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Institute of Vascular Diseases (IVD), Greece
In collaboration with:
Hellenic Society of Vascular and Endovascular Surgery
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International Symposium on Endovascular Therapeutics
Intervention Master Aortic Course
10th ANNIVERSARY

"One step forward to optimum management of SVT"

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Conflict of Interest Disclosure Form

☐ I have no potential conflict of interest to report

☒ I have the following potential conflict(s) of interest to report:

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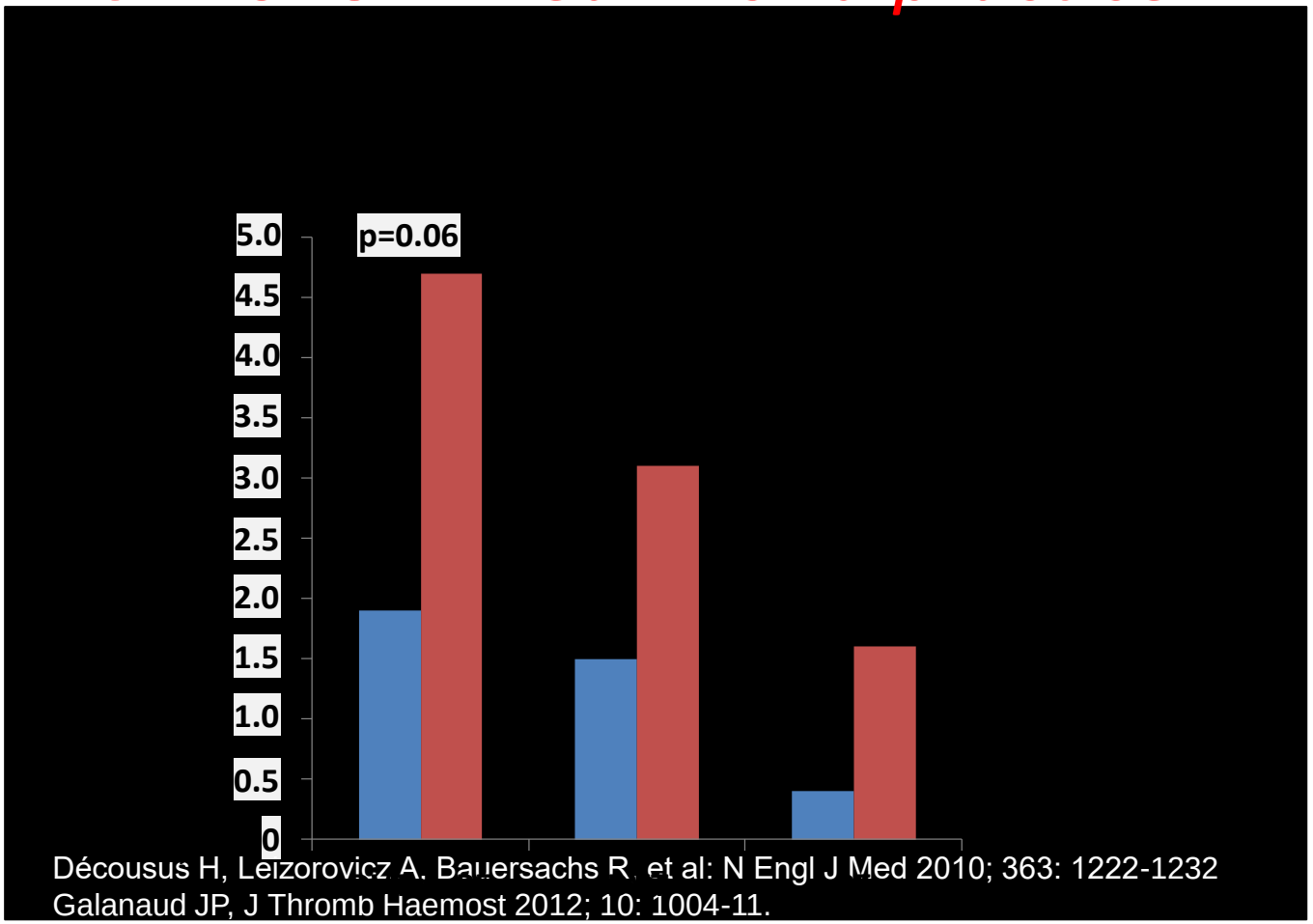
Guidelines (From International Consensus)

- All patients with STP should have bilateral duplex scanning to exclude DVT (Grade 1b)
- **LMWH in intermediate doses** for at least one month is recommended (Grade 2a)
- **Fondaparinux 2.5 mg daily** for at least 4 weeks is an effective treatment (Grade 1b)
- **Surgery** is not better than **LMWHs** (Grade 2b)

CALISTO in *Real-world practice*



Décousus H, Leizorovicz A, Bauersachs R, et al: N Engl J Med 2010; 363: 1222-1232
Galanaud JP, J Thromb Haemost 2012; 10: 1004-11.

