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Clinical outcomes of cancer-associated isolated superficial vein thrombosis in daily practice

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ABSTRACT

Background: Despite significant progress in the understanding of paraneoplastic deep vein thrombosis (DVT) and pulmonary embolism (PE), little is known about the outcomes of cancer-associated superficial vein thrombosis (SVT) in daily practice.
Methods: INSIGHTS-SVT was a prospective observational study on patients with acute isolated SVT. Primary outcome measure was symptomatic venous thromboembolism (VTE), a composite of DVT, PE, and SVT extension/recurrence, at 3 months. Clinically relevant bleeding was also assessed.
Results: Of 1151 patients included, 6.7 % either had active cancer at baseline or were diagnosed with cancer during 12 months of follow-up. At 3 months, symptomatic VTE had occurred in 13.0 % and 5.4 % of cancer and non-cancer patients, respectively (HR 2.6, 95 % CI 1.3–5.0). Regarding secondary outcomes, cancer patients had increased risks of DVT and PE (HR 3.9, 95 % CI 1.3–11.8) and hospitalization due to VTE (HR 11.0, 95 % CI 2.5–49.0). The rate of clinically relevant bleeding was numerically higher in the cancer cohort (3.9 % vs 1.3 %, HR 3.1, 95 % CI 0.9–10.7). At 12 months, the primary composite outcome had occurred in 15.6 % and 11.9 % of cancer and non-cancer patients, respectively (HR 1.9, 95 % CI 1.0–3.5). After adjusting for additional risk factors, including age, history of DVT/PE and cardiovascular risk factors/diseases, the association of cancer with the primary outcome remained statistically significant.
Conclusion: Cancer patients with isolated SVT are at significant risk of symptomatic VTE. While most events occur within 3 months, the VTE risk remains elevated up to one year of follow-up.
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1. Introduction

Cancer patients are at increased risk of venous thromboembolism (VTE), a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rates of cancer-associated thromboembolism (CAT) range from 4 % to 20 % [1], mainly dependent on the types of cancer, which can be divided into very high risk (i.e., pancreas, stomach, high-grade glioma), high risk (e.g., lung, colorectal, gynecological), and low

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risk (e.g., breast, prostate) entities [2,3]. This suggests that there are cancer type-specific pathways in CAT pathophysiology [4,5]. Increased levels of leukocytes, platelets, plasma D-dimers, inflammatory cytokines, and tissue factor-positive microvesicles are among the many potential factors that alone or in combination may contribute to CAT development [4,6]. In addition, several patient- (e.g., history of VTE, thrombophilia, varicose veins) and treatment-related risk factors (e.g., surgery, hormone, chemo- and radiotherapy) are critically involved in CAT development [7].

Superficial vein thrombosis (SVT) is characterized by partial or total thrombotic obstruction of the lumen of the affected vein and by inflammatory alterations of the vessel wall [8,9]. SVT is often perceived as a more benign condition than DVT or PE and has thus received less medical attention. However, it has become clear that SVT, DVT and PE are related entities, which may occur concomitantly or in sequence [10]. A recent study has found an 8.7 % cancer prevalence in patients with SVT [11]. In that study, cancer was the strongest determinant for the occurrence of concomitant DVT/PE.

The management of cancer-associated VTE, including SVT, poses a challenge to the treating physician, because cancer patients are more prone to bleeding than non-cancer patients [12]. In addition, the optimal type, duration, and intensity of anticoagulation in hematology-oncology patients with acute isolated SVT are unclear.

Until today, the highly variable real-life management and outcomes of SVT are poorly defined. The prospective observational Investigating SIGnificant Health TrendS in the management of Superficial Vein Thrombosis (INSIGHTS-SVT) study aimed at collecting representative data on patient characteristics, diagnosis, management, and outcomes of acute isolated SVT in Germany under real-life conditions [13,14]. Here, we compare the subgroup of patients with cancer, either diagnosed or treated within 1 year prior to enrolment or diagnosed during 12 months of follow-up, with non-cancer patients to obtain additional information on treatment outcomes in this vulnerable patient population.

2. Methods

2.1. Study design

The rationale, design and methods of the study have previously been reported in detail [13].

In brief, this was a prospective, multicenter, non-interventional (observational) study with a 1-year follow-up period. The study protocol was approved by the institutional review board of the physician chamber in Hessen, Germany, and all patients provided written informed consent. The study was registered by the regulatory authority (BfArM) under NIS 6781 and by ClinicalTrials.gov under NCT 02699151. The 3-month outcomes of the total patient cohort have recently been reported [14].

Hospital- and office-based physicians, who regularly treated patients with SVT and who were board-certified for compression ultrasound (CUS) diagnostics, were invited to participate in INSIGHTS-SVT, including vascular physicians, vascular surgeons, phlebologists, and general internists or practitioners.

