

Management and Outcomes of Patients with Isolated Superficial Vein Thrombosis under Real Life Conditions (INSIGHTS-SVT)

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WHAT THIS PAPER ADDS

Isolated superficial vein thrombosis (SVT) is a common but underrated condition. This study shows that patients' risk profiles, clinical presentation, and treatment patterns are very heterogeneous. Patients with SVT bear a significant risk of recurrent venous thromboembolism and recurrent or extended SVT at three months despite a high rate of initial anticoagulation. While recognising the methodological limitations of the prospective observational study design, the results suggest a beneficial effect of fondaparinux vs. low molecular weight heparin in isolated SVT under clinical practice conditions, in line with previous controlled and observational studies.

Objective: Management and outcomes of superficial vein thrombosis (SVT) are highly variable and not well described. Therefore, the INvestigating SIGNificant Health Trends in the management of SVT (INSIGHTS-SVT) study collected prospective data under real life conditions.

Methods: Prospective observational study of objectively confirmed acute isolated SVT. The primary outcome was a composite of symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), and extension or recurrence of SVT at three months. The primary safety outcome was clinically relevant bleeding.

Results: A total of 1 150 patients were included (mean age 60.2 ± 14.7 years; 64.9% women; mean BMI 29.4 ± 6.3 kg/m²). SVT was below the knee in 54.5%, above the knee in 26.7%, above and below the knee in 18.8%. At baseline, 93.6% received pharmacological treatment (65.7% fondaparinux, 23.2% heparins, 4.3% direct oral anticoagulants [DOACs], 14.5% analgesics), 77.0% compression treatment, and 1.9% surgery; 6.4% did not receive any anticoagulation. The primary outcome occurred in 5.8%; 4.7% had recurrent or extended SVT, 1.7% DVT, and 0.8% PE. Clinically relevant non-major bleeding occurred in 1.2% and major bleeding in 0.3%. Complete clinical recovery of SVT was reported in 708 patients (62.4%). Primary outcome adjusted by propensity score and for treatment duration was lower with fondaparinux compared with low molecular weight heparin (4.4% vs. 9.6%; hazard ratio [HR] 0.51; 95% confidence interval [CI] 0.3 – 0.9; $p = .017$). On multivariable analysis, associated factors for primary outcome included another SVT prior to the present SVT event (HR 2.3), age per year (HR 0.97), duration of drug treatment per week (HR 0.92), and thrombus length (HR 1.03).

Conclusion: At three month follow up, patients with isolated SVT are at risk of thromboembolic complications (mainly recurrent or extended SVT), despite anticoagulation. In this real life study, about one third had received either heparins, oral anticoagulants, or no anticoagulation.

Keywords: Superficial vein thrombosis, venous thrombosis, low molecular weight heparin, fondaparinux, treatment

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INTRODUCTION

Superficial vein thrombosis (SVT) describes partial or total thrombotic obstruction of the lumen of the affected vein and inflammatory alterations of the vessel wall.^{1,2} Because of the inflammatory processes, SVT requires considerable time to heal and is associated with pain and discomfort. In clinical practice, SVT frequently manifests in the saphenous veins of the lower limbs, predominantly in varicose veins.

SVT is a common disease. In a retrospective cohort study in The Netherlands, the incidence of coded SVT events in primary care was 1.3 per 1 000 patient years.³ Despite its frequent occurrence, SVT is less well studied than deep vein thrombosis (DVT). Previously SVT was erroneously considered to be a minor, self limiting disease that is easily diagnosed on clinical grounds and that requires only symptomatic treatment.^{4,5} However, it has become clear that SVT, DVT, and pulmonary embolism (PE) are related entities, and they may occur concomitantly or in sequence. According to a meta-analysis by Di Minno *et al.* based on 4 358 patients in 21 studies, the concomitant prevalence of DVT and PE at SVT diagnosis was 18.1% (95% confidence interval [CI] 13.9 – 23.3%) and 6.9% (95% CI 3.9 – 11.8%), respectively.⁶

Lower limb SVT may propagate into the deep veins or may be accompanied by independent DVT, and it may have a complicated and potentially fatal course with PE. The placebo controlled CALISTO trial included the largest prospective cohort of patients with spontaneous SVT not receiving anticoagulant treatment. In the study arm with untreated patients, 6.3% of patients developed symptomatic complications up to day 77. These complications included symptomatic extension of the SVT into the saphenofemoral junction (SFJ) in 3.6%, recurrent SVT in 1.7%, symptomatic DVT in 1.3%, PE in 0.4% and death from any cause in 0.1% of patients.⁷

A Cochrane review on the treatment of isolated SVT of the legs, i.e., SVT without concomitant DVT or PE classified the available data only for the injectable selective Xa-inhibitor fondaparinux as good evidence, based on the CALISTO trial with a treatment duration of 45 days.⁸ Fondaparinux is the only anticoagulant explicitly approved by the European Medicines Agency (EMA) for the treatment of SVT.

Until today, the highly variable real life management and outcomes of SVT are poorly defined by prospective studies. The Investigating SIGNificant Health Trends in the management of Superficial Vein Thrombosis (INSIGHTS-SVT) study aimed to collect representative data on patient characteristics, diagnosis, management and outcomes of isolated SVT in Germany under real life conditions. Further, it undertook analyses to identify associated factors for subsequent events.