Patients that could have been included in CALISTO

Patients that would not have been included in CALISTO

STEFLUX trial

Superficial ThromboEmbolism and Fluxum: A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis

- 664 outpatients with SVT of the long or short saphenous vein or collateral veins that was at least 4 cm long

- Patients were randomly assigned to 1 of 3 different doses and durations of LMWH (parnaparin).

- ✓ **The 30-day intermediate dose of LMWH** was superior to either the **30-day prophylactic dose** or **the 10-day intermediate dose** in reducing the primary outcome (a composite of symptomatic and asymptomatic DVT, symptomatic PE, and relapse and/or symptomatic or asymptomatic SVT recurrence in the first 3 days) with 60-day follow-up.

- ✓ No increase in major bleeding occurred

Cosmi B et al. J Thromb Haemost. 2012;10(6):1026-1035

CALISTO: High-risk patients

- In the **placebo group,** subgroup analyses showed **an increased incidence of symptomatic VTE complications at Day 47** (primary efficacy endpoint) in patients presenting one of the following characteristics at inclusion:
  - **Age > 75 yrs**
  - **BMI ≥ 30 kg/m^2**
  - **CrCl < 50 mL/min**
  - **History of DVT/PE (> 6 months previously)**
  - **History of SVT (> 3 months previously)**
  - **Absence of varicose veins at inclusion**
  - **SVT above the knee**
  - **SVT involving the great saphenous vein**
  - **Distance between the thrombus head and the SFJ < 10 cm**

BMI = body mass index; CrCl = creatinine clearance; DVT = deep vein thrombosis; PE = pulmonary embolism; SFJ = sapheno-femoral junction; SVT = superficial vein thrombosis; VTE = venous thromboembolism.

Decousus H. et al. for the CALISTO Study Group. N Engl J Med 2010; 363:1222–1232.

SURPRISE STUDY

	Rivaroxaban group (n=236)	Fondaparinux group (n=236)
Age (years)	61 (51–73)	61 (50–70)
Age (>65 years)	89 (38%)	87 (37%)
Men	100 (42%)	87 (37%)
Women	136 (58%)	149 (63%)
Previous DVT, PE, or SVT	117 (50%)	112 (48%)
Cancer	20 (9%)	25 (11%)
Autoimmune disease	3 (1%)	4 (2%)
Involvement of non-varicose veins	66 (28%)	76 (32%)
Number of risk factors at baseline	2 (1-2)	1 (1-2)
BMI (kg/m²)	28·7 (25·8–33·0)	29·0 (25·8–33·4)
Use of systemic non-steroidal anti-inflammatory drugs	24 (10%)	22 (9%)
Treatment duration (days)	45 (44–46)	45 (44–46)
Duration of follow-up (days)	92 (90–94)	91 (90–93)

Data are median (IQR) or n (%). DVT=deep-vein thrombosis. PE=pulmonary embolism. SVT=superficial-vein thrombosis.

Table 1: **Demographic and clinical characteristics of the patients**

	Rivaroxaban group		Fondaparinux group	
	Day 45	Day 90	Day 45	Day 90
Efficacy (per-protocol analysis set)*				
Primary efficacy endpoint†	7 (3%; 1·6–6·7)	15 (7%; 4·4–11·4)	4 (2%; 0·7–4·5)	15 (7%; 4·1–10·8)
Superficial-vein thrombosis extension	0	2 (1%; 0·3–3·4)	0	1 (<1%; 0·1–2·5)
Superficial-vein thrombosis recurrence	4 (2%; 0·7–4·8)	8 (4%; 1·9–7·3)	3 (1%; 0·5–3·9)	12 (5%; 3·1–9·1)
Deep-vein thrombosis	3 (1%; 0·5–4·1)	6 (3%; 1·3–6·1)	1 (<1%; 0·1–2·5)	2 (1%; 0·3–3·2)
Pulmonary embolism	0	0	0	0
Death	0	0	0	0
Surgery for superficial-vein thrombosis	0	0	0	2
Safety (safety analysis set)‡				
Major bleeding	0	0	0	0
Clinically relevant non-major bleeding	6 (3%; 1·2–5·4)	6 (3%; 1·2–5·4)	1 (<1%; 0·1–2·4)	2 (1%; 0·2–3·1)
Minor bleeding	15 (6%; 3·9–10·2)	16 (7%; 4·2–10·7)	15 (6%; 3·9–10·3)	17 (7%; 4·6–11·3)
Any bleeding§	20 (9%; 5·5–12·7)	21 (9%; 5·9–13·2)	16 (7%; 4·2–10·8)	19 (8%; 5·2–12·3)