Patient inclusion criteria were as follows: objectively confirmed (by ultrasound, including CUS and duplex ultrasound [DUS]), acute (time interval between onset of SVT symptoms and study inclusion <3 weeks), isolated SVT of the lower extremities (concomitant DVT was excluded by CUS or DUS, and patients had no clinical symptoms of PE). Patients were ineligible, if they met any of the following exclusion criteria: proximal extension of SVT to ≤3 cm of the saphenofemoral junction (SFJ); subject unlikely to comply with the requirements of the protocol (e.g., due to cognitive and/or language limitations); subject likely not available for 1-year follow-up.

Patients had a follow-up visit at 3 months and 1 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 the follow-up period were at the investigator's discretion. DUS refers to ultrasound systems with both pulsed-wave Doppler and color technology.

Information on pharmacological and non-pharmacological therapy (i.e., the type of utilized drugs, their dosing and duration of application) was collected. Anticoagulant drugs were categorized as prophylactic (<50 % of full-therapeutic dose), intermediate (50–75 % of full-therapeutic dose) or therapeutic (>75 % of full-therapeutic dose). If no anticoagulant drugs were given, or if there was no treatment at all, this was also documented.

This analysis of INSIGHTS-SVT compared cancer patients with non-cancer patients. Active cancer at study inclusion was defined by protocol as cancer diagnosed or treated within the previous 12 months. In addition, the cancer cohort in this report comprised patients diagnosed with new or recurrent cancer during 1 year of follow-up.

2.2. Study outcomes

The primary outcome measure was the incidence of symptomatic VTE, defined as a composite of DVT, PE and recurrent or extending SVT, at 3 months of follow-up. Secondary outcomes included recurrent SVT or extension of SVT into the deep vein system or to 3 cm or less from the SFJ, symptomatic PE, DVT, persistent SVT (i.e., SVT without clinical improvement), asymptomatic SVT, death, and hospitalization because of VTE.

An additional 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 bleeding) [15] and the CALISTO trial (clinically relevant non-major bleeding) [16].

2.3. Statistical analysis

Patient characteristics and the onset of the defined outcomes were reported by standard descriptive statistics. Characteristics for patients with and without cancer were compared by chi^2-test and *t*-test for categorical and continuously distributed variables, respectively. The cumulative incidence of the primary outcome during the 12-month follow-up period was estimated by Kaplan-Meier technique. The likelihood for the onset of outcomes was analyzed by fitting univariate Cox proportional hazards models. For composite outcomes, the first event among all events was considered in the time to event analyses. The risk for primary outcome between patients with and without cancer was also analyzed by a multivariable Cox proportional hazards model including the parameters age, previous DVT or PE, cardiovascular risk factors/diseases, and involvement of great saphenous vein only as a result of variable selection by LASSO (least absolute shrinkage and selection operator) method. A sensitivity analysis was performed in order to force to include the two parameters varicose veins and anticoagulation. The Cox proportional hazards assumption was checked by Schoenfeld residuals. The *P* value threshold for statistical significance was 0.05. All statistical analyses were performed with STATA 12.1.

3. Results

3.1. Patient characteristics

Disposition and flow of INSIGHTS-SVT study participants are shown in Fig. 1. In total, 1159 patients with acute isolated SVT were prospectively enrolled between April 2016 and August 2017. Critical review of individual patient data at study inclusion revealed non-melanoma skin cancer or premalignant hematological conditions in 6 and 2 cases, respectively. These subjects were excluded from further analysis. In 3 additional cases, the presence of active cancer at baseline could not be confirmed. These subjects were included in the non-cancer cohort. Thus, this analysis is based on 1151 patients (100 %), of whom 77 (6.7 %)