MATERIAL AND METHODS

The rationale, design, and methods of the study have been presented in detail previously.⁹ In brief, this was a prospective, multicentre, observational study with a one year

follow up. Here, the results at the three month follow up are reported. The study protocol was approved by the institutional review board of the physician chamber in Hesse, Germany, and all patients provided written informed consent. The study was registered by the regulatory authority (BfArM) under NIS 6781 and by [ClinicalTrials.gov](https://clinicaltrials.gov) under NCT 02699151.

Hospital-based and office-based physicians who regularly treated patients with SVT and were certified for compression ultrasound (CUS) diagnostics, including vascular physicians, vascular surgeons, phlebologists, and general internists or practitioners were invited to participate in INSIGHTS-SVT. In practice, vascular specialists were the dominant investigator group while primary care physicians were infrequent.

Patient inclusion criteria were objectively confirmed (by ultrasound including duplex ultrasound, DUS), acute (time interval between onset of SVT symptoms and inclusion less than three weeks), isolated SVT of the lower extremities; concomitant DVT was excluded by CUS or duplex sonography, and patients had no symptoms of PE. Patients were ineligible, if they met any of the following exclusion criteria: proximal extension of SVT located ≤ 3 cm from the SFJ; subjects unlikely to comply with the requirements of the protocol (e.g., due to cognitive and/or language limitations); subject probably not available for one year follow up. Patients had a follow up visit at three months and at one year; optional visits were at 10 ± 3 days and 45 ± 3 days, respectively. Due to the observational nature of the study, ultrasound examinations, and any other diagnostic or therapeutic decisions during follow up were at the investigators' discretion. DUS refers to ultrasound systems with both pulsed wave Doppler and colour technology.

The primary outcome measure was the incidence of symptomatic venous thromboembolism (VTE), a composite of DVT, PE, and recurrent or extending SVT at three months' follow up. Secondary outcomes included recurrent SVT or extension of the SVT into the deep vein system or 3 cm or less from the SFJ, symptomatic PE, DVT, persistent SVT (clinical non-improvement), asymptomatic SVT, death, new cancer or cancer relapse, and hospitalisation because of VTE.

The primary safety outcome measure was the combination of major or clinically relevant non-major bleeding, with definitions based on American College of Chest Physicians Evidence Based Clinical Practice Guidelines (major bleedings)¹⁰ and the CALISTO trial (clinically relevant non-major bleedings).⁷ Information on pharmacological and non-pharmacological therapy (i.e., the types of drug used, their dosing and duration of application) was collected. For analysis of the impact of different anticoagulant doses, these were categorised as prophylactic ($< 50\%$ of full therapeutic dose), intermediate ($50\% - 75\%$ of full therapeutic dose) or therapeutic ($> 75\%$ of full therapeutic dose). Further, data on surgical interventions for varicose veins were documented, including stripping operation, thrombectomy, sclerotherapy, ligation of the SFJ, and endovascular procedures such as laser or radiofrequency

ablation. Non-pharmacological treatments comprised compression bandages, compression stockings, leg elevation, cooling, and other measures. If no anticoagulant drugs were given, or if there was no treatment at all, this was also documented.

Statistical methods

Categorical variables were reported in frequency tables including information on absolute and relative frequencies as well as the number of missing values. Continuously distributed variables were analysed by reporting the sample mean and its standard deviation. The likelihood of the primary endpoint was analysed by a Cox proportional hazards model. Univariable analyses included potential associated factors for the outcome that had been reported in the literature in the past. The multivariable Cox proportional hazards model was established by LASSO with the Schwarz Bayesian information criterion as model selection criterion. K-fold ($k = 10$) cross validation was used to evaluate the predictive performance (Harrell's c -statistic) of the multivariable model. The p value threshold for statistical significance was .050. As pre-specified analysis, the onset of the primary endpoint, was compared between fondaparinux and low molecular weight heparin (LMWH). A propensity score was estimated to balance the clinical characteristics between the two treatments at treatment start including age, sex, body mass index, history of SVT/DVT, the number of risk factors, comorbidities, age at SVT onset, and SVT characteristics such as location. A propensity score weight was estimated based on the predicted propensity score to weigh the comparison between the two treatments in order to get an unbiased estimate. The proportional hazard assumption in Cox models was tested based on Schoenfeld residuals.

Medications were coded with WHO-DD Drugs Insights by ATC codes. Statistical analyses were conducted with the software package SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) or higher.

The current publication presents the main outcomes at three month follow up (timepoint *a priori* defined for primary endpoint analyses). The one year follow up data, which are compromised by considerable attrition, will be presented in a subsequent publication.

RESULTS

Patient flow is shown in Fig. 1. Of 1 159 patients who were documented at inclusion, 1 150 (99.2%) were available at three months for the primary outcome analysis, and 918 (79.2%) at one year.

Patient characteristics are shown in Table 1. The mean patient age was 60.2 ± 14.7 years, and about two thirds (64.9%) were females. Almost all patients were Caucasian (99.5%). Mean body mass index (BMI) was 29.4 ± 6.3 kg/m², and 36.9% of patients were obese (BMI ≥ 30 kg/m²). Personal history of VTE was reported in 39.1% of patients, including SVT in 30.1% and DVT or PE in 15.4%.

About a quarter (26.2%) of patients had at least three, and 36.8% two risk factors. The most frequent chronic risk factors were varicose veins (75.6%) and chronic venous insufficiency or ulcer (48.3%). As transient, expositional risk factors travel longer than six hours (as reported by 8.2% of patients), trauma (4.0%), and previous major surgery (3.9%) were reported most frequently.

