



Extended-Duration Treatment of Superficial Vein Thrombosis of the Lower Limbs with Tinzaparin

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Purpose: To identify risk factors for recurrent thromboembolic events (RTEs) and define the optimum duration of treatment with tinzaparin in patients with superficial vein thrombosis (SVT) of the lower limbs.

Materials and Methods: A total of 147 consecutive patients with significant SVT were treated with subcutaneously administered tinzaparin. The composite primary endpoint of the study was RTE, deep-vein thrombosis (DVT) and/or pulmonary embolism (PE) at 120 days. Patients were stratified into group A, where patients received a variable dose of tinzaparin for up to 60 days (n=98), and a subsequent group B-ext, where patients received a standardized intermediate dose of tinzaparin (n=49) for 90 days.

Results: RTEs occurred in 15/147 patients (10.2%), including recurrent SVT (n=10), DVT (n=4) and fatal PE (n=1). RTEs were less frequent in group B-ext (0% vs. 15.3% for group A, P=0.004), a difference that remained significant at the one-year follow-up. Clinically extensive SVT was an independent predictor for RTEs (hazard ratio, 5.94; 95% confidence interval, 2.05-17.23; P=0.001, Cox regression). Predictors of DVT or PE in group A included clinically extensive SVT (P=0.004), absence of local pain (P=0.023) and the ultrasound findings of superficial axial vein thrombosis (any, P=0.006 or isolated, P=0.036) and multiple thrombosed superficial venous sites (P<0.001).

Conclusion: An extended three-month regimen of tinzaparin in patients with SVT of the lower limbs is more effective than a shorter course and may be desirable in patients with risk factors.

Key Words: Thrombophlebitis, Heparin, Recurrence, Venous thrombosis

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INTRODUCTION

Superficial vein thrombosis (SVT) was considered for decades as a benign condition and a usual complication of varicose veins. Nevertheless, on initial presentation a subset of patients have already extension of their SVT into the deep-vein system or some of them will develop this complication during the course of follow-up, more often for the

period of the next few weeks. Even nowadays prophylactic anticoagulation is thought to be required only for a subset of patients of SVT [1], like those with location above the knee, particularly in the presence of risk factors including advanced age, male gender, malignancy, etc [2]. Additional areas where consensus of opinion has not been reached include the optimum duration and intensity of anticoagulation. Short courses of anticoagulation are associated with a

high frequency of SVT recurrence so that currently a 30–45 day scheme is suggested based on the results of the CALISTO trial on fondaparinux [3].

However, other studies have shown an appreciable risk for late SVT recurrence occurring after 2–3 months, which indicates that a longer use of anticoagulation may be justified [4,5]. Apart from fondaparinux, low molecular weight heparins have been also investigated, including enoxaparin, nadroparin and parnaparin [4,6,7], which complicate further comparisons between these agents.

The aim of our study was to identify risk factors for recurrent thromboembolic events (RTEs) and the optimum duration of treatment in patients with SVT of the lower limbs treated with tinzaparin.

MATERIALS AND METHODS

In this prospective comparative study, started in January 2015 at the University Hospital of Patras, Greece, we treated consecutive patients with SVT with subcutaneously administered tinzaparin.

1) Inclusion and exclusion criteria

Patients were eligible for inclusion if they had a considerable degree of thrombosis on ultrasound, defined as a thrombus length ≥ 5 cm. Exclusion criteria included a proximal extension of the SVT within 3 cm of the saphenofemoral junction or propagation into the deep system on duplex ultrasound scanning (DUS), a duration of symptoms more than 10 days, a history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within the previous 6 months, SVT after sclerotherapy or venous catheters within the last month, a history of surgery during the past three months, a body mass index (BMI) >35 kg/m², and the presence of a condition considered to be a risk factor for bleeding or a contraindication for anticoagulation (e.g., spinal or epidural anesthesia within the last 48 hours, recent cerebral bleeding, brain surgery or trauma, uncontrolled hypertension, history of stroke, active gastric ulcer or endocarditis, presence of severe hepatic or renal failure and use of antiplatelets or anticoagulants).

