolated superficial vein thrombosis. Journal of thrombosis and haemostasis : JTH. 2017;15(6):1123-31;10.1111/jth.13679.

[13] Decousus H, Prandoni P, Mismetti P, Bauersachs RM, Boda Z, Brenner B, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med. 2010;363(13):1222-32;10.1056/NEJMoa0912072.

[14] Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e96S;10.1378/chest.11-2301.

[15] Beyer-Westendorf J, Schellong SM, Gerlach H, Rabe E, Weitz JI, Jersemann K, et al. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. Lancet Haematol. 2017;4(3):e105-e13;10.1016/s2352-3026(17)30014-5.

[16] Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev. 2018;2(2):Cd004982;10.1002/14651858.CD004982.pub6.

[17] Blin P, Sevestre MA, Pouchain D, Gillet JL. Management and 3-month outcomes of isolated superficial vein thrombosis of the lower limb: A real-world cohort study. Thromb Res. 2017;157:117-9;10.1016/j.thromres.2017.07.009.

[18] Galanaud JP, Bosson JL, Genty C, Presles E, Cucherat M, Sevestre MA, et al. Superficial vein thrombosis and recurrent venous thromboembolism: a pooled analysis of two observational studies. Journal of thrombosis and haemostasis : JTH. 2012;10(6):1004-11;10.1111/j.1538-7836.2012.04704.x.

[19] Jørgensen CT, Tavoly M, Pettersen HH, Førsund E, Roaldsnes C, Olsen MK, et al. The venous thrombosis registry in Østfold Hospital (TROLL registry) - design and cohort description. Research and Practice in Thrombosis and Haemostasis. 2022;6(5);https://doi.org/10.1002/rth2.12770.

[20] Kaatz S, Ahmad D, Spyropoulos A, Schulman S, Anticoagulation SoCo. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2015;13(11):2119-26

[21] Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis : JTH. 2005;3(4):692-4;10.1111/j.1538-7836.2005.01204.x.

[22] Norwegian Society on Thrombosis and Hemostasis. Norwegian Guidelines of antithrombotic treatment 2020 Norway2020 [cited 2023. 01.01.]. Available from: https://app.magicapp.org/#/guideline/4246.

[23] Quenet S, Laporte S, Décousus H, Leizorovicz A, Epinat M, Mismetti P. Factors predictive of venous thrombotic complications in patients with isolated superficial vein thrombosis. J Vasc Surg. 2003;38(5):944-9;10.1016/s0741-5214(03)00607-4.

[24] Bauersachs R, Gerlach HE, Heinken A, Hoffmann U, Langer F, Noppeney T, et al. Management and Outcomes of Patients with Isolated Superficial Vein Thrombosis under Real Life Conditions (INSIGHTS-SVT). Eur J Vasc Endovasc Surg. 2021;62(2):241-9;10.1016/j.ejvs.2021.04.015.

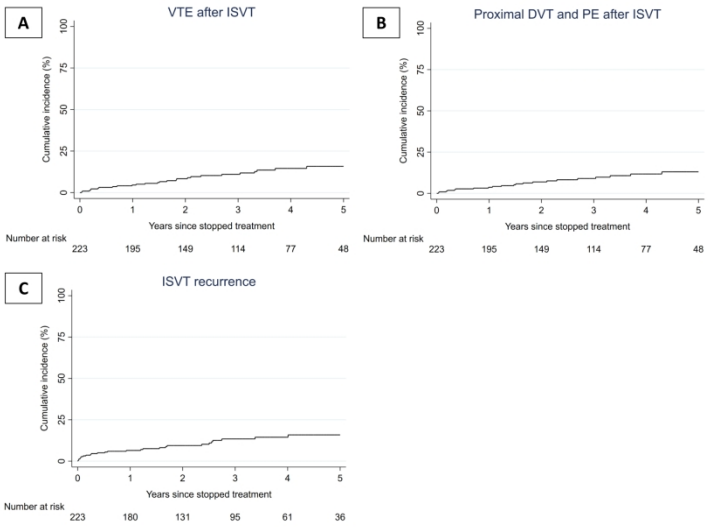


Figure 1 Cumulative incidence of venous thromboembolism (VTE) (panel A), cumulative incidences of proximal deep vein thrombosis (DVT) and pulmonary embolism (PE) (panel B) and cumulative incidences isolated superficial vein thrombosis recurrence (iSVT) (panel C) after high-risk iSVT.

338x190mm (300 x 300 DPI)

Figure 2 Cumulative incidence of venous thromboembolism for women and men after high-risk isolated superficial vein thrombosis

1058x769mm (72 x 72 DPI)

Table 1 Cohort characteristics, provoking factors, localization of the index thrombosis and treatment for patients with high-risk isolated superficial vein thrombosis (iSVT).