Of thrombi, 54.3% were localised in the great or small saphenous trunk. They had a mean extension of 14.5 ± 10.7 cm and a mean distance between the thrombus and the SFJ of 26.2 ± 14.8 cm. On average, patients had 2.2 ± 1.0 affected veins.

Diagnostics

Most commonly, DUS (87.1%) or CUS (67.5%) were used for diagnosis. In addition, D-Dimer tests were performed in 30.5% of patients, while phlebography (0.0%), computed tomography (0.2%), or magnetic resonance imaging (0.0%) were not or very rarely used.

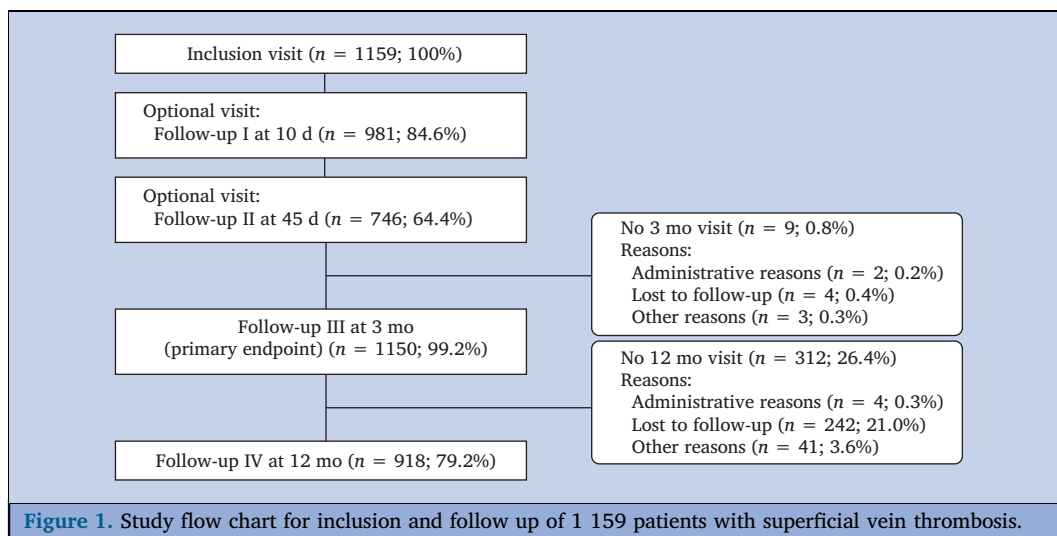


Table 1. Characteristics of 1 159 patients with superficial vein thrombosis (SVT) at inclusion