2) Clinical assessment

Patient clinical characteristics prospectively recorded included age and gender, body weight and height, history of venous thromboembolism (VTE) beyond six months (DVT, PE or SVT) and treatment received (e.g., anticoagulation, compression, etc.), the presence of autoimmune disease or malignancy (active or by history), family history of vari-

cose veins or VTE and number of full-term pregnancies for women. We also recorded the duration and type of symptoms/signs related to SVT (local pain, calf or thigh pain, rubor, visible or palpable lumps and sensation of warmth over the affected area, edema or difficulty moving the leg), the presence of clinically evident varicose veins with laterality, the laterality of SVT (leg affected with SVT) and its clinical location at the calf, thigh or both parts of the leg.

3) Duplex ultrasound scanning

This was performed to confirm the diagnosis, exclude patients with thrombus extension into the deep system or in close proximity to the saphenofemoral junction (≤ 3 cm), provide the location of SVT (varicose veins, great saphenous vein, small saphenous vein), and the presence of venous reflux in the superficial venous system.

Clot length measurement for extensive SVTs was performed with a tape measure, between the ultrasound-marked borders of thrombus extension.

4) Interventions

Patients were stratified into group A, where patients received a variable dose of tinzaparin for up to 60 days (n=98), and a subsequent group B-ext, where patients received a standardized intermediate dose of tinzaparin, i.e., 75.0% of the therapeutic (131 IU/kg, n=49) for 90 days. The decision to perform an extension study (group B-ext) was made on the ground of a number of RTEs observed in group A, indicating insufficient treatment. Patients were also advised to wear graduated elastic compression stockings as soon as local tenderness over the affected area was subsided.

5) Risk stratification

Patients of group A were stratified by the presence of risk factors used in the study SURPRISE (male gender, age >65 years, previous VTE, autoimmune disease, malignancy or SVT of non-varicose veins) [2], separately for the calf and thigh \pm calf locations, in order to assess their impact on RTE occurrence.

6) Follow-up

Patients were seen again two weeks after enrolment to re-assess patient symptoms and repeat DUS of the lower limb veins to determine the location and possible extension of the thrombus (defined as an increased thrombus length), including possible involvement of the deep system. Adherence to tinzaparin use was also assessed. Patients were

instructed to return to the hospital in case of possible RTEs or adverse effects. Follow-up at 90 days was made by telephone interview to evaluate symptoms as in previous assessments, confirm occurrence of RTEs and adverse events, and tinzaparin treatment duration. Follow-up at 120 days focused on occurrence of RTEs and adverse events. Finally a one-year follow-up was performed to register RTEs, compliance to the suggested use of stockings, and interventions if any (saphenectomy or ablation with dates). DUS was also repeated to determine the length of the residual thrombus.

7) Study outcome measures

The composite primary outcome measure of the study was RTE, defined as occurrence of clinically evident SVT recurrence (new symptoms or signs of SVT, confirmed by DUS) or VTE defined as DVT and/or PE, all treated as exit events, up to 120 days after initiation of treatment. Contra-

lateral events were included into the outcome. Secondary endpoints included the components of the primary endpoint, changes in the number of patient symptoms (at 14 and 90 days), thrombus length and asymptomatic extension on DUS (at 14 days), major and clinically relevant non-major bleeding according to the International Society of Thrombosis and Haemostasis definitions [8,9], other side effects, RTEs at one year and death during the study period.