Data are n (%; 95% CI). Primary timpoint: day 45 (end of treatment). Secondary time point: day 90 (end of follow-up). 95% CI of proportions were calculated with the Wilson's score method. *n=211 in the rivaroxaban group, n=224 in the fondaparinux group. †Composite endpoint of extension or recurrence of superficial-vein thrombosis, symptomatic deep-vein thrombosis, or pulmonary embolism, or occurrence of all-cause death. ‡n=236 in the rivaroxaban group, n=235 in the fondaparinux group. §Patients with more than one bleeding event were only counted once.

Table 2: **Clinical outcomes**

The SeVEN Study

Original Article

Phlebology

Tinzaparin in intermediate dose for the treatment of superficial vein thrombosis: Results from an observational multicenter study—SeVEN study

Athanasios Giannoukas[1], Christos Karathanos[1], Konstantinos Nikolakopoulos[2], Georgios Georgiadis[3], Chrisostomos Maltezos[4], Christos Ioannou[5], Spyros Vasdekis[6] and Georgios Trelopoulos[7]; on behalf of the SeVEN Collaborators*

- This study was conducted to assess the treatment outcomes of acute superficial vein thrombosis with intermediate dose of Tinzaparin.

- Retrospective analysis of records from outpatients over a period of 16 months treated in seven centers with Tinzaparin 0.5 ml (10,000 anti-Xa IU) once daily for a period that was at the treating physician's discretion. All the patients were followed up for at least 12 weeks.

Giannoukas A et al. Phlebology Jan 2018;33:636-45

The SeVEN Study

- A total of **296 patients (189 females, mean age 57.4 years) were included**.
- **Two thirds of the patients (191/296, 64.5%) received treatment for approximately five weeks (mean 36.9 days)** and the remaining (105/296, 35.5%) for a shorter period (mean 16.2 days).
- **The presence of thrombus above the knee and restricted daily activity were associated with longer period of treatment.**
- **Only one case with minor bleeding** was observed.
- Recurrence of thrombosis over a 12-week follow-up period occurred in 6% (superficial vein thrombosis in 14 (4.7%), deep vein thrombosis in 3 (1%) and thrombus extension in the superficial veins in 1 (0.3%)).

Conclusions: Intermediate dose of Tinzaparin was an effective and safe treatment for superficial vein thrombosis in the setting of real world practice.

Location of thrombus and status of patients' mobilization were associated with longer duration of treatment.

Future prospective randomized studies are needed to corroborate these findings.

Need to obtain additional data-The SeVEN extension

In order to obtain additional data and confirm SeVEN study findings we conducted SeVEN extension study

- SeVEN extension protocol & CRF was a slightly simplified version of SeVEN study ones
- All core elements of SeVEN study was examined

The SeVEN extension

Inclusion criteria

- Outpatients ≥18 years old, with symptomatic Superficial Venous Thrombosis ≥5 cm, as confirmed by imaging methods
- Onset of symptoms within 10 days prior to treatment onset
- Patients should be treated with Low Molecular Weight Heparin (LMWH) for at least 14 days, in accordance with the recommendations of their physician

The SeVEN extension

Exclusion criteria

- Patient medical history of Deep Vein Thrombosis and/or Pulmonary Embolism within 6 months prior to study inclusion
- Presentation of Superficial Venous Thrombosis due to sclerotherapy or insertion of a venous catheter within 1 month prior to study inclusion or within 3cm of the SFJ or SPJ
- BMI > 35 kg/m2
- Patients receiving medication that affect blood coagulation e.g. acetylsalicylic acid, Vitamin K antagonists, dextran
- Major Surgical Procedure within 3 months prior to study inclusion
- Patients subjected to spinal or epidural anesthesia within 48 hours prior to study inclusion
- Patients who within the past month experienced cerebral bleeding, trauma and/or recently underwent CNS surgery
- Patients with serious hypertension, stroke history, active gastric ulcer, septic endocarditis
- Patients with serious hepatic or renal insufficiency