	Total (n = 1 159)	Treatment with			
		Fondaparinux (n = 761)	LMWH (n = 264)	UFH/VKA/DOAC (n = 60)	No anticoagulant (n = 74)
Age – y	60.2 ± 14.7 (61)	59.8 ± 4.2 (61)	59.5 ± 15.3 (61)	64.1 ± 16.7 (66.5)	62.8 ± 14.3 (62)
Age ≥ 65 years	477 (41.2)	302 (39.7)	109 (41.3)	33 (55.0)	33 (44.6)
Women	752 (64.9)	487 (64.0)	170 (64.4)	37 (61.7)	58 (78.4)
Body mass index – kg/m ²	29.4 ± 6.3 (28.3)	29.5 ± 6.3 (28.4)	29.2 ± 6.2 (27.8)	30.2 ± 7.0 (28.9)	28.0 ± 5.8 (26.5)
Body mass index ≥ 30 kg/m ²	428 (36.9)	287 (37.7)	97 (36.7)	26 (43.3)	18 (24.3)
Caucasian	1 153 (99.5)	761 (100)	259 (98.1)	59 (98.3)	74 (100)
Chronic risk factors for VTE					
None	136 (11.7)	89 (11.7)	36 (13.6)	2 (3.3)	9 (12.2)
Varicose veins	876 (75.6)	573 (75.3)	196 (74.2)	47 (78.3)	60 (81.1)
History of thrombosis					
SVT	349 (30.1)	236 (31.0)	72 (27.3)	22 (36.7)	19 (25.7)
DVT or PE	178 (15.4)	114 (15.0)	41 (15.5)	15 (25.0)	8 (10.8)
VTE (SVT, DVT, or PE)	453 (39.1)	304 (40.0)	94 (35.6)	31 (51.7)	24 (32.4)
Family history of DVT or PE	186 (16.1)	127 (16.7)	37 (14.0)	12 (20.0)	10 (13.5)
Chronic venous insufficiency or ulcer	560 (48.3)	368 (48.4)	124 (47.0)	41 (68.3)	27 (36.5)
Cancer	81 (7.0)	50 (6.6)	21 (8.0)	5 (8.3)	5 (6.8)
Known thrombophilia	57 (4.9)	36 (4.7)	12 (4.6)	8 (13.3)	1 (1.4)
Hormone replacement therapy	18 (1.6)	12 (1.6)	2 (0.8)	1 (1.7)	3 (4.1)
Oral contraception	84 (11.2)	52 (10.7)	21 (12.4)	5 (13.5)	6 (10.3)
Current smoking	190 (16.4)	129 (17.0)	37 (14.0)	11 (18.3)	13 (17.6)
Hemiplegia	6 (0.5)	4 (0.5)	2 (0.8)	0 (0.0)	0 (0.0)
Chronic inflammatory disease	57 (4.9)	32 (4.2)	13 (4.9)	5 (8.3)	7 (9.5)
Immobility or bedridden	43 (3.7)	20 (2.6)	14 (5.3)	4 (6.7)	5 (6.8)
Arterial risk factors*	606 (52.3)	397 (52.2)	132 (50.0)	38 (63.3)	39 (52.7)
Heart failure	31 (2.7)	20 (2.6)	4 (1.5)	6 (10.0)	1 (1.4)
Respiratory insufficiency	35 (3.0)	22 (2.9)	9 (3.4)	1 (1.7)	3 (4.1)
Number of chronic risk factors					
0	136 (11.7)	89 (11.7)	36 (13.6)	2 (3.3)	9 (12.2)
1	293 (25.3)	204 (26.8)	59 (22.4)	10 (16.7)	20 (27.0)
2	426 (36.8)	280 (36.8)	98 (37.1)	26 (43.3)	22 (29.7)
3 or more	304 (26.2)	188 (24.7)	71 (26.9)	22 (36.7)	23 (31.1)
Transient, expositional risk factors for VTE					
None	950 (81.9)	624 (82.0)	211 (79.9)	52 (86.7)	63 (85.1)
Trauma in last 4 weeks	46 (4.0)	33 (4.3)	8 (3.0)	3 (5.0)	2 (2.7)
Travel in > 6 hours by car or plane	95 (8.2)	66 (8.7)	21 (8.0)	4 (6.7)	4 (5.4)
Major surgery in last 12 weeks	45 (3.9)	29 (3.8)	13 (4.9)	1 (1.7)	2 (2.7)
Severe systemic infection	11 (1.0)	7 (0.9)	1 (0.4)	0 (0.0)	3 (4.1)
Pregnancy	8 (0.7)	5 (0.7)	2 (0.8)	0 (0.0)	1 (1.4)
Postpartum	13 (1.1)	4 (0.5)	8 (3.0)	0 (0.0)	1 (1.4)
Characteristics of SVT					
Great or small saphenous vein	629 (54.3)	395 (51.9)	159 (60.2)	42 (70.0)	33 (44.6)
Other veins	530 (45.7)	366 (48.1)	105 (39.8)	18 (30.0)	41 (55.4)
Great saphenous vein only	445 (38.4)	279 (36.7)	114 (43.2)	31 (51.7)	21 (28.4)
Distance between thrombus and saphenofemoral junction – cm	25 (15–40)	25 (15–40)	20 (11.5–35)	25 (17.5–40)	30 (20–50)
Distance between thrombus and saphenofemoral junction < 10 cm	50 (10.9)	34 (11.8)	14 (12.5)	1 (3.1)	1 (4.0)
Distance between thrombus and saphenofemoral junction ≥ 10 cm	407 (89.1)	254 (88.2)	98 (87.5)	31 (96.9)	24 (96.0)
Small saphenous vein only	58 (5.0)	35 (4.6)	12 (4.6)	5 (8.3)	6 (8.1)
Number of affected veins	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–2)	2 (1–3)
Localisation					
Above knee only	301 (26.7)	199 (26.6)	68 (27.4)	19 (32.8)	15 (20.8)
Below knee only	614 (54.5)	408 (54.5)	132 (53.2)	30 (51.7)	44 (61.1)
Above and below knee	212 (18.8)	142 (19.0)	48 (19.4)	9 (15.5)	13 (18.1)
Extension – cm					
< 20 cm	12 (6–20)	12 (6–20)	14 (6–20)	17 (10–25)	7 (4–15)
≥ 20 cm	778 (67.5)	503 (66.2)	185 (71.4)	30 (50.9)	60 (81.1)
	374 (32.5)	257 (33.8)	74 (28.6)	29 (49.2)	14 (18.9)

Data are presented as n (%), mean ± standard deviation (median), or median (interquartile range). Percentages refer to the number of patients with valid observations. LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Treatment

Almost all patients (93.6%) received anticoagulation at baseline. Non-pharmacological treatment was administered in 77.0%, and 1.9% underwent immediate surgery (venous stripping in 11 patients, crosssection in nine patients, phlebectomy in seven, endovenous thermal ablation in six, thrombectomy in four, other procedures in two). Drug treatment at the various visits is shown in Table 2. Fondaparinux was administered at baseline to 761 patients (65.7%), heparins to 269 patients (LMWH 22.8%, unfractionated heparin [UFH] 0.4%), and DOAC to 50 patients (4.3%), respectively. Prophylactic, intermediate and therapeutic doses were given for fondaparinux in 92.5, 4.8 and 0.0%, respectively, for LMWH in 48.7, 38.8, 12.5% and for others (UFH, vitamin K antagonist [VKA], DOAC) in 11.7, 56.7 and 31.7% of patients, respectively.

Over time, the rate of anticoagulation treatment decreased. At three months, only 7.4% of patients received some kind of anticoagulation. Mean treatment duration for fondaparinux was 34.8 ± 15.2 days (median 38), and for LMWH 23.3 ± 19.3 days (median 21) (Supplementary Fig. S1 displays details by treatment). Non-pharmacological treatment was used by 49.2% of patients at three months. The rate of any type of surgery for SVT increased to 7.8% at three months.