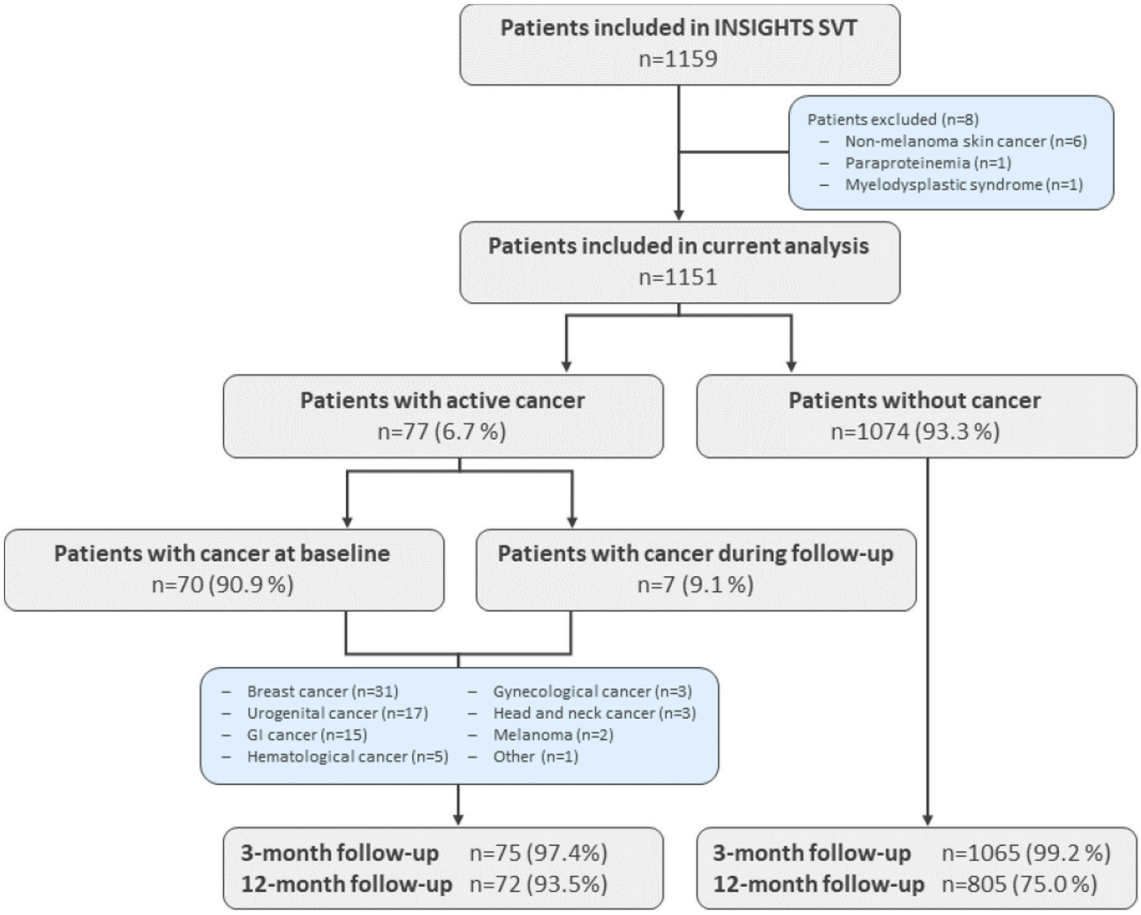

Fig. 1. Patient disposition and flow.
Abbreviation: GI gastrointestinal.

either had active cancer at baseline ($n = 70$) or were diagnosed with new or recurrent cancer during follow-up (n = 7), as compared to the previously published analysis of this study, which reported 81 patients with known active cancer at study inclusion [14]. Tumor types included breast ($n = 31$), urogenital ($n = 17$), gastrointestinal ($n = 15$), hematological ($n = 5$), gynecological (n = 3) or head-and-neck cancer (n = 3), melanoma ($n = 2$), and cancer of unknown primary (n = 1). Specific information on tumor stage or treatment was not captured in case report forms (CRFs). Follow-up at 3 and 12 months was almost complete in the cancer cohort, while about 25 % of patients were lost to follow-up between 3 and 12 months in the non-cancer cohort (Fig. 1).

Demographic and clinical characteristics of cancer and non-cancer patients are compared in Table 1. Cancer patients were significantly older than non-cancer patients (65.5 ± 11.0 vs 59.7 ± 14.8 years, $P < 0.001$), but did not show statistically significant differences with respect to sex, ethnic background, or body mass index. Hormone replacement therapy (5.2 % vs 1.3 %, $P = 0.008$) and use of oral contraceptives (33.3 % vs 9.5 %, $P < 0.001$) were more frequent in the cancer than in the non-cancer cohort. Compared to patients without cancer, cancer patients were also more likely to suffer from hemiplegia (2.6 % vs 0.4 %, $P = 0.032$), immobility/bedriddenness (11.7 % vs 3.2 %, $P < 0.001$), or cardiovascular risk factors/diseases (66.2 % vs 51.1 %, $P = 0.010$) at the time of SVT diagnosis. Of note, cancer patients more frequently had major surgery during the preceding 12 weeks than non-cancer patients (11.7 % vs 3.4 %, P < 0.001). There were no differences in localization (proximal vs distal) or extension of SVT. Exclusive involvement of the great saphenous vein was less frequent in the cancer compared to the non-cancer cohort (24.7 % vs 39.4 %, P = 0.010).

3.2. Study outcomes

Pre-analyses of the data aimed to test whether there was a selective drop-out during the 12-month follow-up period. We could not find statistically significant differences in terms of demographics. However, patients with 12-month assessment, as compared to patients with incomplete follow-up, showed slightly higher rates in history of thrombotic events and cardiovascular risk factors/diseases, while the index SVT was less often proximal.

At 3 months of follow-up (Table 2), the primary composite outcome had occurred in 10 cancer patients (13.0 %) and 57 non-cancer patients (5.4 %), with a hazard ratio (HR) of 2.56 (95 % CI 1.31–5.01, $P = 0.006$). Regarding secondary outcomes at 3 months, cancer patients had increased risks of DVT and PE (HR 3.92, 95 % CI 1.30–11.80, $P = 0.015$), persistent SVT (HR 3.22, 95 % CI 1.42–7.31, $P = 0.005$), or hospitalization due to VTE (HR 10.96, 95 % CI 2.45–48.99, $P = 0.002$). The rate of clinically relevant bleeding was numerically higher in the cancer cohort (3.9 % vs 1.3 %, HR 3.08, 95 % CI 0.88–10.70, $P = 0.077$).