The SeVEN extension

Methods

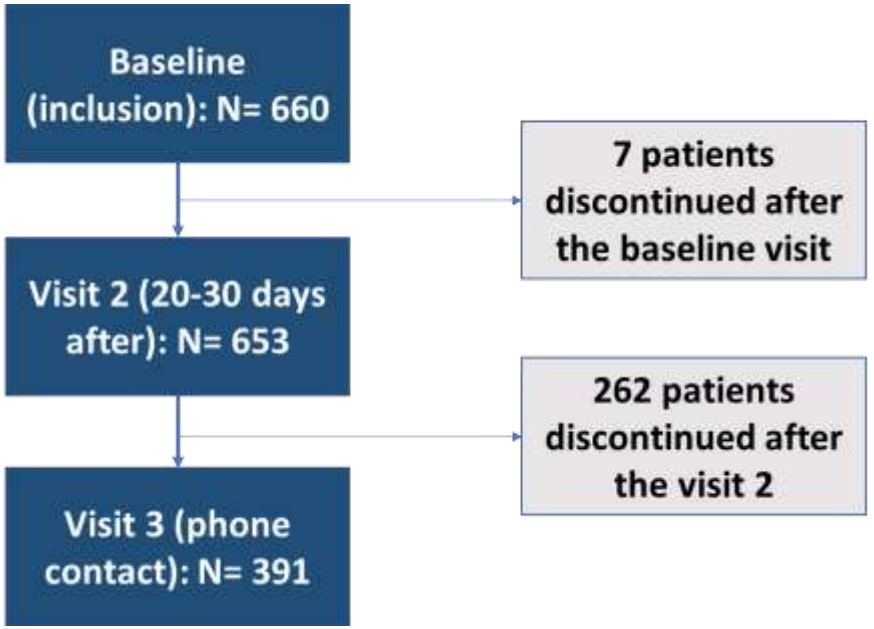
We collected:

- Demographic data
- Somatometric data
- VTE related medical history
- Co-morbitities
- SVT presentation (symptoms, signs, location, thrombus length)
- Anticoagulant treatment

Primary objective

The evaluation of incidence of thromboembolic complications or death in patients with Superficial Venous Thrombosis treated with tinzaparin in intermediate dose

Patient flow-chart



The SeVEN extension

Κατανομή ασθενών ανά ερευνητή

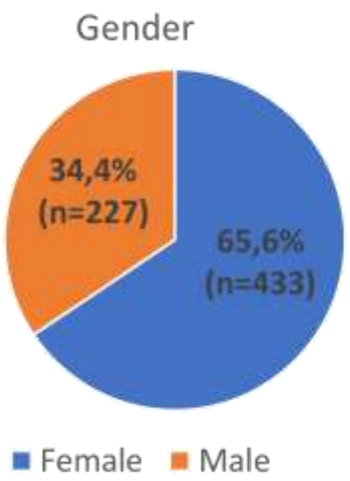
	N	%
Αλεξανδρόπουλος Δημήτριος	45	6.8
Γεωργιάδης Γεώργιος	38	5.8
Γκούμας Κωνσταντίνος	46	7.0
Ιορδανίδης Τριαντάφυλλος	40	6.1
Λάτσιος Παναγιώτης	50	7.6
Λυκόπουλος Δημήτριος	30	4.5
Παπακώστας Ιωάννης	49	7.4
Παπασιδέρης Χρήστος	30	4.5
Πετρούλης Μιχαήλ	38	5.8
Ρηγόπουλος Χρήστος	44	6.7
Σαλίβερος Απόστολος	30	4.5
Σαλεπτσής Βασίλειος	36	5.5
Σερέτης Κωνσταντίνος	35	5.3
Σιαφάκας Αθανάσιος	35	5.3
Τζορμπατζόγλου Ιωάννης	30	4.5
Τζώρτζης Ηλίας	30	4.5
Χατζής Δημήτριος	54	8.2
Σύνολο	660	100.0