Outcomes at three months

Primary and secondary outcomes at three months are shown in Table 3. The primary outcome (DVT, PE, recurrent or extended SVT) occurred in 67 (5.8%) of patients. As secondary outcome, recurrent or extended SVT occurred in 54 (4.7%) and DVT or PE were diagnosed in 19 (1.7%) and 9 (0.8%) of patients at three months, respectively. Clinically relevant non-major bleeding occurred in 1.2% and major bleeding in 0.3% of the patients.

Complete recovery of SVT at three months was reported in 708 patients (62.4%), improvement in 343 patients (30.2%), unchanged status in 56 patients (4.9%), and worsening in 28 patients (2.5%) (Supplementary Table S1).

Associated factors for venous thromboembolism events

On univariable analysis of the primary outcome (SVT recurrence or extension, DVT, PE), the following factors were significantly ($p < .050$) associated with the occurrence of the primary outcome at three months: age per year (HR 0.98), history of SVT (HR 2.4), history of SVT/PE/DVT (HR 2.1), intermediate doses of drugs (HR 2.4), duration of drug treatment (HR 0.51 per week), known thrombophilia (HR 2.2), and SVT extension ≥ 20 cm (HR 1.9) (Supplementary Table S2). Thrombi above the knee did and below the knee did not show a different likelihood for recurrent events (5.0% vs. 5.1%; HR 0.99; 95% CI 0.53 – 1.83; $p = .97$).

On multivariable analysis, factors that were significantly associated with the likelihood for recurrent VTE events included history of SVT (HR 2.3), age per year (HR 0.97), duration of drug treatment per week (0.92), and thrombus length (HR 1.03) (Table 4). The proportional hazards assumption was not violated for the included parameters. The Harrel's C-statistic was 0.68 (95% CI 0.58 – 0.74) indicating an acceptable model performance.

Risk of symptomatic recurrent venous thromboembolism by treatment and duration of drug treatment

Patients treated with fondaparinux compared with LMWH had a 5.2% absolute reduction in the probability of the primary VTE outcome after adjusting for the propensity score and duration of drug treatment (4.4% vs. 9.6%; 95% CI 0.30 – 0.88; HR 0.51, $p = .017$, Fig. 2). The proportional hazards assumption was not violated (chi squared = 0.9,

Table 2. Treatment at baseline and during follow up for 1 159 patients with superficial venous thrombosis

	Baseline (n = 1 159)	10 d (n = 981)	45 d (n = 746)	3 mo (n = 1 150)
<i>Medication</i>				
<i>Anticoagulation</i>	1 085 (93.6)	800 (81.5)	190 (25.5)	85 (7.4)
Fondaparinux	761 (65.7)	524 (53.4)	108 (14.5)	27 (2.3)
<i>Heparins</i>	269 (23.2)	216 (22.0)	33 (4.4)	13 (1.1)
Low molecular weight heparin	264 (22.8)	184 (18.8)	30 (4.0)	11 (1.0)
Unfractionated heparin	5 (0.4)	32 (3.3)	3 (0.4)	2 (0.2)
Vitamin K antagonist*	5 (0.4)	5 (0.5)	1 (0.1)	0 (0.0)
DOAC	50 (4.3)	55 (5.6)	48 (6.4)	45 (3.9)
Platelet inhibitors†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Analgesics‡	168 (14.5)	75 (7.6)	20 (2.7)	15 (1.3)
Other medication for SVT treatment	15 (1.3)	7 (0.7)	1 (0.1)	2 (0.2)
<i>Physical therapy</i>				
Compression	893 (77.0)	675 (68.8)	556 (74.5)	521 (45.3)
Cooling	426 (36.8)	170 (17.3)	36 (4.8)	22 (1.9)
Other	75 (6.5)	37 (3.8)	4 (0.5)	0 (0.0)
Surgery	22 (1.9)	22 (2.2)	31 (4.2)	83 (7.2)

Data are presented as n (%). DOAC = direct oral anticoagulant.

* Phenprocoumon.

† Aspirin, other platelet inhibitors.

‡ Topical or systemic non-steroid anti-inflammatory drugs, COX-2 inhibitors, other analgesics.

Table 3. Primary and secondary outcomes of 1 150 patients with superficial venous thrombosis (SVT) at three months by treatment

	Total (n = 1 150)	Fondaparinux (n = 756)	LMWH (n = 261)	UFH/VKA/DOAC (n = 59)	No anticoagulant (n = 74)
<i>Primary outcome</i>					
Symptomatic VTE; DVT, PE, recurrent or extending SVT*	67 (5.8)	33 (4.4)	25 (9.6)	5 (8.5)	4 (5.4)
<i>Secondary outcome</i>					
SVT, recurrent or extending*	54 (4.7)	25 (3.3)	21 (8.1)	5 (8.5)	3 (4.1)
PE	9 (0.8)	4 (0.5)	4 (1.5)	0 (0.0)	1 (1.4)
DVT	17 (1.5)	11 (1.5)	5 (1.9)	1 (1.7)	0 (0.0)
DVT or PE	19 (1.7)	11 (1.5)	6 (2.3)	1 (1.7)	1 (1.4)
Death	3 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
New cancer or relapse	9 (0.8)	5 (0.7)	3 (1.2)	0 (0.0)	1 (1.4)
Hospitalisation due to VTE	7 (0.6)	2 (0.3)	4 (1.5)	0 (0.0)	1 (1.4)
Bleeding	17 (1.5)	9 (1.2)	7 (2.7)	1 (1.7)	0 (0.0)
Major bleeding	3 (0.3)	1 (0.1)	2 (0.8)	0 (0.0)	0 (0.0)
Clinically relevant non-major bleeding	14 (1.2)	8 (1.1)	5 (1.9)	1 (1.7)	0 (0.0)

Data are presented as *n* (%). LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant. DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

* Extension into the deep vein system or ≤ 3 cm from the saphenofemoral junction.