At 12 months of follow-up (Table 3), the primary composite outcome had occurred in 15.6 % of cancer patients and 11.9 % of non-cancer patients (HR 1.89, 95 % CI 1.04–3.45, $P = 0.037$), while rates of clinically relevant bleeding were 3.9 % and 1.9 %, respectively (HR 2.86, 95 % CI 0.83–9.87, $P = 0.097$).

Estimated cumulative incidence rates of the primary composite outcome are shown in Fig. 2. Cumulative incidence rates of symptomatic VTE at 3 and 12 months were 13.8 % (95 % CI 7.7–24.2 %) and 18.2 % (95 % CI 10.6–30.4 %), respectively, in the cancer cohort and 5.3 % (95 % CI 4.0–6.8 %) and 12.9 % (95 % CI 10.5–15.7), respectively, in the non-cancer cohort (HR 2.02, 95 % CI 1.11–3.70, $P = 0.02$).

Table 1
Demographic and clinical patient characteristics.

	Patients without cancer	Patients with cancer	P value
	$n = 1074$	$n = 77$	
Age (years), mean ± SD	59.7 ± 14.8	65.5 ± 11.0	<0.001
Age ≥ 65 years, n (%)	431 (40.1)	42 (54.6)	0.013
Women, n (%)	694 (64.6)	54 (70.1)	0.327
Body mass index (kg/m^2), mean ± SD	29.4 ± 6.4	28.7 ± 4.9	0.328
Body mass index ≥30 kg/m^2, n (%)	398 (37.1)	29 (37.7)	0.916
Caucasian, n (%)	1069 (99.5)	76 (98.7)	0.327
Chronic, dispositional risk factors for VTE, n (%)			
Varicose veins	809 (75.3)	62 (80.5)	0.305
History of thrombosis			
SVT	321 (29.9)	25 (32.5)	0.633
DVT or PE	171 (15.9)	6 (7.8)	0.056
VTE (SVT, DVT or PE)	422 (39.3)	28 (36.4)	0.611
Family history of DVT or PE	177 (16.5)	8 (10.4)	0.160
CVI/ulceration	513 (47.8)	45 (58.4)	0.070
Known thrombophilia	53 (4.9)	4 (5.2)	0.919
Hormone replacement therapy	14 (1.3)	4 (5.2)	0.008
Oral contraception	66 (9.5)	18 (33.3)	<0.001
Current smoking	176 (16.4)	13 (16.9)	0.910
Hemiplegia	4 (0.4)	2 (2.6)	0.032
Chronic inflammatory disease	52 (4.8)	5 (6.5)	0.519
Immobility/bedriddenness	34 (3.2)	9 (11.7)	<0.001
Cardiovascular risk factors/ diseases[a]	549 (51.1)	51 (66.2)	0.010
Heart failure	30 (2.8)	1 (1.3)	0.434
Respiratory failure	30 (2.8)	4 (5.2)	0.229
Transient, expositional risk factors for VTE, n (%)			
Trauma (past 4 weeks)	46 (4.3)	0 (0.0)	0.064
Travel (>6 h by car or flight)	91 (8.5)	4 (5.2)	0.313
Major surgery (past 12 weeks)	36 (3.4)	9 (11.7)	<0.001
Severe systemic infection	9 (0.8)	2 (2.6)	0.125
Pregnancy	8 (0.7)	0 (0.0)	0.447
Postpartum	13 (1.2)	0 (0.0)	0.332
Number of chronic dispositional risk factors (other than cancer), n (%)			
0	135 (12.6)	9 (11.7)	0.990
1	281 (26.2)	20 (26.0)	
2	409 (38.1)	29 (37.7)	
3+	249 (23.2)	19 (24.7)	
Characteristics of SVT events			
Great or small saphenous vein, n (%)	579 (53.9)	45 (58.4)	0.441
Other veins, n (%)	495 (46.1)	32 (41.6)	
Great saphenous vein only, n (%)	423 (39.4)	19 (24.7)	0.010
Distance between thrombus and SFJ (cm), mean ± SD	25.8 ± 14.8	33.1 ± 12.7	0.018
Distance between thrombus and SFJ < 10 cm, n (%)	49 (11.4)	0 (0.0)	0.080
Distance between thrombus and SFJ ≥ 10 cm, n (%)	382 (88.6)	24 (100.0)	
Small saphenous vein only, n (%)	55 (5.1)	2 (2.6)	0.324
Number of affected veins (n), mean ± SD	2.2 ± 1.0	1.5 ± 0.7	0.338
Localization, n (%)			
Proximal only	285 (27.3)	16 (21.1)	0.185
Distal only	559 (53.6)	49 (64.5)	
Proximal and distal	199 (19.1)	11 (14.5)	
Extension (cm), mean ± SD	14.6 ± 10.8	13.0 ± 9.4	0.207
< 20 cm	719 (67.3)	55 (72.4)	0.328
≥ 20 cm	350 (32.7)	21 (27.6)	

Abbreviations: VTE venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis, SFJ saphenofemoral junction, SD standard deviation.