8) Statistics

All data were analyzed with IBM SPSS Statistic ver. 24.0 software (IBM Co., Armonk, NY, USA). Baseline characteristics of the two main study groups (A and B-ext) were compared. Categorical variables were analyzed with the chi-square or Fisher's exact test, where appropriate. The Kolmogorov-Smirnov test did not show a normal distribution for most continuous variables, prompting reporting of

Table 1. Patient demographics, clinical and ultrasound characteristics, and treatment details of the two study groups, short and extended-duration treatment

Patient characteristic	Group A (short course, n=98)	Group B-ext (n=49)	P-value	Patients (n=147)
Age (y)	60 (47-70)	58 (49-65)	0.610	59 (47-69)
Gender (male/female)	33/65	13/36	0.380	46/101
Body mass index (y)	27.5 (24.5-29.5)	27.1 (24.5-30.3)	0.910	27.3 (24.5-30.1)
Presence of ipsilateral varicose veins	86 (87.8)	48 (98.0)	0.060	134 (91.2)
Presence of contralateral varicose veins	72 (73.5)	44 (89.8)	0.020	116 (78.9)
History of venous thromboembolism beyond 6 months	6 (12.2)	12 (12.2)	1.000	18 (12.2)
Leg affected (L/R)	45/53	23/26	0.910	68/79
Duration of symptoms (d)	2 (2-4)	2 (2-3)	0.710	2 (2-4)
Number of symptoms ^a	4 (3-5)	5 (4-5)	0.020	4 (4-5)
Superficial vein thrombosis location				
Calf	68 (69.4)	27 (55.1)	0.090	95 (64.6)
Thigh	15 (15.3)	8 (16.3)	0.870	23 (15.6)
Calf & thigh	15 (15.3)	14 (28.6)	0.060	29 (19.7)
Ultrasound findings				
Superficial axial vein thrombosis				
Isolated	3 (3.1)	1 (2.0)	1.000	4 (15.6) ^d
All	17 (17.3) ^b	26 (53.1) ^c	<0.001	43 (29.3)
Length of thrombosed segment (mm)	79 (50-103)	100 (70-196)	0.006	80 (60-110)
Superficial vein incompetence	85 (86.7)	49 (100)	0.005	134 (91.2)
Tinzaparin dose (IU/kg)	133 (118-156)	131 (131-136.5)	0.940	131 (123-151)
Treatment duration (d)	30 (29.5-40)	90 (90-90)	<0.001	40 (30-90)

Values are presented as median (interquartile range), number only, or number (%).

^aRecorded symptoms included pain over the thrombosed varicosities, pain in the calf, pain in the thigh, redness, hardness and hot sensation over the affected area, swelling and dyskinesia.

^bGreat saphenous vein (GSV) in 16 cases (in combination with short saphenous vein [SSV] in 2 cases) and SSV in 1 case.

^cGSV in all cases.

^dAll four patients had superficial vein incompetence.

medians (interquartile range) and use of the non-parametric Mann-Whitney test to compare the two groups. Related samples Friedman’s two-way analysis of variance was used to assess the change in the number of symptoms over time. RTE and VTE rates were calculated with the Kaplan-Meier method and compared with the Log-rank (Mantel-Cox) test. Multivariate survival analysis was performed with Cox regression. A P-value less than 0.05 was considered as statistically significant. Because no events occurred in group B-ext, analysis of predictors for RTEs was restricted to group A.

RESULTS

A total of 147 consecutive patients were included in the study. The two study groups were mostly comparable, as shown in Table 1.

However, compared to participants of group A, patients in group B-ext had a higher number of symptoms and a greater amount of thrombus based on its length, location and axial superficial vein (mostly the great saphenous vein) involvement. History of varicose veins and superficial vein incompetence were more often in group B-ext than in group A. On ultrasound scanning, varicose vein thrombosis (often affecting multiple clusters) was present in all but four patients, where isolated thrombosis of an incompetent axial superficial vein was visualized, findings that indicated chronic venous disease as the cause of SVT in all patients. The median dose of tinzaparin (expressed as IU/kg body weight) that was used in the two groups was comparable, although in group A there was a wider interquartile range compared to group B-ext, where the fixed dose resulted in minimal variation.