Table 4. Variables correlated with symptomatic thromboembolic events at three months in multivariable analysis* in 1 150 patients with superficial venous thrombosis (SVT)

	HR (95% CI)	<i>p</i>
Age per year	0.97 (0.96–0.99)	.008
Prior SVT	2.33 (1.44–3.78)	.001
Duration of medical therapy per week	0.92 (0.83–0.99)	.046
Thrombus length in cm	1.03 (1.02–1.05)	<.001

CI = confidence interval; HR = hazard ratio.

* LASSO with the Schwarz Bayesian information criterion as model selection criterion.

p = .34). Patients treated with fondaparinux had lower rates of primary VTE outcome in each treatment duration category. However, this association was only significant in patients treated for > 38 days (3.7% vs. 10.5%; HR = 0.37, *p* = .044, Table 5).

DISCUSSION

INSIGHTS-SVT is a large prospective observational study on current SVT treatment, providing comprehensive information on the characteristics of SVT patients, their diagnosis, management, and outcomes. The study shows that patients' risk profiles, clinical presentation and treatment patterns are very heterogeneous. Despite of a high rate of initial anticoagulation treatment, the patients' risk of recurrent vascular complications was remarkably high.

Between 2010 and 2017, three observational studies on patients with isolated SVT were performed in France: POST (2010),¹¹ OPTIMEV (2011),¹² and PERSEUS (2017)¹³ were conducted to investigate the characteristics of patients with isolated SVT, real life treatment and outcomes up to three months after presentation. While the general set up of

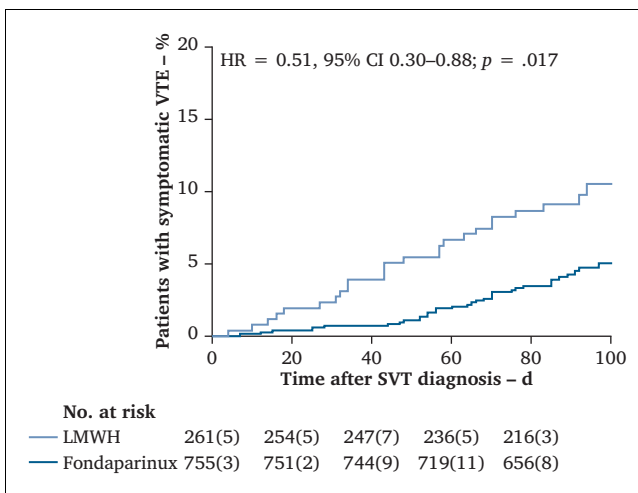


Figure 2. Cumulative Kaplan–Meier estimate for symptomatic venous thromboembolism (VTE; deep venous thrombosis, pulmonary embolism, recurrent or extending superficial venous thrombosis [SVT]) in 1 016 patients with SVT treated with fondaparinux (*n* = 33, 4.4% of 756) or low molecular weight heparin (LMWH; *n* = 25, 9.6% of 261). Hazard ratio (HR) for Fondaparinux vs. LMWH adjusted for propensity score and treatment duration estimated from a Cox proportional hazard model; proportional hazard assumption was not violated tested by Schoenfeld residuals. Note the adapted scale for y axis.

these studies was similar, they showed differing results with respect to documented VTE events during the observation periods. Overall rates of symptomatic recurrent VTE (SVT, DVT, or PE) at three months were 8.3% (6.0 – 10.6) in POST, 3.0% (1.7 – 4.9) in OPTIMEV, 3.3% (2.1 – 4.8) and 5.5% (2.3 – 11.0) in the fondaparinux or heparin treated patient groups in PERSEUS, respectively.

Furthermore, two randomised clinical trials, CALISTO⁷ and SURPRISE,¹⁴ are lined up to investigate the use of the pentasaccharide fondaparinux, or to compare fondaparinux with the DOAC rivaroxaban in the treatment of SVT patients

Table 5. Risk of symptomatic venous thromboembolism (VTE) by treatment with fondaparinux or low molecular weight heparin (LMWH) and treatment duration (days)

Duration of treatment with LMWH or fondaparinux	Fondaparinux		LMWH		VTE risk	
	Total – n	Events – n (%)	Total – n	Events – n (%)	HR (95% CI)	p
≤ 14 d	70	5 (7.1)	91	12 (13.2)	0.57 (0.60–5.14)	0.300
15–25 d	222	9 (4.1)	77	4 (5.2)	0.76 (0.38–4.39)	0.681
26–37 d	90	5 (5.6)	36	3 (8.3)	0.63 (0.38–6.61)	0.521
≥ 38 d	374	14 (3.7)	57	6 (10.5)	0.37 (1.03–7.03)	0.044

with a “high” thromboembolic risk, respectively. As a learning from former randomised clinical evidence^{15,16} these two studies implemented a longer treatment duration of six weeks. SURPRISE was a randomised non-inferiority study, that enrolled a higher risk profile population and showed a non-significant trend toward higher rate of primary outcome, concluding a non-inferiority of rivaroxaban to fondaparinux.^{14,15} The CALISTO results were subsequently implemented in various international guidelines recommending fondaparinux, to be preferred over other treatment options (according to the European Society for Vascular Surgery [ESVS] 2021 guidelines, an intermediate dose of a low molecular weight heparin should be considered as an alternative to fondaparinux).^{17–19} As shown in PERSEUS and INSIGHTS-SVT, fondaparinux evolved as a preferred treatment option, with shares of 75.2% and 65.7% of patients receiving this drug, showing LMWH as second choice. However, there has been a lasting discussion about VTE risk assessment and suitable treatment strategies for SVT patients with “high” thromboembolic risk.