[a] Diabetes mellitus, arterial hypertension, coronary artery disease, cerebrovascular disease, peripheral artery disease, atrial fibrillation, renal failure.

Table 2
Study outcomes after 3 months.

	Patients without cancer		Patients with cancer		P value	HR[c]	95 % CI
	n = 1065		n = 77				
	n	%	n	%			
Primary outcome							
Symptomatic VTE (DVT, PE, recurrent or extending[a] SVT)	57	5.4	10	13.0	0.006	2.56	1.31–5.01
Secondary outcomes							
SVT (recurrent or extending[a])	48	4.5	6	7.8	0.186	1.77	0.76–4.14
PE	7	0.7	2	2.6	0.077	4.12	0.86–19.84
DVT	14	1.3	3	3.9	0.077	3.08	0.88–10.70
DVT and PE	15	1.4	4	5.2	0.015	3.92	1.30–11.80
Persistent SVT	32	3.0	8	10.4	0.005	3.22	1.42–7.31
Asymptomatic SVT[b]	2	0.2	0	0.0	–	–	–
Death	1	0.1	2	2.6	–	–	–
Hospitalization due to VTE	4	0.4	3	3.9	0.002	10.96	2.45–48.99
Bleeding	14	1.3	3	3.9	0.077	3.08	0.88–10.70
Severe bleeding	2	0.2	1	1.3	–	–	–
Clinically relevant non-major bleeding	12	1.1	2	2.6	0.255	2.39	0.53–10.66

Abbreviations: VTE venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis, HR hazard ratio, CI confidence interval.

[a] Extension into the deep vein system or to ≤ 3 cm of the saphenofemoral junction.

[b] Detectable only on compression or duplex ultrasound.

[c] Cancer vs no cancer.

After adjusting for additional risk factors (Table 4), the cancer-associated risk of the primary composite outcome remained statistically significant at 3 months (HR 3.63, 95 % CI 1.79–7.35, $P < 0.001$) and 12 months (HR 2.40, 95 % CI 1.30–4.45, $P = 0.005$). Findings were consistent when including varicose veins and anticoagulant therapy as additional variables in the Cox regression model (supplementary Table 1).

3.3. Anticoagulant treatment of SVT

As initial anticoagulant therapy, about 65 % of cancer and non-cancer patients each were treated with fondaparinux. Only 3.9 % of cancer patients did not receive any anticoagulant, as compared to 6.6 % of non-cancer patients (Table 5). When considering all drugs used for initial anticoagulant therapy, there was no difference in the duration or intensity of anticoagulation between the two groups. However, treatment duration with low-molecular-weight heparin (LMWH) was significantly longer in the cancer than in the non-cancer cohort (36.8 ± 32.4 vs 25.3 ± 21.9 days, $P = 0.034$).

4. Discussion

More than 150 years ago, the French Physician Armand Trousseau described the association of cancer with superficial migratory thrombophlebitis [17]. Today, the term *Trousseau's syndrome* is used for virtually all clinically relevant coagulation abnormalities, including SVT, in patients with malignancies [6]. Despite significant progress in the understanding of paraneoplastic DVT and PE, including pathophysiology, epidemiology, and pharmacological treatment, less is known about the clinical presentation, management, and outcomes of cancer-associated SVT in daily practice.

In INSIGHTS-SVT, out of 1151 patients included in this analysis, 70

Table 3
Study outcomes after 12 months.

	Patients without cancer		Patients with cancer		P value	HR[c]	95 % CI
	n = 805		*n* = 77				
	n	%	n	%			
Primary outcome							
Symptomatic VTE (DVT, PE, recurrent or extending[a] SVT)	96	11.9	12	15.6	0.037	1.89	1.04–3.45
Secondary outcomes							
SVT (recurrent or extending[a])	75	9.3	8	10.4	0.235	1.56	0.75–3.22
PE	11	1.4	3	3.9	0.034	3.98	1.11–14.25
DVT	15	1.9	3	3.9	0.097	2.86	0.83–9.87
DVT and PE	28	3.5	4	5.2	0.162	2.11	0.74–6.02
Persistent SVT	34	4.2	8	10.4	0.009	2.98	1.32–6.72
Asymptomatic SVT[b]	5	0.6	0	0.0	–	–	–
Death	7	0.9	5	6.5	0.364	1.79	0.51–6.25
Hospitalization due to VTE	5	0.6	3	3.9	0.003	8.87	2.12–37.12
Bleeding	15	1.9	3	3.9	0.097	2.86	0.83–9.87
Severe bleeding	2	0.3	1	1.3	–	–	–
Clinically relevant non-major bleeding	13	1.6	2	2.6	0.303	2.19	0.49–9.69

Abbreviations: VTE venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis, HR hazard ratio, CI confidence interval.

[a] Extension into the deep vein system or to ≤ 3 cm of the saphenofemoral junction.

[b] Detectable only on compression or duplex ultrasound.

[c] Cancer vs no cancer.