Characteristics	**n = 229**
Female, n (%)	125 (54.6)
Male, n (%)	104 (45.4)
Age, median (IQR)	60 (48-71)
BMI, median (IQR) *	28.4 (25.5-31.6)
Known thrombophilia, n (%)	19 (8.3)
VTE in first-degree relatives, n (%)	53 (23.1)
Varicose veins, n (%)	92 (40.2)
Provoking factors	
Surgery, n (%)	18 (7.9)
Trauma, n (%)	9 (3.9)
Immobilization, n (%)	1 (0.4)
Estrogen-containing contraceptives, n (%)	9 (3.9)
Hormone replacement therapy, n (%)	6 (2.6)
Pregnancy or puerperium, n (%)	10 (4.4)
Long-haul flights, n (%)	21 (9.2)
Unprovoked, n (%) †	163 (71.2)
Location of iSVT	
Saphenous veins, n (%)	141 (61.6)
Other superficial veins, n (%)	88 (38.4)
Over knee, n (%)	39 (17.0)
Below knee, n (%)	124 (54.2)
Whole extremity, n (%)	65 (28.4)
Unknown, n (%)	1 (0.4)
Type and duration of treatment	
Treatment duration, days, median (IQR)	45 (44.0-54.5)
LMWH, n (%)	59 (25.8)
Enoxaparin, n (%)	41 (17.9)
Dalteparin, n (%)	18 (7.9)
DOAC, n (%)	170 (74.2)
Rivaroxaban, n (%)	163 (71.2)
Apixaban, n (%)	7 (3.0)

* Missing BMI=6

† None of the provoking factors listed

IQR: interquartile range, LMWH: low-molecular weight heparin, DOAC: direct oral anticoagulants, BMI: Body Mass Index calculated in kg/m^2

Long-haul flights are defined as flights over four hours. Immobilization is defined as immobilization

for medical reason, other than surgery and trauma.
Known thrombophilia comprises factor V Leiden, prothrombin G20210A, protein C-, S or antithrombin deficiencies and antiphospholipid syndrome (APS)

Table 2 Incidence rates per 100 person years and cumulative incidence after high-risk isolated superficial vein thrombosis

n=229	Incidence rates per 100 person years (95% CI)	1-year cumulative incidence, % (95% CI)	5-years cumulative incidence, % (95% CI)
VTE *	3.5 (2.4–5.2)	4.6 (2.5-8.3)	15.9 (10.8–22.9)
Proximal DVT and PE only	2.9 (1.9-4.4)	3.7 (1.9-7.2)	13.1 (8.4-19.9)
iSVT recurrence †	4.4 (3.1–6.4)	6.5 (3.9-10.7)	15.9 (10.8–23.1)

VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, iSVT: isolated superficial vein thrombosis, CI: confidence interval

* All VTE diagnosis (distal and proximal DVT, PE and splanchnic veins), † Recurrence of iSVT with no VTE diagnosis

Table 3 Characteristics of venous thromboembolism after high-risk isolated superficial vein thrombosis

VTE (n=26)	**N (%)**
PE	13 (50.0)
DVT	12 (46.2)
Proximal DVT*	8 (66.7)
Distal DVT*	4 (33.3)
Contralateral*	4 (33.3)
Splanchnic veins	1 (3.9)

VTE: venous thromboembolism, PE: pulmonary embolism, DVT: deep vein thrombosis
* % of all DVTs

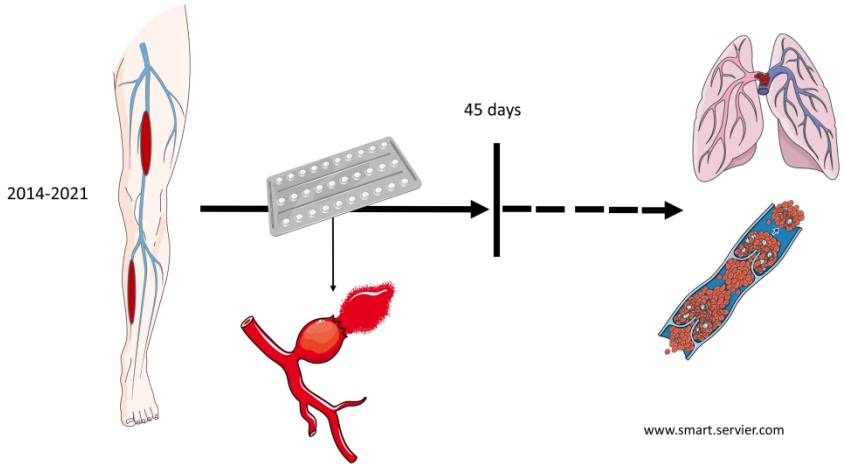
Table 4 Cumulative major and clinically relevant non-major bleeding incidences overall and restricted to direct oral anticoagulants (DOACs)

n=229	**45 days cumulative incidence, % (95% CI)**
Major bleeding *	0.4 (0.1 – 3.1)
CRNMB †	1.8 (0.7 – 4.6)
Restricted to DOAC (n=170)	
Major bleeding	0
CRNMB	1.2 (0.3 – 4.6)

CI: confidence interval, CRNMB: clinically relevant non-major bleeding, DOAC: direct oral anticoagulants

* Major bleeding: Dalteparin; postoperative bleeding after caesarian section

† CRNMB: Enoxaparin; rectal bleeding and hematuria. Rivaroxaban; vaginal bleeding and bleeding in Bakers cyst



Graphical abstract

338x190mm (300 x 300 DPI)