No patients were lost to follow-up. The median number (interquartile range) of symptoms for groups A and B-ext was 1 (1-2) and 2 (2-2) at two weeks (P<0.001) and 1 (0-1) and 0 (0-1) at 90 days (P=0.016), respectively. A significant improvement of symptoms over time was observed for both groups (P<0.001, related samples Friedman’s two-way analysis of variance). Median (interquartile range) thrombus length was reduced at two weeks to 50 mm (30-80 mm) and 53 mm (35-103 mm), and at one year to 0 mm (0-10

mm) and 0 mm (0-13 mm), for groups A and B-ext, respectively. Asymptomatic extension of thrombosis within the superficial system at two weeks was observed in 7 patients (7.1%) of group A and none of group B-ext (P=0.010).

RTEs occurred in 15/147 patients (10.2%), including 10 cases of recurrent SVT (including a single case of contralateral SVT), four cases of DVT and one case of fatal PE. RTE rates were lower in group B-ext (0% vs. 15.3% for group A, P=0.004, Fig. 1 and Table 2).

Statistically significant predictors and non-significant predictors with a trend of RTEs and VTE are shown in Table 3.

Statistically significant predictors of RTEs in group A included clinically extensive SVT (i.e., involving both the calf and thigh, P=0.037, Fig. 2A) and the ultrasound finding of superficial axial vein (great and/or small saphenous vein) thrombosis (P=0.008, Fig. 2B), but not other variables including tinzaparin dose or the presence of a SURPRISE risk factor. The latter was not a predictor even when stratified by SVT clinical location.

Duration of treatment (stratified into two subgroups, up to 30 days and more than 30 days) also had no effect on RTEs in group A (P=0.260), although at 45 days the difference was significant in favor of those receiving tinzaparin

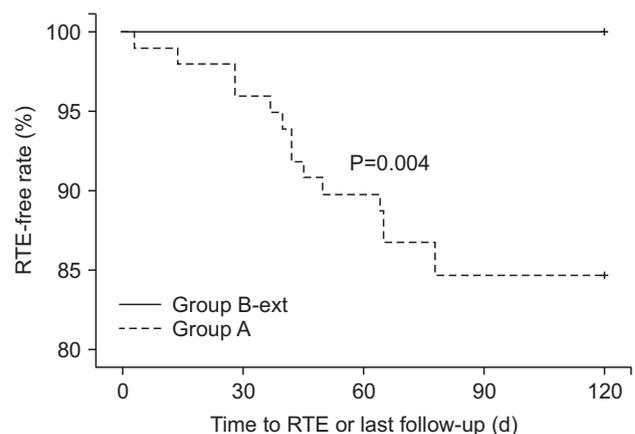


Fig. 1. Recurrent thromboembolic event (RTE) rates were lower in group B-ext compared to group A, 0% and 15.3%, respectively.

Table 2. Recurrent thromboembolism event-free rates during treatment and follow-up

	Event-free rate (day)				P-value
	30	60	90	120	
Group A					
Tinzaparin ≤30 days (n=60)	93.3±0.032	85.0±0.046	81.7±0.05	81.7±0.05	0.002
Tinzaparin 31-60 days (n=38)	100±0.0	97.4±0.026	89.5±0.05	89.5±0.05	0.021
Group B-ext					
Tinzaparin 90 days (n=49)	100±0.0	100±0.0	100±0.0	100±0.0	Reference