Despite anticoagulant and non-pharmacological treatment, 5.8% of INSIGHTS-SVT participants had thromboembolic events, including recurrent or extending SVT 4.7%, DVT 1.1%, and PE 0.8% within the first three months after inclusion into the study. As observed in other observational studies before, it was found that at three months’ follow up thromboembolic event rates with fondaparinux were lower than other treatment options (4.4% with fondaparinux and 9.6% with LMWH treatment, $p = .017$), while the effect in PERSEUS¹³ (3.3% with fondaparinux treatment and 5.5% with LMWH treatment) did not reach statistical significance. For comparison, the respective event rates in the randomised controlled trials were in CALISTO⁷ 0.9% in the fondaparinux group and 5.9% in the placebo group ($p < .001$), and in SURPRISE¹⁵ both 7% in the fondaparinux group and the rivaroxaban group at 90 days.

As discussed by Geersing *et al.*, a potential explanation for the relatively high event rate in INSIGHTS-SVT could be, that GPs may have only referred patients with a higher age or other factors determining higher risk to the specialists for confirmation of SVT, while keeping lower risk patients in their own management.³ By design, this was also true for PERSEUS which has the greatest similarity with regard to methodology to INSIGHTS-SVT. The available data do not show substantial differences in the patients’ risk profile between the PERSEUS and INSIGHTS-SVT studies, as age (62.9 ± 15.2 years vs. 60.2 ± 14.7 years), BMI (27.3 ± 4.9

kg/m² vs. 29.4 ± 6.3 kg/m²), male sex (35.8% vs. 35.1%), and previous DVT or PE (17.8 vs. 15.4%) were similar. Active cancer, however, was more frequent in INSIGHTS-SVT than in PERSEUS (7.0% vs. 3.0%), while patients with varicose veins were more common in the PERSEUS study (86.1% vs. 75.6%). Whether cancer patients in the PERSEUS study were at a higher risk of developing recurrent VTE, has not been published.¹³

Compared with CALISTO,⁷ patients in INSIGHTS-SVT were similar in terms of sex ratio, with nearly two thirds being female, and BMI, with one third being obese in both studies. However, in INSIGHTS-SVT, patients were substantially older (mean age, 59.8 ± 14.2 vs. 57.1 ± 13.3 years for the fondaparinux treated patients; characteristics for total group not reported) and fewer patients had varicose veins (75.3 % vs. 88.6 %). While in INSIGHTS-SVT the history of SVT was a significant predictor for thromboembolic outcomes which were mainly driven by recurrent or extending SVT, patients in CALISTO with a history of SVT ≤ 3 months were excluded, and rates of previous SVT (11.9%), DVT or PE (7.0 %) were comparatively low. This fact may have added much more to the low risk profile and low rates of thromboembolic events than the exclusion of patients with active cancer.⁷

Previous studies found several associated factors for the development of thromboembolic complications during the study period, such as higher age, male sex, personal history of VTE, varicose veins, or cancer.^{11–13} For the first time, the SURPRISE study introduced a “high risk” definition, only including patients who had an isolated SVT above the knee and at least one more risk factor, such as age above 65 years, male sex, previous DVT, PE, or SVT, active or history of cancer, autoimmune disease, or SVT of non-varicose veins.¹⁵ In this analysis, multivariable analysis identified age and duration of drug treatment per week as independent “protective” factors for recurrent VTE, while prior SVT and thrombus length constituted independent factors which increased the risk of recurrent VTE. Of note, malignancy was not a significant factor in this model.

The German national guidelines issued in 2015 (consensus based, not systematic) which were applicable during the duration of INSIGHTS-SVT recommend that the indication for anticoagulation treatment should be evaluated in all patients with SVT of the great and small saphenous vein, and all accessory veins. Furthermore, patients with SVT of the saphenous veins or larger calibre side branches with a thrombus length of at least 5 cm should be anticoagulated for

a minimum of four weeks.¹⁷ Nearly half of patients in the study (48.6%) did not receive anticoagulant treatment beyond 25 days, indicating a gap in adherence between guideline recommendation and clinical practice. The majority (70%, 487 of 696) of fondaparinux treated patients were treated for at least four weeks, compared with only 28% (85/305) of LMWH patients; the reasons for a lower duration of LMWH therapy than with fondaparinux is unclear. Compared with LMWH, fondaparinux treated patients in particular seem to benefit regarding recurrent VTE events if treatment is extended beyond 38 days duration (3.7 vs. 10.5%; HR 0.37; 95% CI 1.03 – 7.03; $p = .044$). In the multivariable analysis drug treatment duration was found to be a significant independent factor for reduction of VTE events, decreasing the risk by 2% per treatment day (HR 0.98; 95% CI 0.98 – 0.99; $p = .048$), supporting the need for an adequate treatment duration of isolated SVT in line with the current ESVS venous thrombosis guidelines that suggest the use of a prophylactic anticoagulant for 45 days.¹⁹ Furthermore, thrombus length appeared to increase the risk of recurrent VTE events by 4% per centimetre (HR 1.04; 95% CI 1.02 – 1.06; $p < .001$). This result may suggest that thrombus length should be included in future SVT monitoring and treatment strategies. There is a clear reason for performing ultrasound examinations during the follow up of patients with SVT, as an extension to the SFJ or to the deep venous system can occur without clinical signs nor symptoms.