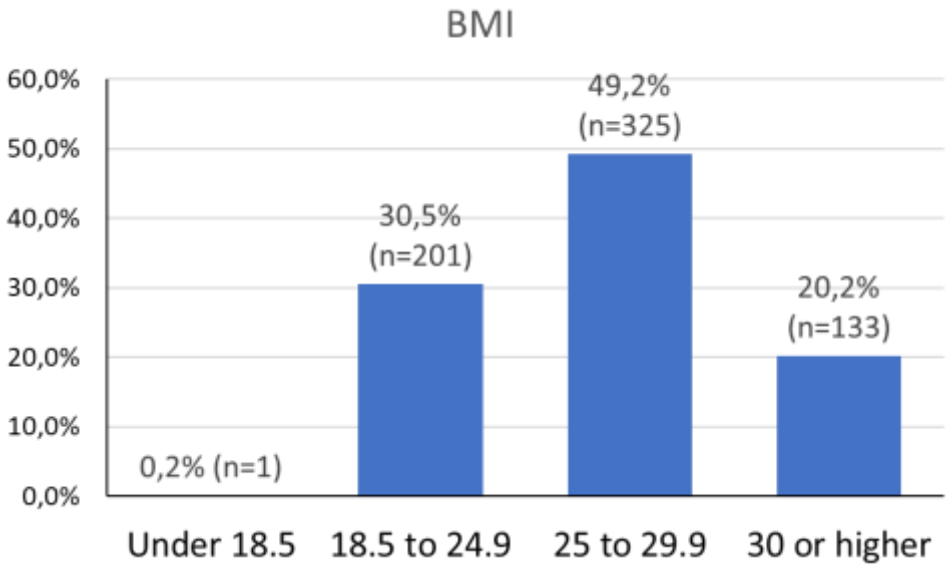
The SeVEN extension Study

PRELIMINARY RESULTS

The SeVEN extension

Patient demographics (n=660)





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Medical History at Baseline (N=660)

Thromboembolic events	N (%)
Total	660
Thromboembolic events	88 (13.3)
Deep vein thrombosis	27 (4.1)
Pulmonary embolism	7 (1.1)
Family history	91 (13.8)
Post-thrombotic syndrome	22 (3.3)
Superficial vein thrombosis	187 (28.3)

Significant comorbidities	N (%)
Cardiac or respiratory deficiency	23 (3.5)
Autoimmune diseases	23 (3.5)
Soft tissue infection	10 (1.5)

The SeVEN extension

Medical History at Baseline (N=660)

Permanent or recent prolonged immobility	N (%)
Hospitalization	41 (6.2)
Long-hour travelling	56 (8.5)
Bed rest	40 (6.1)
Long Standing	318 (48.2)

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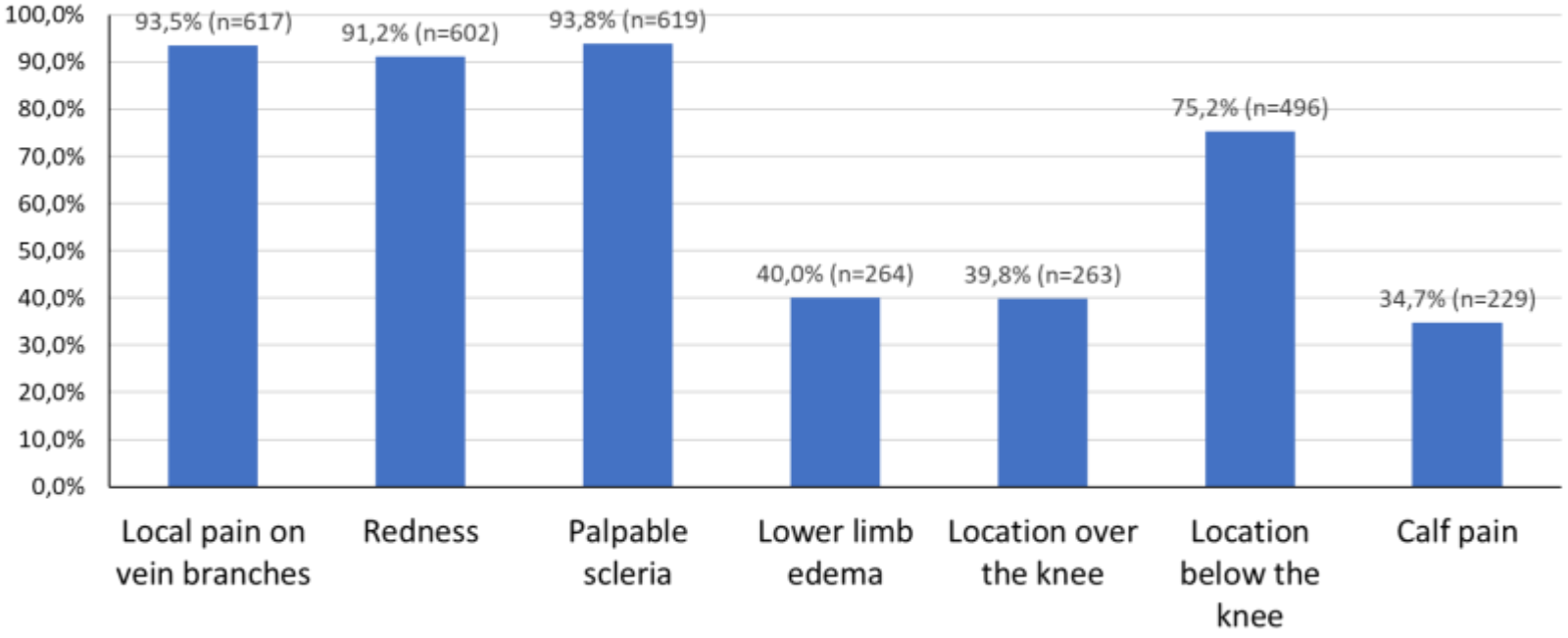
Clinical examination findings at baseline