Table 3. Predictors of RTEs and VTE on univariate and multivariate analysis

Outcome measure/variable	Results		
	Event rates at 120 days ^a	Univariate analysis ^b	Multivariate analysis ^b
RTE			
Extensive SVT	12.0% vs. 33.3%, P=0.037	HR, 2.96; 95% CI, 1.01-8.68; P=0.047	
Superficial axial vein thrombosis	11.1% vs. 35.3%, P=0.008	HR, 3.70; 95% CI, 1.32-10.40; P=0.013	HR, 5.94; 95% CI, 2.05-17.23; P=0.001
Thigh pain	0% vs. 18.3%, P=0.073	HR, 27.1; 95% CI, 0.09-8501; P=0.260	
Difficulty moving the leg	6.1% vs. 20.0%, P=0.077	HR, 3.50; 95% CI, 0.79-15.53; P=0.099	HR, 5.87; 95% CI, 1.27-27.21; P=0.024
VTE			
Extensive SVT	2.4% vs. 22.2%, P=0.004	HR, 8.77; 95% CI, 1.46-52.51; P=0.017	
Absence of local pain	3.6% vs. 21.2%, P=0.023	HR, 6.12; 95% CI, 1.02-36.67; P=0.047	
Superficial axial vein thrombosis	2.6% vs. 19.8%, P=0.006	HR, 8.22; 95% CI, 1.37-49.29; P=0.021	
Isolated superficial axial vein thrombosis ^c	4.4% vs. 33.3%, P=0.036	HR, 7.35; 95% CI, 0.82-65.76; P=0.075	
Multiple thrombosed superficial sites	3.5% vs. 33.3% vs. 50%, P<0.001 ^d	HR, 6.78; 95% CI, 2.11-21.70; P=0.001	
Thrombus length ≥110 mm (4th quartile)	2.8% vs. 13.5%, P=0.050	HR, 4.98; 95% CI, 0.83-29.81; P=0.080	

The data indicate statistically significant and demonstrating a non-significant statistical trend.

RTE, recurrent thromboembolic event; VTE, venous thromboembolism; SVT, superficial vein thrombosis; HR, hazard ratio; CI, confidence interval.

^aComparison with the Log-rank test, ^bDerived from Cox regression, ^cAbsence of thrombosed varicosities, ^dOne vs. two vs. three sites.

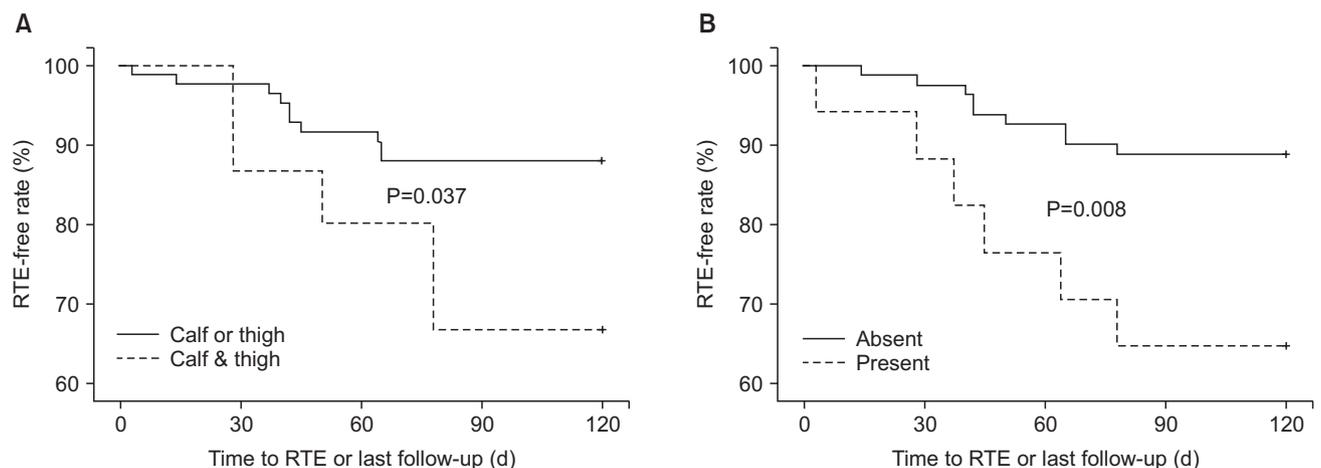


Fig. 2. (A) Predictors of recurrent thromboembolic events (RTEs) in group A included clinically extensive superficial vein thrombosis involving both the calf and thigh, (B) and the ultrasound finding of superficial axial vein (great and/or small saphenous vein) thrombosis.

for 31-60 days (P=0.013, Fig. 3).