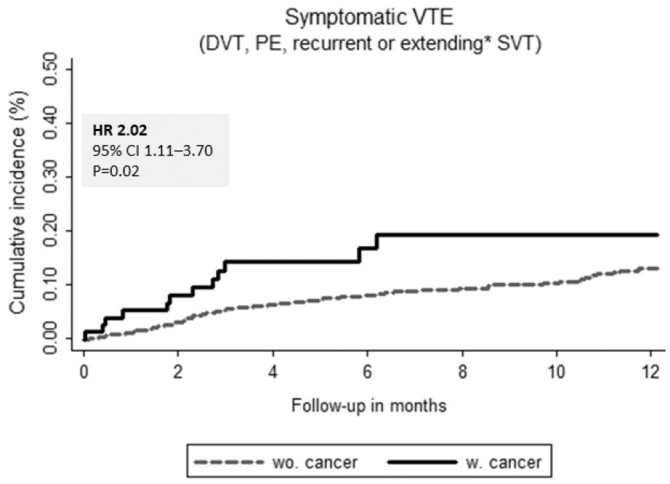

Fig. 2. Cumulative incidence of the primary composite outcome.
*Extension into the deep vein system or to ≤3 cm of the saphenofemoral junction.
Abbreviations: VTE venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis, HR hazard ratio, CI confidence interval, wo. without, w. with.

patients (6.1 %) had active cancer at baseline, while new cancer was revealed during follow-up in an additional 7 patients (0.6 %). Thus, in 6.7 % of patients, an underlying malignancy likely contributed to SVT pathogenesis. Tumor entities detected after SVT diagnosis comprised colorectal ($n = 2$), pancreatic, ovarian, breast, lung, and head-and-neck cancer ($n = 1$ each). Importantly, 6 out of the 7 newly diagnosed malignancies were detected within 3 months of follow-up (supplementary Table 2), further supporting a pathophysiological link between cancer and SVT development.

In earlier randomized controlled trials (RCTs) on the initial treatment of DVT or PE, the proportions of patients with active or previous cancer were 10–12 % and 5–7 %, respectively [18,19]. Regarding the prevalence of underlying malignancy in patients with acute isolated SVT, active cancer was an exclusion criterion in the CALISTO fondaparinux RCT, which, in the placebo arm, included the largest prospective cohort of patients with spontaneous SVT not receiving anticoagulant treatment [16]. However, about 2 % of patients in CALISTO had a history of cancer. In the recently published open-label, randomized, non-inferiority phase-3b trial that compared rivaroxaban with fondaparinux for the treatment of proximal SVT, 45 out of 472 patients (9.5 %) had active cancer or a history of cancer at study

Table 4
Multivariable analysis of the primary composite outcome of symptomatic VTE (DVT, PE, recurrent or extending SVT[a]).

	HR	95 % CI	*P* value
After 3 months			
Cancer vs no cancer	3.63	1.79–7.35	<0.001
Age (years)	0.97	0.95–0.99	0.003
Previous DVT or PE	1.69	0.93–3.09	0.086
Cardiovascular risk factors/diseases	0.95	0.54–1.65	0.846
Great saphenous vein only	1.50	0.92–2.44	0.101
After 12 months			
Cancer vs no cancer	2.40	1.30–4.45	0.005
Age (years)	0.98	0.96–0.99	0.001
Previous DVT or PE	1.78	1.13–2.80	0.012
Cardiovascular risk factors/diseases	1.09	0.71–1.68	0.697
Great saphenous vein only	1.16	0.79–1.72	0.447

Abbreviations: VTE venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis, HR hazard ratio, CI confidence interval.

[a] Extension into the deep vein system or to ≤ 3 cm of the saphenofemoral junction.

Table 5
Initial anticoagulant and physical therapy.

	Patients without cancer n = 1074		Patients with cancer n = 77		P value
Medical therapy duration (days), mean ± SD	32.1 ± 20.3		34.4 ± 26.1		0.409
≥4 weeks, n (%)	531	49.4	35	45.5	0.499
≥6 weeks, n (%)	279	26.0	21	27.3	0.803
≥3 months, n (%)	23	2.1	4	5.2	0.087
≥12 months, n (%)	0	0.0	0	0.0	–
Dosing regimen, n (%)					
Prophylactic	797	74.2	59	76.6	0.365
Intermediate	158	14.7	14	18.2	
Therapeutic	49	4.6	1	1.3	
No anticoagulant	70	6.5	3	3.9	
Fondaparinux, n (%)	719	65.4	50	64.9	0.886
Duration (days), mean ± SD	33.7 ± 16.6		32.3 ± 17.2		0.510
LMWH, n (%)	251	22.8	20	26.0	0.487
Duration (days), mean ± SD	25.3 ± 21.9		36.8 ± 32.4		0.034
Others (UFH, VKA, NOAC), n (%)	56	5.1	4	5.2	0.994
Duration (days), mean ± SD	42.4 ± 39.1		48.5 ± 68.4		0.775
No anticoagulant, n (%)	73	6.6	3	3.9	0.362
Physical therapy					
Compression	835	77.7	53	68.8	0.147
Cooling	406	37.8	18	23.4	0.013
Other	71	6.6	4	5.2	0.669

Abbreviations: LMWH low-molecular-weight heparin, UFH unfractionated heparin, VKA vitamin K antagonist, NOAC non-vitamin K-dependent oral anticoagulant, SD standard deviation.

inclusion [20].