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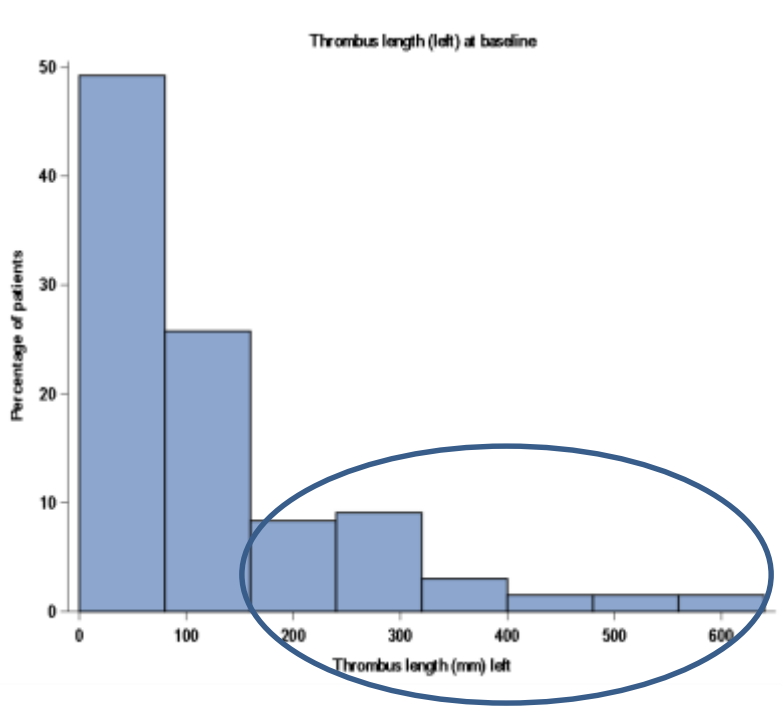
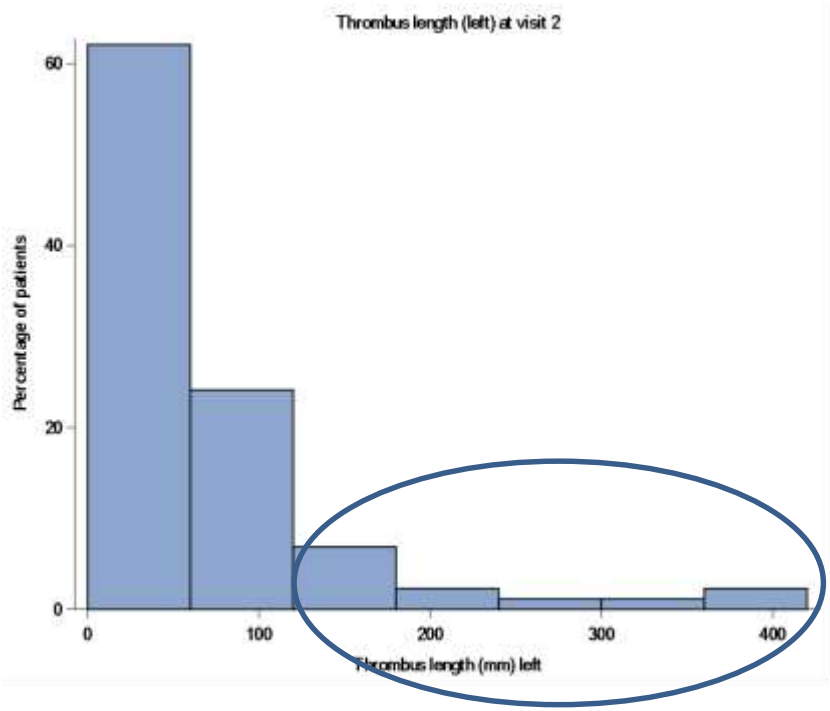
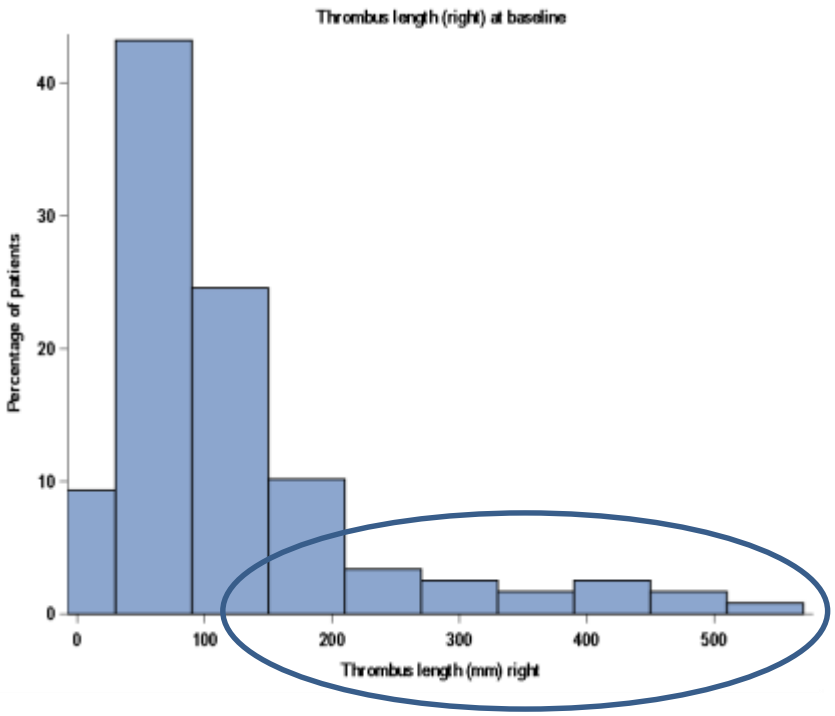
Thrombus length (left) at baseline and visit 2