The analysis found a meliorating effect on the outcome of the factor age, which has unclear cause and significance. While the risk of suffering an initial VTE is strongly age dependent, the risk of recurrent VTE is less clear. An individual patient data meta-analysis reported a HR of 0.99 (0.98 – 1.00) per each year of age for recurrent VTE.²⁰

A significant beneficial effect for fondaparinux vs. LMWH was found in isolated SVT treatment in a real life population (4.4% vs. 9.6%; HR 0.51; 95% CI 0.30 – 0.88; $p = .017$). A pathophysiological explanation for the benefit of fondaparinux could be offered by the mode of action because the drug (unlike LMWHs) is a selective, indirect factor Xa inhibitor. In vitro experiments have shown that fondaparinux, as a small molecule, can accelerate the lysis by changing the texture of thrombi (pro-fibrinolytic activity).^{21,22} Targeted clinical or in situ studies on the relevance of the results are still lacking, which opens the opportunity for further clinical evaluation of the specific mode of action.

The main limitations of the study derive from the fact that the included patients were almost completely treated by vascular specialists, not by general physicians. Taking the number of thromboembolic risk factors and high rate of primary outcome into account, however, results may have been biased by the selection of patients with more severe SVT, or higher risk patients that were referred from the primary care physicians to the secondary care level specialists. This assumption has also been reported for other studies (POST,¹¹ OPTIMEV,¹² PERSEUS¹³), and is further supported by incidence rates for isolated SVT from different data sources.²

Studies trying to assess real word management and outcomes can enrol a large number of patients; however, often have the drawback that a substantial number of

patients are lost to follow up, e.g., 4.8 % in PERSEUS,¹³ 2.3 % in POST,¹¹ and 0.6 % in OPTIMEV,¹² respectively. In INSIGHTS-SVT, data completeness was very high, with only 4% lost to follow up at three months, and data reporting was supported monitoring with source data verification. Furthermore, three month data were documented by personal contact between patients and their doctors. As the large number of patients that was included in the study were treated by investigators with expertise in SVT, the study population and treatment results seen in routine practice at secondary care level can be classed as representative. However, participants in the study may represent a positive selection in terms of patient adherence and of compliant physicians, who have a higher than average level of expertise, who are interested in the research questions and are willing to undergo quality control measures, such as on site monitoring visits with source data verification. This may indicate that real life outcomes may be worse than observed here. The selected centres all had CUS devices, however, the type of devices was not specified; yet physicians were required to have obtained board certification to comply with required standards for the ultrasound examination including personal expertise and equipment standards and using only validated devices. Chronic venous insufficiency and venous ulceration were listed as a combined variable in the data collection. These two entities might have differential impact on outcomes which could not be corrected for by propensity score matching.

A general limitation of an observational study is lack of randomisation. Therefore, more intensive or longer anticoagulant treatment may have been chosen for high risk patients. To account for these imbalances a propensity score adjustment was applied. Most importantly, a consistent, well known risk stratification for broadly accepted risk factors for recurrence are not available.

Conclusion

The prospective INSIGHTS-SVT registry shows a high risk of thromboembolic complications in real life management of acute isolated SVT in spite of antithrombotic treatment, and 7.4 % of patients were not improved, or worsened after three months. Importantly, INSIGHTS-SVT identified factors associated with a higher risk of complications. By taking these into account, it is probable that the outcomes of SVT patients can be improved by better risk stratification and guideline adherence. The study underlines the need to continue the anticoagulant therapy for a sufficient period of time.

CONFLICT OF INTEREST

R.B. has received research support and honoraria for lectures and advisory boards from Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim and Daiichi Sankyo, and Aspen. HG has received honoraria for lectures and advisory boards from Aspen, Bayer, Boehringer-Ingelheim and Leo Pharma. ER has received honoraria for lectures and advisory boards from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Leo Pharma and Pfizer. D.P. has

received honoraria for consultancy, advisory boards or lectures by Actelion, Bayer, Biogen, Aspen, Amgen, Boehringer Ingelheim, Novartis, Daiichi Sankyo, Genzyme. F.L. has received honoraria for lectures or consultancy from Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, LEO, Novartis, and Pfizer. U.H. has received research support and honoraria for lectures and advisory boards from Bayer HealthCare Pharmaceuticals, Bristol-Myers-Squibb, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Leo Pharma and Aspen. T.N. has received honoraria for consultancy from Medi Bayreuth, honoraria for presentations from Aspen, Bayer, and Bristol-Myers Squibb. A.H. is full-time employee of Aspen Pharma GmbH, Munich. J.K. reports no conflict of interest related to this study.

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AUTHOR CONTRIBUTIONS

R.B., A.H., and D.P. designed the study and wrote the first draft of the manuscript. All authors are members of the steering board and contributed to the design, the data collection form and the analysis plan. All authors contributed to the manuscript and approved the final version of the manuscript. J.K. performed the statistical analyses.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.04.015>.

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