Before INSIGHTS-SVT, evidence from observational studies involving patients with isolated SVT was predominantly limited to the situation in France. In POST, out of 634 patients with isolated SVT, 24 (3.8 %) and 29 patients (4.6 %) had active or previous cancer, respectively [21]. In OPTIMEV, out of 556 patients with isolated SVT, 28 patients (5.0 %) had active cancer, and 16 patients (2.9 %) had a history of cancer [22,23]. In PERSEUS, out of 978 patients with isolated SVT, 29 patients (3.0 %) had active cancer, and 66 patients (6.7 %) had a history of cancer [24].

It is important to point out that there is no universally accepted definition of the term 'active cancer' [25]. In most contemporary RCTs on anticoagulant treatment of VTE, active cancer is defined as follows: cancer diagnosed or treated within the previous 6 months (excluding non-melanoma skin cancer); recurrent, locally advanced, or metastatic solid cancer; hematological cancer not in complete remission. A more stringent definition of patients with active cancer includes patients with measurable tumor manifestations and ongoing (or an indication for) specific anticancer therapy. The risk of recurrent VTE is generally considered to be lower in patients with a history of cancer, while some evidence indicates that patients with cancer diagnosed or treated within the previous 2 years have a risk of VTE recurrence that is in the same magnitude as the risk of VTE recurrence in patients with active cancer [26]. Patients diagnosed with cancer during follow-up (i.e., within 6–12 months after VTE occurrence) are at exceedingly high risk for both VTE recurrence and bleeding [27], because these patients may not only have particularly aggressive malignancies, but may also undergo diagnostic or therapeutic procedures requiring interruption of anticoagulant therapy. Consistent with this notion, 3 out of 6 patients, whose cancer was diagnosed within 3 months after the index SVT event, experienced symptomatic VTE during follow-up (supplementary Table 2).

Following critical review of individual CRFs we feel that the final cohort of cancer patients reported herein adequately reflects the impact of malignancy and its treatment on SVT outcomes in daily practice, even though we cannot comment on clinical tumor stages or specific anticancer therapies.

The term *Trousseau's sign of malignancy* implicates the diagnosis of hitherto hidden cancer after SVT occurrence. In a population-based study from Denmark, the risk of cancer during the first year of follow-up was 2.2 % in patients with SVT, corresponding to a standardized incidence ratio (SIR) of 2.46 (95 % CI 2.10–2.86) and being similar to the risk of subsequent cancer in patients with DVT (SIR 2.75, 95 % CI 2.60–2.90) or PE (SIR 3.27, 95 % CI 3.03–3.52) [28]. From these data it may be concluded that the 0.6 % risk of new cancer detection during 1 year of follow-up, as observed in INSIGHTS-SVT, is close to what might be expected in the general population. This hypothesis is supported by a case-control study of 737 consecutive patients with isolated SVT not involving the saphenofemoral junction, of whom 3.5 % were diagnosed with cancer during 26 ± 8 months (range, 3–45 months) of follow-up, as compared to 3.9 % of 1438 controls [29]. Albeit limited by a quite small sample size, an observational study from the Netherlands has also not found an increased risk of subsequent cancer in 250 patients with a first episode of unprovoked SVT [30].

The risk of an underlying malignancy, however, may be dependent on certain SVT characteristics, such as absence of varicose veins [31]. In INSIGHTS-SVT, the prevalence of varicose veins was similar between cancer (80.5 %) and non-cancer patients (75.3 %). In addition, there was no clear evidence for increased thrombus burden or other SVT characteristics suggestive of a more aggressive clinical presentation in the cancer cohort (Table 1). Taken together, findings from our analysis and other studies do not support an extensive screening strategy for occult cancer in unselected patients with acute isolated SVT.