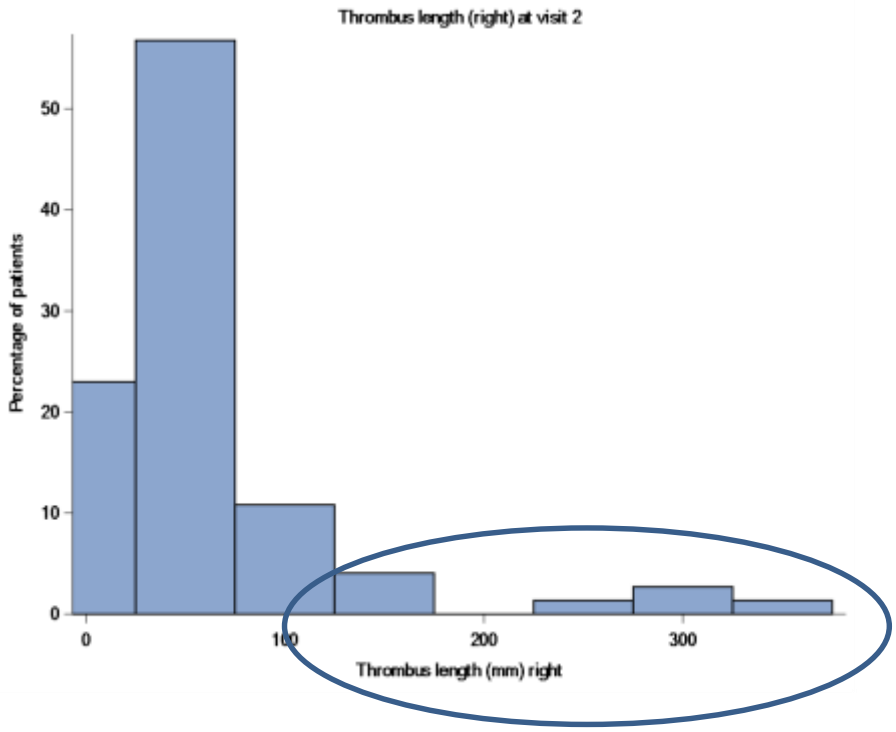




The SeVEN extension

Thrombus length (right) at baseline and visit 2





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Dosage information at baseline and at visits 2 & 3*