Clinically extensive SVT (HR, 5.94; 95% CI, 2.05-17.23; P=0.001) and difficulty moving the leg (HR, 5.87; 95% CI,

1.27-27.21; P=0.024) were the only independent predictors of RTEs. During the one-year follow-up, five additional RTEs occurred, including two cases of DVT (one of them

was a calf DVT early after stripping) and three cases of SVT (on the ipsilateral side, n=1, and the contralateral side, n=2). RTE rates were still numerically fewer in group B-ext (4.1%

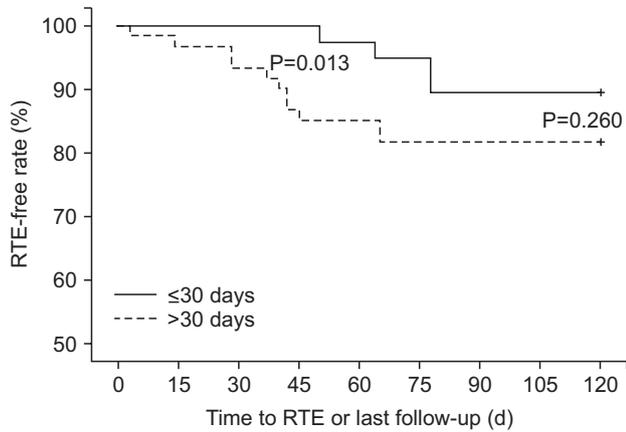
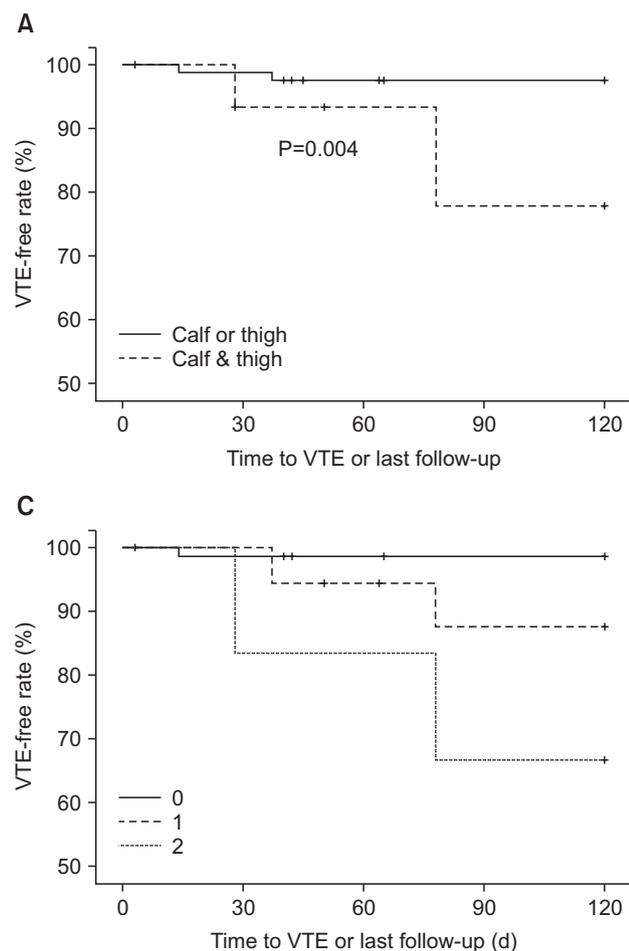


Fig. 3. Duration of treatment in patients of group A (stratified into two subgroups, up to 30 days and more than 30 days) had no effect on recurrent thromboembolic events (RTEs). However, at 45 days the difference was significant in favor of those who received tinzaparin for 31-60 days.



vs. 18.4% for group A, P=0.017). During this time period 10 patients had stripping and 5 more percutaneous ablation of the ipsilateral great saphenous vein (GSV), equally distributed into the two groups (P=0.930). All-cause mortality at one year was 2.7% (4/147) and VTE was the cause of death in two patients with PE and venous gangrene causing sepsis, respectively.

VTE predictors included clinically extensive SVT (P=0.004, Fig. 4A), superficial axial vein thrombosis (any, P=0.006, Fig. 4B or isolated, P=0.036), absence of local pain (P=0.023) and multiple thrombosed superficial sites (P<0.001, Table 3). A synergism of two of these risk factors (clinically extensive SVT and axial superficial vein thrombosis, Fig. 4C) was observed, but formal multivariate regression was not performed due to the small number of events.