Despite initial anticoagulant and non-pharmacological treatment, 15.6 % of the cancer patients in INSIGHTS-SVT experienced a thromboembolic event up to 12 months of follow-up, including recurrent or extending SVT (10.4 %), DVT (3.9 %), and PE (3.9 %). Thus, our analysis shows that active cancer, as defined before, is a substantial and independent risk factor for symptomatic VTE in patients with isolated SVT, both after 3 months (HR 3.63, 95 % CI 1.79–7.35, $P < 0.001$) and after 12 months (HR 2.40, 95 % CI 1.30–4.45, $P = 0.005$). This finding is consistent with a pooled analysis of POST and OPTIMEV, according to which cancer is a risk factor for recurrent VTE, including DVT, PE or new SVT, at 3 months of follow-up (HR 2.31, 95 % CI 1.03–5.22) [23]. Similarly, a longitudinal analysis of ICARO, involving 411 patients with isolated SVT and sufficient follow-up, identified active solid malignancies as an independent risk factor for DVT or PE, with model-dependent adjusted HRs of 3.12 (95 % CI 1.11–8.93) and 4.62 (95 % CI 1.48–14.42) [32]. Finally, in SURPRISE, the composite efficacy endpoint of symptomatic DVT or PE, progression or recurrence of SVT, and all-cause mortality occurred in 20 % (9/45) of cancer and 5.4 % (23/427) of non-cancer patients during the entire observation period of 90 days, with DVT/PE incidences of 6.7 % (3/45) and 1.2 % (5/427), respectively [20]. Based on these findings and our observations from INSIGHTS-SVT [14], it is tempting to speculate that cancer patients with acute isolated SVT may benefit from prolonged, e.g. up to 3 months, and more intensive anticoagulation, e.g. with intermediate or therapeutic dosages, to sufficiently control the hypercoagulable state. In support of this hypothesis, although the risk of VTE remained elevated during the entire observation period of 1 year, most events in the cancer cohort occurred within the first 3 months, suggesting that cancer drives VTE occurrence during the early phase, while other established risk factors continue to play a role during the later phase of follow-up. It is important to point out that due to the multifactorial pathogenesis of CAT it is highly likely that risk factors in addition to the cancer itself, such as surgery, immobility/bedriddenness, cardiovascular risk factors/diseases and hormone therapy (Table 1), significantly contributed to VTE development in the cancer cohort.

Albeit not statistically significant, we observed an increased all-cause mortality in the cancer (6.5 %) versus the non-cancer (0.9 %) cohort (HR 1.79, 95 % CI 0.51–6.25, $P = 0.364$). Considering average 6-month mortality rates of 20–30 % in recent CAT trials [33,34], this finding points to the inclusion of patients with less advanced malignancies in INSIGHTS-SVT. Other studies have linked lower-limb venous thrombosis, including DVT and SVT, to poor survival in patients with cancer [32,35,36].

Our study has several limitations. First, a general shortcoming of observational studies such as ours is lack of randomization. However, we prospectively followed a large and broad spectrum of consecutive patients with acute isolated SVT in a real-world setting, which is consistent with our previous conclusions and may be considered a strength of our study. Second, a substantial number of non-cancer patients were lost to follow-up at 12 months, which may be a source of bias. However, we did not find any significant differences between patients with and without 12-month assessment in demographics. In fact, patients with available 12-month follow-up appeared to have a slightly more severe risk profile. Third, the relatively high event rate in our study could be explained by the setting (secondary care level): general practitioners may have only referred patients with an advanced age or other factors determining higher risk to the specialists for confirmation of SVT, while keeping lower risk patients in their own management [37]. Finally, as discussed before, we cannot comment on important tumor characteristic such as clinical stage or specific anticancer treatment.

In addition to the prospective study design and large patient cohort, strengths of INSIGHTS-SVT include high data completeness [14], with a lost to follow-up at 3 months of only 0.4 %, which is lower compared to 4.8 % in PERSEUS [24] and 2.3 % in POST [21]. Data reporting was supported through monitoring with source data verification. Furthermore, 3-month data were documented based on personal contacts of patients with their physicians (before the COVID-19 restrictions), and selected centers all had CUS devices. Study participants, however, 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 scientific research, and who are willing to undergo quality control measures, such as on-site monitoring visits with source data verification.

In summary, the prospective INSIGHTS-SVT registry shows that cancer patients are exposed to a high risk for thromboembolic complications during real-life management of acute isolated SVT despite antithrombotic treatment. While most events occurred within 3 months, the risk remained elevated up to 1 year of follow-up. The study thus underlines the need to keep the high VTE risk of cancer patients in mind and to consider prolonged and more intensive anticoagulation on an individual basis.

CRediT authorship contribution statement

FL, RB, and DP developed the concept for the present analysis and wrote the first draft of the manuscript. All authors are members of the Steering Committee and contributed to the design, the data collection form, and the analysis plan. JK performed the statistical analyses.

All members of the Steering Committee contributed to the interpretation of results, revised, and approved all versions of the manuscript, and vouch for the accuracy and completeness of the reported data and the fidelity of this article to the study protocol.

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Compliance with ethical standards

The study fully complies with ethical standards (as described in the methods section).

Declaration of competing interest

FL has received honoraria for lectures or consultancy from Aspen, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, LEO, Pfizer, Sanofi, and Viatris.

HG has received honoraria for lectures and advisory boards from Aspen, Bayer, Boehringer-Ingelheim and Leo Pharma.

AS is full-time employee of Mylan Pharmaceuticals GmbH, Germany.

AH was at the time of the study full-time employee of Aspen Pharma GmbH, Munich, and is now employee of Amgen GmbH, Germany.

UH 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.

TN has received honoraria for consultancy from Medi Bayreuth, honoraria for presentations from Aspen, Bayer, and Bristol-Myers Squibb.

DP has received honoraria for consultancy, advisory boards, or lectures by Actelion, Bayer, Biogen, Aspen, Amgen, Boehringer Ingelheim, Novartis, Daiichi Sankyo, Genzyme.

JK reports no conflict of interest related to this study.

ER has received honoraria for lectures and advisory boards from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Leo Pharma and Pfizer.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.10.022.

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