Dose at treatment initiation	Category: Patients who did not experience any events	Category: Patients who experienced an event	Total
	N (%)	N (%)	N (%)
0.4	1 (0.2)	-	1 (0.2)
0.45	7 (1.1)	-	7 (1.1)
0.5	**497 (77.1)**	**12 (80.0)**	**509 (77.1)**
0.6	1 (0.2)	-	1 (0.2)
0.7	**106 (16.4)**	**2 (13.3)**	**108 (16.4)**
0.9	32 (5.0)	1 (6.7)	33 (5.0)
1.25	1 (0.2)	-	1 (0.2)
Total	645 (100.0)	15 (100.0)	660 (100.0)

	N	%
N of patients continuing treatment at visit 2	392	100.0
Dose at visit 2		
Dose increased	17	4.3
Same dose	375	95.7

	N	%
N of patients continuing treatment at visit 3	61	100.0
Dose at visit 3		
Dose increased	2	3.3
Same dose	59	96.7

*for patients continuing treatment

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Treatment duration for patients with event or not and overall

		Category		Total
		Patients who did not experience any events		
Duration of treatment with XMBH (in days)	N	**631**	12	643
	Mean (SD)	**37.6 (19.5)**	54.8 (52.7)	37.9 (20.7)
	Median	**31.0**	35.5	31.0
	Min-Max	3-180	7-200	3-200

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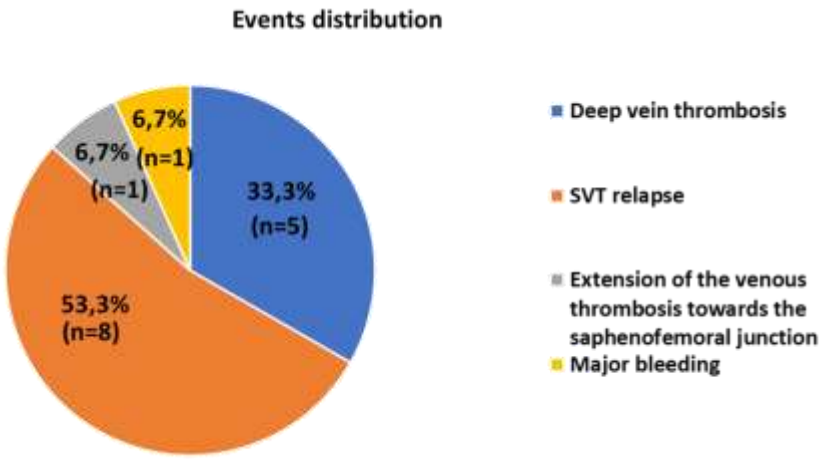
Number of patients with event & time to event

	N	%
Patient with event		
No	**645 (97.7)**	**97.7**
Yes	15 (2.3)	2.3

		Total
Time to event (days)	N	14*
	Mean (SD)	29.1 (18.7)
	Median	24.5
	Min-Max	8-90

		Total
Time to relapse (in days)	N	8
	Mean (SD)	26.5 (5.2)
	Median	26.5
	Min-Max	20-34



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Patients status at the end of treatment (n=660)

	N (%)
Recovered	189 (28.6)
Satisfying recovery	207 (31.4)
Completion of treatment (reason to stop anticoagulation)	65 (9.8)
Surgery	23 (3.5)
Switched to other treatment	13 (2.0)
Lost to follow-up	10 (1.5)
Other	10 (1.5)
SVT relapse	8 (1.2)
Deep vein thromvosis	5 (0.8)
Pulmonary embolism	1 (0.2)
Extension of the venous thrombosis towards the saphenofemoral junction	1 (0.2)
Major bleeding or clinically significant non-major bleeding (according to ISTH)	1 (0.2)
Patient decision (reason to stop anticoagulation)	16 (2.4)
Unknown	111 (16.8)

Only 15 (2,3%) VTE events & only one major/CRNM bleeding event

The SeVEN extension
Summary

- **SVT treatment with Tinzaparin at intermediate doses is effective and safe in real world**

- **This was a prospective observational study and its findings should be corroborated by randomised studies**


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