VTE rates in relation to the number of these two risk factors are shown in Fig. 4C, where the presence of two risk factors (n=6, P<0.001 compared to no risk factors) or one risk factor (n=20, P=0.039 compared to no risk factors) was associated with a higher VTE rate than their absence (n=72).

In the subgroup of patients with superficial axial vein thrombosis, a non-significant trend for increased VTE rates in those with extensive superficial axial vein thrombosis

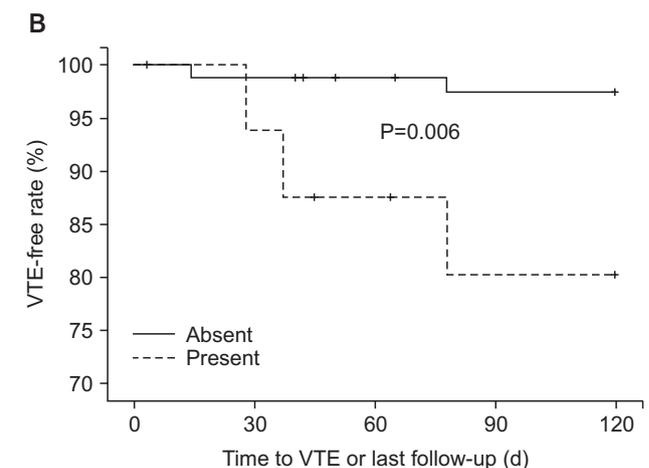


Fig. 4. Venous thromboembolism (VTE) predictors are shown in this figure; (A) these included clinically extensive superficial vein thrombosis, (B) and the ultrasound finding of superficial axial vein thrombosis. VTE rates in relation to the number of these two risk factors are shown in (C), where the presence of two risk factors (n=6, P<0.001 compared to no risk factors) or one risk factor (n=20, P=0.039 compared to no risk factors) was associated with a higher VTE rate than their absence (n=72).

(length >100 cm) compared to the remainder was observed (40% vs. 0% at 120 days, respectively, $P=0.060$).

There were no statistically significant predictors of SVT recurrence. A non-significant trend for increased recurrence rates in patients complaining for difficulty moving their affected leg was observed ($P=0.098$).

In group A, one case of clinically relevant non-major bleeding occurred in a 78 year old female patient with a BMI of 19.5 kg/m² four days after using 3,500 IU tinzaparin once daily, necessitating discontinuation of anticoagulation and event up to her 120 day follow-up. Two additional patients discontinued tinzaparin injection because of thrombocytopenia and raised transaminase levels, on the 8th and 10th day of administration, respectively. Additional reasons of stopping tinzaparin injection included financial reasons ($n=1$, after 11 days), patient inconvenience ($n=1$, after 14 days) or other reasons ($n=2$, after 6 days and 30 days, respectively). There was one death (fatal PE) that occurred in a patient on the 28th day while on nearly therapeutic tinzaparin doses, included already in RTEs described in detail above. No other side effects or deaths were observed. In group B-ext, compliance was 94%, with three patients discontinuing tinzaparin injections after 40 days, 60 days and 60 days, respectively, because of inconvenience caused by the injections. No adverse events or deaths were observed.

DISCUSSION

Our study in patients with SVT has identified sound risk factors, i.e., clinical involvement of the thigh & calf and involvement of the GSV and/or short saphenous vein (SSV) on DUS, for the development of recurrence and VTE events. The large difference in event rates of patients with and without such risk factors indicates the clinical significance of these findings. Surprisingly, the risk factors used in the SURPRISE study were not confirmed to be predictors of RTEs. The optimum duration of treatment was 90 days, much longer than shorter courses of treatment like up to 30 days or 31–60 days.

We observed an unexpectedly high frequency (15.3%) of recurrent events in group A during the 120 days of our study; the vast majority of them occurred after tinzaparin discontinuation. A similar frequency of thromboembolic events (15.5%) has been reported in the STEFLUX study at 93 days, mostly after anticoagulation was stopped [10]. Others have reported much higher RTE rates (approximately 25%–30%), which may have been modulated by a longer length of patient follow-up [5,11,12], or the selective inclusion of patients with SVT of the GSV [5], or on the other hand significantly lower RTE rates [3,13,14].

Anticoagulation intensity of our study, mostly interme-

diately or therapeutic, was very effective, as only 2 events (4%) occurred during the treatment course in group A and none in group B-ext. These findings are consistent with what previously reported by another study, where prophylactic and intermediate doses of parnaparin were associated with a frequency or RTEs in 7.6% and 1.9% at 33 days, respectively [10]. A third relatively small, likely to be underpowered for most outcome measures, randomized controlled study comparing prophylactic ($n=30$) with unmonitored intermediate ($n=30$) doses of unfractionated heparin in patients with SVT of the GSV reported a four week RTE rate of 37% and 10%, respectively [5]. However, two other studies failed to demonstrate superiority for a therapeutic regimen of low molecular weight heparin (LMWH) compared to prophylactic doses of LMWH [6,7], likely to the effect of the short duration of follow-up in one of them that used enoxaparin [6]. Additionally, the CALISTO trial demonstrated a very low rate of RTEs during the 45 day period of treatment with prophylactic 2.5 mg of fondaparinux (0.5%) and also the 30 day period after anticoagulation was stopped (0.025%) [3].

Our study has identified involvement of a superficial axial (saphenous) vein as a novel risk factor for SVT recurrence and also VTE. Untreated proximal (above the knee) GSV thrombosis has been reported to extend more frequently into the deep system than patients with SVT affecting the distal GSV or varicosities [15]. Separate results for the latter two sites were not provided nor SVT recurrence rates [15]. Others have reported a high PE rate in patients with SVT affecting the proximal GSV [16]. Our results do not support a strategy of treating only SVTs affecting the proximal GSV, because an isolated calf SVT with GSV and/or SSV involvement may still make the patient prone to develop SVT recurrence and/or VTE, presumably because of their proximity to the deep veins. Thigh involvement is thought to be associated with a higher risk of recurrence compared to isolated calf involvement. As a result the latter clinically defined situation has been considered as low risk, not requiring anticoagulation; such an association was not confirmed by our study and only clinically extensive SVT was associated with an increased RTE rate compared to isolated, above or below the knee SVT. Absence of varicose veins was not a risk factor for RTEs, as described by others [10,13]. We could not confirm the association between recurrence and history of VTE [10,13], male gender [13], or cancer [13,17] likely as a result of a small study sample. Asymptomatic extension during follow-up with ultrasonography was not a predictive factor, as previously described [18]; however, the role of a complete baseline DUS is of paramount importance to map venous pathology, as recently reiterated [19]. Side effects of treatment, including heparin-induced thrombo-

cytopenia, were rare in our study as previously reported [20].

Our study has certain limitations. It was not randomized to present a high level of evidence and its before-and-after design may have introduced some additional bias due to possible patient selection. Tinzaparin dose and duration of treatment for the first part of the study were not standardised. Compliance to graduated elastic compression stockings was not monitored to assess any effect on RTEs, although they have not found to offer symptomatic improvement in patients with SVT treated with anticoagulation [21]. Future studies should exclude patients at negligible risk for recurrence, where possible benefits are offset by potential side-effects, mainly bleeding, and randomise the remainder into short duration anticoagulation and ex-

tended duration anticoagulation. Further investigations have been also recommended by a Cochrane review [22].

In conclusion, an extended three-month regimen of tinzaparin in patients with SVT of the lower limbs is more effective than a shorter course and may be desirable in patients with extensive or superficial axial vein thrombosis, or causing thigh pain or functional leg problems. Future randomized trials should compare the effectiveness of extended-duration against short-duration anticoagulation for SVT.

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